CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3 Multicenter, Randomized, Open-label, Clinical Trial of Telavancin Versus Standard Intravenous Therapy in the Treatment of Subjects with *Staphylococcus aureus* Bacteremia Including Infective Endocarditis
Sponsor Study No.:	0112
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This study will be conducted according to the principles of Good Clinical Practice.

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: Study 0112: A Phase 3 Multicenter, Randomized, Open-label Clinical Trial of Telavancin Versus Standard Intravenous Therapy in the Treatment of Subjects with *Staphylococcus aureus* Bacteremia Including Infective Endocarditis.

Estimated Number of Study Centers and Countries or Regions: Approximately 120 study centers in the United States, Europe, and Latin America

Background and Rationale:

Bacteremia due to *Staphylococcus aureus* (*S. aureus*) is a frequently encountered serious infection that is often associated with infective endocarditis [1-3]. Treatment of bacteremia is challenging; infection metastasis and relapse are common, as is the involvement of antibiotic-resistant bacterial strains, including methicillin-resistant *S. aureus* (MRSA) [4]. In the treatment guidelines for MRSA bacteremia from the Infectious Diseases Society of America, only two agents are recommended: vancomycin, the traditional first-line therapy for MRSA infections, and daptomycin [5]. Both of these agents have recognized shortcomings. Vancomycin has limited tissue penetration, is slowly bactericidal [6], is suboptimal against methicillin-susceptible *S. aureus* (MSSA) [7, 8] and evidence suggests decreasing susceptibility among Gram-positive pathogens [7, 9, 10]. Resistance to daptomycin has more recently emerged, together with evidence suggesting that reduced susceptibility to vancomycin may also impact susceptibility to daptomycin [11, 12]. As such, there is a critical need for additional agents appropriate for the treatment of *S. aureus* bacteremia.

Telavancin is a rapidly bactericidal lipoglycopeptide antibiotic that is active against a range of clinically relevant Gram-positive pathogens, including MRSA. Telavancin exhibits concentration-dependent bactericidal effects via a dual mechanism of action (inhibition of bacterial cell wall synthesis and disruption of bacterial cell membrane barrier function), which may help to minimize the potential for the selection of resistance. In global surveillance studies, telavancin has demonstrated consistent in vitro microbiologic activity within the telavancin susceptible ranges against Gram-positive isolates, including MRSA, regardless of susceptibility to other agents or geographic region. Telavancin minimum inhibitory concentration (MIC) MIC_{50}/MIC_{90} values consistently show activity against *S. aureus* comparable or superior to other agents.

In vitro pharmacokinetic (PK)/pharmacodynamic models of simulated endocardial vegetations have demonstrated superior telavancin bactericidal activity against *S. aureus* strains compared with vancomycin and daptomycin. In vitro biofilm studies have demonstrated the potential efficacy of telavancin in the treatment of staphylococcal biofilm-associated infections [13]. Furthermore, studies using animal models of infection also have supported the potential for telavancin in the effective treatment of *S. aureus* bacteremia and infective endocarditis. In murine models of bacteremia and rabbit models of infective endocarditis, telavancin has demonstrated greater efficacy than

vancomycin [14].

The efficacy and safety of telavancin have been demonstrated in Phase 3 clinical trials for the treatment of subjects with complicated skin and skin structure infections (cSSSI) due to Gram-positive pathogens (ATLAS studies) and subjects with hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP) due to Gram-positive pathogens (ATTAIN studies). Telavancin, 10 mg/kg administered intravenously (IV) over 60 minutes, once every 24 hours for 7 to 14 days is the currently approved dosage for the treatment of adult patients with cSSSI caused by susceptible Gram-positive bacteria. The same telavancin dose, for a duration of 7 to 21 days, is the currently approved dosage for the treatment of adult patients with HABP/VABP caused by susceptible isolates of *S. aureus*, when alternative treatments are not suitable.

Limited data are available from post hoc analyses of subjects with concurrent bacteremia from these Phase 3 cSSSI and HABP/VABP studies. Of the 1784 subjects in the ATe population in the 2 cSSSI trials, 32 subjects had baseline *S. aureus* bacteremia: 21 (2.4%, including 13 with MRSA) subjects were treated with telavancin and 11 (1.2%, including 4 with MRSA) subjects were treated with vancomycin. In these bacteremic subjects, the clinical cure rate at test of cure (TOC) was 57.1% (12/21) for the telavancin-treated subjects and 54.6% (6/11) for the vancomycin-treated subjects. In subjects with Gram-positive bacteremic HABP/VABP in the ATTAIN studies, the clinical cure rates for telavancin and vancomycin were 46% (11/24) versus 37% (10/27), respectively. Moreover, only one telavancin-treated subject (1/34) compared with six vancomycin-treated subjects (6/39) had bacteremia that persisted beyond baseline cultures.

In a Phase 2 proof-of-concept study, comparing telavancin with standard therapy (vancomycin or anti-staphylococcal penicillin) for treatment of subjects with uncomplicated *S. aureus* bacteremia (ASSURE study), compared with standard therapy, similar proportions of the clinically evaluable (CE) population (n = 17) were cured at a long-term follow-up visit (Day 84; 88% vs. 89%, respectively). However, the number of clinically evaluable subjects limits the strength of a conclusion regarding the comparative safety and efficacy of telavancin and standard therapy in this population.

In a retrospective case series, telavancin provided a favorable cure rate and rapid clearance of bacteremia in difficult-to-treat subjects with refractory MRSA bacteremia with or without infective endocarditis [15]. Additional case reports of subjects with vancomycin-intermediate *S. aureus* (VISA) or MRSA endocarditis have demonstrated successful treatment with telavancin [16, 17].

To explore means by which the telavancin risk: benefit profile could be improved, the Sponsor recently performed additional integrated retrospective analyses of PK and outcomes data from the VIBATIV® (telavancin) Phase 3 studies for cSSSI and HABP/VABP. Based on the results of the integrated retrospective data analyses, the Sponsor believes that a reduction in the telavancin dose could optimize the risk: benefit profile of telavancin for the treatment of bacteremia. In separate independent CART and logistic regression analyses of data from the Phase 3 studies, a telavancin exposure-response relationship with acute kidney injury was confirmed. The analyses

support the conclusions that a dose reduction from 10 mg/kg to 7.5 mg/kg once daily would decrease the risk of nephrotoxicity and improve overall safety while having little to no impact on efficacy. Mortality was also examined in these analyses and despite small numbers and confounding factors, there was an exposure-response relationship in a subset of HABP/VABP subjects with creatinine clearance (CrCl) ≤50 mL/min. This risk may also be decreased with the proposed dose reduction. Therefore, the Sponsor proposes to reduce the exposure of telavancin by incorporating the following three changes in the dose and dosing regimen: 1) decreasing the dose by 25% in all subjects; 2) decreasing the dose by 62% to 3.8 mg/kg from 10 mg/kg and altering the dosing schedule for severe renal impairment (creatinine clearance of 10 to <30 mL/min) to once daily rather than every 48 hours; and 3) recommending the dose not exceed 750 mg (or 560 and 380 mg in moderate or severe renal impairment) for subjects weighing greater than 100 kg. In addition, for subjects undergoing chronic hemodialysis, telavancin should be administered IV at a dose of 3.8 mg/kg (maximum dose of 380 mg) once daily by infusion over 60 minutes (following hemodialysis on hemodialysis days).

Telavancin dosed at 7.5 mg/kg has been studied in Phase 2 and Phase 3 studies in 192 patients with cSSSI. In the Phase 2 and Phase 3 cSSSI studies, the cure rates at TOC in the CE population are similar for the two dosing regimens (93.2% [150/161] for 7.5 mg/kg and 89.1% [732/822] for 10 mg/kg), supporting the efficacy of the 7.5 mg/kg dose. No noticeable difference between telavancin 7.5 mg/kg and 10 mg/kg was observed regarding the adverse events (AEs) profile in the Phase 2 and Phase 3 cSSSI studies. However, the difference in sample size between the two telavancin doses limits the ability to derive a conclusion about AE rates, especially in cases where the incidence was low (eg, serious adverse event [SAE] or renal AE).

This study will be conducted in a population of subjects who are seriously ill with *S. aureus* bacteremia. Extra precautions have been built into the protocol to protect subject safety; however, by utilizing the proposed alterations in telavancin dose, the Sponsor believes that safety risks could potentially be reduced without loss of efficacy. This study will allow evaluation of the revised telavancin dose in a prospective, controlled fashion, and in an appropriate population of subjects.

Regarding the rationale for standard IV therapy as the comparator in this trial, in adult patients with MRSA bacteremia or infective native valve endocarditis, current recommendations include treatment with vancomycin or daptomycin. Vancomycin is recommended for empiric therapy for *S. aureus* bacteremia in healthcare settings with an elevated prevalence of MRSA. Guidelines recommend that vancomycin be administered at doses providing trough concentrations of 15 to 20 µg/mL. For institutions in which the preponderance of MRSA isolates have vancomycin minimum inhibitory concentration (MIC) values >2 µg/mL, alternative agents, such as daptomycin, should be used [18]. Daptomycin is currently approved at a dosage of 6 mg/kg for the treatment of *S. aureus* bacteremia, including those with right-sided infective endocarditis, however, some experts recommend higher doses of up to 8 to 10 mg/kg [19-23]. For patients with methicillin-susceptible *S. aureus*, a β-lactam antibiotic with anti-staphylococcal activity (eg, nafcillin, oxacillin,

cefazolin) is the recommended treatment.

Guidelines recommend treatment durations of at least 2 weeks for uncomplicated bacteremia (UCB), 4 to 6 weeks for complicated bacteremia (CB), and 6 weeks for infective native valve endocarditis [18].

To summarize, the use of telavancin for this study is supported by data from the post hoc analyses of subjects with bacteremia included in the Phase 3 studies of cSSSI and HABP/VABP, a Phase 2 proof-of-concept study of telavancin in subjects with uncomplicated *S. aureus* bacteremia, retrospective case series of subjects with refractory MRSA bacteremia, and case reports of subjects with VISA or MRSA endocarditis [15-17]. The available data describing telavancin for the treatment of bacteremia are limited, but are supportive of additional evaluation in larger, prospective studies including subjects with bacteremia due to *S. aureus* (specifically MRSA). Further prospective clinical studies are needed to assess the efficacy and safety of telavancin therapy in larger numbers of subjects with bacteremia and infective endocarditis.

Objectives: The primary objective of the study is as follows:

- To compare telavancin to standard intravenous therapy (ie, vancomycin, daptomycin, anti-staphylococcal penicillin, or cefazolin) clinical outcomes in the treatment of *S. aureus* bacteremia including *S. aureus* right-sided infective endocarditis (SA-RIE).

The secondary objectives of the study are as follows:

- To evaluate the safety and tolerability of telavancin compared with standard intravenous therapy in the treatment of *S. aureus* bacteremia, including SA-RIE.
- To evaluate the PK profiles of telavancin and vancomycin in subjects with *S. aureus* bacteremia, including SA-RIE.

Study Design: This is a multicenter, randomized, open-label, noninferiority trial of telavancin versus standard IV therapy control (ie, vancomycin, daptomycin, or a β-lactam antibiotic with anti-staphylococcal activity [eg, nafcillin, oxacillin, cefazolin]) in the treatment of subjects with complicated *S. aureus* bacteremia and SA-RIE. The primary efficacy endpoint is clinical outcome at TOC, analyzed in subjects with a baseline diagnosis of UCB, CB, or right-sided infective endocarditis (RIE) in the microbiological all-treated (mAT) population. The baseline diagnosis and the clinical outcome will be assessed by a blinded Independent Efficacy Adjudication Committee (IEAC). Safety will be monitored by an Independent Data Monitoring Committee (IDMC).

Eligible subjects with confirmed *S. aureus* bacteremia will be randomized in a ratio of 1:1 to receive open-label telavancin or standard IV therapy. Randomization will be stratified by geographic region. Standard IV therapy, depending on the antibacterial susceptibility of the causative pathogen, will include vancomycin or daptomycin for subjects with known or suspected MRSA (daptomycin should be used for subjects with *S. aureus* with vancomycin MIC values >1 µg/mL); or a protocol-specified β-lactam antibiotic with anti-staphylococcal activity (ie, nafcillin, oxacillin, cloxacillin, or cefazolin) for subjects with known MSSA.

Subjects with a confirmed or suspected mixed polymicrobial infection with a Gram-negative pathogen requiring coverage with an antibiotic with Gram-negative activity at enrollment will be excluded from participation in the study. Subjects that develop an infection during study participation requiring coverage with an antibiotic with gram-negative activity may be allowed to continue on study after discussing the concomitant antibiotic treatment with the medical monitor.

Each subject must have at least one blood culture positive for *S. aureus* before randomization, referred to as the qualifying blood culture (QBC). The initial identification of *S. aureus* in the QBC can be done via standard culture identification methods or by use of a rapid diagnostic test. Use of a rapid diagnostic system, if available, is preferred, but not obligatory, for determination of *S. aureus* bacteremia. Regardless of method or the time that the blood sample was obtained, the identification of *S. aureus* bacteremia must be within 48 hours prior to randomization.

The study population will be enriched for subjects with CB by requiring subjects to have at least one risk factor for CB at enrollment. All subjects with CB will receive study drug for a minimum of 4 weeks and a maximum of 6 weeks (28 to 42 days) of therapy. Subjects with infective endocarditis, will receive 6 weeks (42 +/- 3 days) of therapy. Subjects with UCB will receive a minimum of 2 weeks and a maximum of 4 weeks (14 to 28 days) of therapy as per standard of care.

The calendar day of first study drug administration is designated as Day 1; subsequent calendar days are Days 2, 3, etc.

Procedures to control or eliminate the infection source, eg, by removal of intravascular lines or drainage and debridement of the primary infection site, will be completed within the first 3 days of study drug treatment.

Follow-up blood cultures will be performed daily until two successive post-randomization blood cultures are negative for *S. aureus.*

On or before Day 8, each subject must undergo echocardiogram (either transthoracic echocardiogram [TTE] or transesophageal echocardiogram [TEE]; TEE is strongly preferred) and will be evaluated by a physician investigator to determine the origin and extent of the *S. aureus* infection to establish the classification of infection type as one of the following:

- Uncomplicated bacteremia (UCB): A QBC, defined as a blood culture positive for *S. aureus* before randomization, no evidence of infective endocarditis, and all of the following:
  - Catheter-associated infection and removal of the catheter or cutaneous infection-associated infection and source control within 3 days after randomization.
  - A negative post-QBC blood culture drawn within 72 hours after start of study medication.

- Defervescence within 3 days after start of study medication.
- Absence of valvular findings on echocardiography predisposing to infective endocarditis.
- No signs or symptoms suggestive of metastatic infection.

- Complicated bacteremia (CB): A QBC, defined as a blood culture positive for *S. aureus* before randomization, no evidence of infective endocarditis, and at least one of the following:
  - Follow-up post-QBC blood culture positive for *S. aureus* drawn after Day 3 and with known *S. aureus* identification on or before Day 8.
  - For subjects febrile at screening, persistence of fever on or beyond Day 3 after the start of study medication.
  - Evidence of metastatic infection (eg, septic arthritis, septic thrombophlebitis, deep tissue abscess).
  - Evidence of venous catheter line thrombosis or septic thrombosis associated with a venous catheter.

    NOTE: On or before Day 8, subjects with a central venous catheter as the presumed source of the infection should also undergo central venous ultrasound to evaluate for venous thrombosis associated with the central line. Subjects who have documented central venous thrombosis, and therefore septic thrombophlebitis, should be classified as CB.
- Right-sided infective endocarditis (RIE): Defined as having a QBC and Definite or Possible endocarditis according to Modified Duke Criteria [24] (Appendix 1) without predisposing abnormalities or active infection of mitral or aortic valve.
- Left-sided infective endocarditis (LIE): Defined as having a QBC and Definite or Possible LIE according to Modified Duke Criteria [24] (Appendix 1).

On or before Day 8, subjects will be assigned to receive therapy based on the classification of infection type:

- For UCB, subjects will receive a minimum of 2 weeks and maximum of 4 weeks (14 to 28 days) of therapy.
- For CB, subjects will receive a minimum of 4 weeks and a maximum of 6 weeks (28 to 42 days) of therapy.
- For endocarditis, subjects will receive 6 weeks (42 days +/- 3 days) of therapy.

Prior to or on Day 8, a signs and symptoms worksheet will be completed to determine the infection type including metastatic disease (UCB, CB, RIE, LIE) and sent to the medical monitor to review. Subsequently, weekly worksheets noting signs and symptoms of potential metastatic *S. aureus* infection will be reviewed and completed by the physician investigator and forwarded to the medical monitor to optimize diagnosis and treatment of both the primary infection source and new metastatic foci of *S. aureus*.

Development of new signs or symptoms consistent with *S. aureus* infection will be assessed daily, during the hospital stay or during the study drug treatment period as clinically indicated, by clinical evaluation and other diagnostic modalities, eg, chest X-ray, ultrasonography, bone scan, computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET).

After Day 8, if signs and symptoms lead to a subsequent confirmed diagnosis of new metastatic foci, it will be criteria for clinical failure. Management of the subject (eg, discontinuation of study drug) will be at the discretion of the investigator based on his/her standard routine care.

Study visits for endpoint assessment will be conducted as follows:

- End of therapy (EOT) Visit: Within 3 days after the last dose of study drug
- Test of cure (TOC) Visit:
  - For subjects with UCB and assigned to receive 2 to 4 weeks (14 to 28 days) of treatment, their TOC is 38 (+/-2) days after randomization regardless of the total duration of study drug therapy
  - For subjects with CB and assigned to receive 4 to 6 weeks of treatment (28 to 42 days), their TOC is 52 (+/- 2) days after randomization regardless of the total duration of study drug therapy
  - For subjects with endocarditis assigned to receive 6 weeks (42 +/-3 days) of treatment, their TOC is 52 (+/- 2) days after randomization regardless of the total duration of study drug therapy

A post-EOT blood culture will be obtained at least 4 days after the EOT visit, and results must be available prior to the TOC visit. The results of this blood culture will be part of the assessment of clinical outcome at TOC.

Subjects who are discharged from the hospital during the treatment or follow-up period will return to the hospital once per week for a study visit. After all the weekly visits are complete, the subject will also return to the hospital for the End of Therapy Visit, the Post-End of Treatment Visit, and the TOC visit.

The TOC visit will occur based on infection classification as described above and is also the end of study (EOS).

Duration of Study Participation: The duration of study involvement for each subject will be up to approximately 8 weeks (ie, up to 52 days [+/- 2] days after randomization [to TOC evaluation]).

Number of Subjects per Group: The planned enrollment is 248 subjects (124 subjects per treatment group).

Study Population:

This study will enroll adult subjects with confirmed MSSA or MRSA bacteremia.

Inclusion Criteria:

1. Male or female at least 18 years old at the time of consent
2. Subject has signed an informed consent form. If a subject is unable to give consent, when legally permitted, consent must be obtained from the subject's legally acceptable representative

   NOTE: Subject, or appropriate legal representative, must be able to communicate effectively with investigator and site staff

3. At least one blood culture positive for *S. aureus* within 48 hours before randomization, referred to as the QBC
4. In addition to the QBC, subject must have at least one of the following signs or symptoms of bacteremia:
   - Temperature ≥ 38.0°C
   - White blood cell (WBC) count > 10,000 or < 4,000 cells/μL, or > 10% immature neutrophils (bands) regardless of total peripheral WBC count
   - Tachycardia (heart rate > 90 bpm)
   - Tachypnea (respiratory rate >20 breaths/min)
   - Hypotension (systolic blood pressure <90 mmHg)
   - Signs and symptoms of localized catheter-related infection (tenderness and/or pain, erythema, swelling, purulent exudate within 2 cm of entry site)
5. Subject must, at enrollment, have either 1) known right-sided infective endocarditis by Modified Duke's Criteria, 2) known CB, demonstrated as signs or symptoms of metastatic foci of *S. aureus* infection (eg, any infection remote from the primary focus caused by hematogenous seeding or extension of infection beyond the primary focus), or 3) known bacteremia with at least one of the following risk factors for CB [25-28]:
   - Any venous catheter considered to be the source of the infection, demonstrated by inflammation or purulent drainage from the catheter insertion site AND evidence of catheter-associated thrombosis upon removal

     NOTE: A peripheral venous catheter with just inflammation or purulent drainage from the catheter insertion site without evidence of thrombus is not consistent with CB.
   - A central venous catheter (CVC) considered to be the source of infection, demonstrated by inflammation or purulent drainage from the CVC insertion site or presence of thrombus on ultrasound
   - A long-term intravascular catheter (eg, tunneled cuffed intravascular catheter or subcutaneous port catheter) considered to be the source of infection, demonstrated by inflammation or purulent drainage from the catheter insertion site or presence of thrombus on ultrasound
   - New onset cardiac murmur consistent with tricuspid regurgitation

- Community onset bacteremia (eg, subject does not live in a healthcare facility)
- Pathogen known to be MRSA at enrollment
- Duration of symptoms ≥2 days at time of presentation (prior to start of antibiotic therapy)
- Skin exam findings suggesting acute systemic infection (ie, petechiae, vasculitis, infarcts, ecchymoses or pustules due to the infection)

6. Willing to receive intravenous antibiotics for the duration of treatment
7. Expected survival of at least 3 months
8. Female subjects must be non-pregnant and non-lactating. If a female subject is of childbearing potential, must have a documented negative pregnancy test at screening

   NOTE: All females are considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 2 years) or documented to be surgically sterile (bilateral tubal ligation or total hysterectomy). A subject may be admitted to the study on the basis of a negative urine pregnancy test (local laboratory), pending the result of the serum pregnancy test.

9. If sexually active, must agree to use a highly effective method of birth control with partners of childbearing potential during the study and for 1 month after study drug dosing

   NOTE: A highly effective method of birth control is defined as one that results in a low failure rate (ie, < 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intra-uterine devices (IUDs), sexual abstinence, or a vasectomized partner. Male subjects must agree to use medically acceptable birth control for at least one month following last dose of study medication. A vasectomy or a condom used with a spermicide is a medically acceptable birth control method for males.

10. Considered likely to comply with the study procedures and to return for scheduled evaluations.

Exclusion Criteria:

1. Treatment regimen greater than 60 hours with any potentially effective (anti-staphylococcal) systemic antibiotic(s) within 7 days before randomization

   NOTE: It is preferable to have no more than 48 hours of total prior antibiotic therapy within 7 days before randomization.

   EXCEPTION: Documented resistance to the prior systemic antibacterial therapy, confirmed by a microbiological laboratory report.

2. Requirement or anticipated requirement of non-study systemic antibiotics during the study
3. Presence of an infection source (eg, intravascular line, abscess, septic arthritis, infected prosthetic material, infected wound) that will not be managed or controlled

(eg, removal or replacement of the infected line, drainage of abscess, aspiration or drainage of septic arthritis, removal or replacement of infected prosthesis, or debridement of infected wound) within the first 3 days of study drug treatment

4. Presence of prosthetic cardiac valve or cardiac device (eg, implantable cardioverter defibrillator [ICD]), permanent pacemaker, or cardiac valve support ring)
5. Known or suspected LIE at enrollment, according to Modified Duke Criteria (Appendix 1)

   NOTE: Right-sided infective endocarditis (RIE) is permitted. If the subject is diagnosed with LIE after enrollment, subject will be allowed to remain on study.
6. At the time of enrollment, known or highly suspected osteomyelitis, meningitis, or metastatic septic foci involving the central nervous system (CNS)

   NOTE: Investigators should use clinical judgment to determine whether additional imaging studies (eg, X-ray, computed tomography scan, magnetic resonance imaging) are indicated at screening to rule out the presence of osteomyelitis, meningitis, or metastatic septic foci in the CNS.
7. Known at the time of enrollment to have MRSA bacteremia that is non-susceptible to daptomycin AND has a vancomycin MIC ≥2 µg/mL
8. Confirmed evidence (identification or Gram stain) of a mixed polymicrobial infection with a Gram-negative pathogen that requires non-study antibiotic treatment with agent(s) that have activity against Gram-negative pathogens
9. Previous participation in an anti-infective study during the past 12 months
10. A history of significant hypersensitivity, allergy or intolerance to telavancin

    NOTE: Caution should be taken in subjects with a history of severe hypersensitivity reaction to vancomycin. If the pathogen is known MRSA, allergy to both vancomycin and daptomycin may require exclusion. If the pathogen is known MSSA, allergy to both anti-staphylococcal penicillin (PCN)/cephalosporin and daptomycin may require exclusion. Investigator discretion is advised on a case-by-case basis.
11. Solid organ transplantation or bone marrow transplantation within 6 months before randomization
12. Severe neutropenia, defined as an absolute neutrophil count (ANC) <500 cells per microliter, or expected development of severe neutropenia during study
13. Known or suspected human immunodeficiency (HIV) infection with a CD4+ T-cell count <200/µL within the previous 6 months
14. Subjects requiring concomitant administration of anti-coagulation therapy (eg, intravenous heparin sodium) AND requiring specific coagulation testing known to have interference by telavancin (prothrombin time/international normalized ratio, activated partial thromboplastin time, or activated clotting time, or coagulation-based Factor X activity assay)

    NOTE: Although telavancin does not interfere with coagulation, it interferes with some assays used to monitor coagulation. The use of unfractionated heparin or a low molecular weight heparin AND testing using an Anti-Xa chromogenic testing assay

would be permissible.

15. Severe liver disease, ie, Child-Pugh Class C (Appendix 2), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 10 times the upper limit of normal (ULN)
16. Requirement for acute renal replacement therapy; or acute kidney injury (AKI) defined as an acute decrease in CrCl to < 30 mL/min and at least one of the following:
    - ≥2x increase in serum Cr or 50% decrease in glomerular filtration rate (GFR) within the 2 weeks prior to enrollment (RIFLE stage 2 injury (Appendix 3)
    - Oliguria defined as urine output <0.5 mL/kg per hour for ≥12 hours at any time during screening

    NOTE: Chronic renal insufficiency with a stable CrCl <30 mL/min, including chronic hemodialysis, is permitted.
17. Shock or hypotension (supine systolic blood pressure <80 mm Hg) unresponsive to fluids or pressors within 24 hours prior to randomization
18. QTc >460 ms (using either the Bazett or Fridericia formula), congenital long QT syndrome, uncompensated or new onset heart failure, aortic stenosis, aorticinsufficiency, or mitral insufficiency
19. Serum creatine kinase (CK) ≥2000 U/L
20. Breast-feeding or pregnant or intending to become pregnant (self or partner) at any time during the study
21. Any other condition that in the opinion of the investigator would jeopardize the safety or rights of a subject or would render the subject unable to comply with the protocol; or any other condition that in the opinion of the investigator may confound the data.

Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment:
For subjects with normal renal function: Telavancin, 7.5 mg/kg, IV in either 5% dextrose injection (D5W); sterile water for injection; or 0.9% sodium chloride; in 100 to 250 mL over 60 (+/- 10) minutes, once every 24 hours.

Subjects with renal impairment, either at baseline or which develops during the course of study treatment, should have the dosage of telavancin modified, based on estimated creatinine clearance, as follows:

Creatinine Clearance[a] (mL/min)	Telavancin Dosage Regimen	Maximum Daily Dose
>50	7.5 mg/kg every 24 hours	750 mg
30-50	5.6 mg/kg every 24 hours	560 mg
10 to <30	3.8 mg/kg every 24 hours	380 mg
Stable chronic hemodialysis[b]	3.8 mg/kg every 24 hours	380 mg

[a] For subjects receiving telavancin, the creatinine clearance for dosing should be calculated using the Cockcroft-Gault formula and ideal body weight (IBW). Use actual body weight if it is less than IBW.

[b] On days when subject receives hemodialysis, telavancin should be administered following completion of hemodialysis.

For subjects weighing more than 100 kg, the daily telavancin dose should not exceed 750 mg for those with normal renal function, 560 mg for those with moderate renal impairment, and 380 mg for subjects with severe renal impairment (creatinine clearance of 10 to <30 mL/min) or those undergoing chronic hemodialysis (see dosing table).

Reference Therapy, Dose, and Route of Administration; Regimen; Duration of Treatment: Open-label standard IV therapy, administered for 2 to 6 weeks, includes:

- Vancomycin (recommended dose of 15 mg/kg IV q12 hours); dose may be adjusted per local or regional product information/guidelines or local standard of care
- Daptomycin (recommended dose of 6 mg/kg IV q24 hours); dose may be adjusted per local or regional product information/guidelines or local standard of care
- Anti-staphylococcal penicillin (ie, nafcillin, oxacillin, or cloxacillin) recommended dose of 2 gm IV q4 hours or 12 gm IV continuous infusion over 24 hours; dose may be adjusted per local or regional product information/guidelines or local standard of care
- Cefazolin (recommended dose of 2 gm IV q8 hours); dose may be adjusted per local or regional product information/guidelines or local standard of care.

Study Evaluations

Safety Assessments:

Adverse events (AE) (including SAEs), clinical laboratory tests (including hematology, serum chemistry, urinalysis, and creatine kinase), vital signs, use of concomitant medications, and physical examination will be used to assess safety. Additional information regarding renal AEs (eg, laboratory and radiographic results at the time of potential renal injury) will be obtained and recorded in the renal AE eCRF.

Efficacy Assessments:

Efficacy assessments include evaluation of signs and symptoms consistent with *S. aureus* infection such as blood cultures, physical examination, and echocardiography (TEE, or TTE if TEE is not possible); and may also include, but are not limited to, chest X-ray, additional specimen cultures, ultrasonography, bone scan, CT, MRI, and PET scan.

Pharmacokinetic Assessments:

Pharmacokinetic samples will be collected while in the hospital setting and, as feasible, in the outpatient setting, from randomized subjects who receive telavancin or vancomycin as follows:

For all subjects receiving telavancin:

- On Day 1: At 1 hour (+15 min window) after the start of the infusion, between 4 to 8 hours after the start of the infusion. On Day 2 prior to the start of the infusion (within 30 minutes before dosing). On Days 3 and 5, predose (within 30 minutes before dosing). On Day 7, predose (within 30 minutes before dosing), and between

4 to 8 hours after the start of the infusion. On Day 14, predose (within 30 minutes before dosing).

- As feasible, following each change in telavancin dosing during the first 2 weeks of therapy due to a change in renal function classification: Predose (within 30 minutes before dosing), between 1 to 4 hours after the start of the infusion (sample must be collected following completion of the infusion), and on the next day prior to the start of the next infusion (within 30 minutes before dosing).

NOTE: These blood samples are in addition to scheduled samples. In the case where the additional sample coincides with a planned time point, then only one sample is to be drawn at that time.

For all subjects receiving vancomycin:

- On Day 1: At 1 hour (+15 min window) after the beginning of the infusion. On Day 3, predose (within 30 minutes before dosing). On Day 5, predose (within 30 minutes before dosing), and at 1, 5, 8, and 12 hours after the beginning of the infusion (+15 minute window). On Day 14, predose (within 30 minutes before dosing).

For subjects receiving vancomycin, trough levels as determined by the hospital for use in determining the dosing amount will be recorded.

Study Endpoints:

The primary efficacy endpoint is clinical outcome at TOC analyzed in subjects with a baseline diagnosis of UCB, CB or RIE in the mAT population.

The key secondary efficacy endpoints are as follows:

- Clinical outcome at TOC by baseline diagnosis in the mAT and microbiological evaluable (ME) populations
- Clinical response at EOT in the mAT and ME populations
- Development of new metastatic foci of *S. aureus* infection after Day 8 in the mAT and ME populations
- Duration of treatment with study medication by baseline clinical diagnosis in the mAT and ME populations
- For subjects with a positive *S. aureus* blood culture on Day 1, time to all blood cultures negative for *S. aureus* for two days in succession (ie, clearance of bacteremia) (does not have to be consecutive calendar days) in the mAT and ME populations; date will be first of the two days in succession
- 28-day all-cause mortality for subjects with a baseline diagnosis of CB or RIE in the mAT and ME populations
- Incidence of AEs, treatment-emergent AEs, SAEs, and deaths in the safety population
- Incidence of key laboratory indices in the safety population, to be further described in the Statistical Analysis Plan (SAP).

The efficacy endpoint of clinical outcome at TOC will be determined by the investigator and adjudicated by the blinded IEAC. Specific evaluability criteria (outlined in the SAP) will be applied to determine subject eligibility for each population.

Exploratory analyses will be conducted to assess a variety of health utilization variables. Methods of analysis for these variables will be outlined in a separate health economics outcomes statistical analysis plan (HEOR SAP). The results of these analyses will be presented separately and not included in the clinical study report (CSR).

Statistical Methods

Analysis Populations:

The All-Treated (AT) population is defined as all randomized subjects who have received at least one dose of study drug and were enrolled after protocol Amendment 1. Subjects enrolled prior to Protocol Amendment 1 will be excluded from all efficacy analyses, because the dose of telavancin was decreased following Protocol Amendment 1. Analyses conducted based on the AT population will assign subjects according to their randomized treatments.

The mAT population includes subjects in the AT population who have a mono-microbial QBC positive for *S. aureus*.

The ME population is a subset of the mAT population and includes subjects who meet the following criteria:

1. Completed at least 80% of prescribed study medication for their baseline diagnosis
2. Did not miss more than 2 consecutive doses of study medication
3. Completed the TOC visit
4. Did not have any recorded major protocol deviations
5. If assessed as failure at TOC, received at least 2 days of study medication
6. If assessed as cure at TOC, received at least 5 days of study medication
7. Did not receive any prohibited concomitant, potentially effective antibiotic (other than study medication).

The safety population will be defined as all subjects from the AT population and subject assignment according to actual study treatments they receive.

The PK population will be defined as all subjects from the safety population who provide evaluable PK data from at least one postdose sample in plasma.

Analysis:

The primary analysis will test both clinical noninferiority and superiority of telavancin relative to standard IV therapy in the treatment of *S. aureus* bacteremia including SA-RIE. Both tests will be conducted at a one-sided 2.5% significance level. No adjustment of the

Type I error rate is necessary for conducting these two tests sequentially as the process is supported by the closed-testing principle.

Secondary efficacy endpoints will be tested in a hierarchical fashion at the two-sided 5% level of significance until a failure to reject occurs. For all supportive analyses, p-values and confidence intervals will be evaluated at the two-sided 5% level with no adjustment for multiplicity.

The analysis of the primary endpoint will be conducted based on the mAT population with a diagnosis of UCB, CB, or RIE, and the point estimate and confidence interval (CI) for the treatment difference in clinical cure rates will be calculated using the normal approximation to the binomial distribution without continuity correction.

Analysis of other endpoints focusing on incidence of occurrence (eg, development of new metastatic foci of infection) will be similar to the primary analysis of clinical outcome previously described.

Time-to-event endpoints will be reported graphically using Kaplan-Meier survival curves and, as appropriate, treatment differences will be evaluated using log-rank tests, stratified by geographic region.

Safety endpoints will be evaluated for the safety population. Unless specified otherwise, safety assessments will be summarized descriptively by treatment group.

For subjects who receive telavancin or vancomycin and have at least one post-dose PK sample collected, plasma concentration profiles will be estimated. Estimated PK parameters may include:

Time of maximum concentration (T_{max})

Maximum observed plasma concentration (C_{max})

Area under the plasma concentration versus time curve from time 0 to the last sample with measurable analyte concentration (AUC_{0-t})

Area under the concentration versus time curve extrapolated to infinity ($AUC_{0\text{-}inf}$)

Terminal elimination half-life ($t_{1/2}$)

Plasma clearance (CL_p)

Volume of distribution at steady-state (Vd_{ss})

Noncompartmental and nonlinear mixed-effects modeling methods will be used for determination of PK parameters, as appropriate.

All PK parameters will be presented as individual listings and as summary statistics (mean, geometric mean, median, range, standard deviation, coefficient of variation, minimum, maximum, and number of subjects).

Sample Size:

Assuming a population clinical cure rate of 70% for standard IV therapy and 72.5% for telavancin, a total sample size of 210 (105 per treatment group) is deemed sufficient (80% power) to demonstrate noninferiority based on a noninferiority margin of 15% at a one-sided significance level of 2.5%. This calculation does not take into account potential stopping for futility at an interim analysis. A total of 248 subjects will be enrolled to allow for exclusion of up to 15% of subjects from the primary analysis set due to an LIE diagnosis or not meeting the mAT population criteria.

Interim Analysis: A single interim assessment allowing early stopping for futility will be performed based on the subjects who completed or discontinued from the study on or before October 31, 2017.

Conditional power to show non-inferiority under the current trend will be computed using the normal approximation to the non-inferiority test statistic. The IDMC may recommend stopping for futility, if the conditional power is 50% or less.

SCHEDULE OF STUDY PROCEDURES

Table 1: Schedule of Study Procedures

Procedure	Screening/ Enrollment[a]	Treatment Period					Post-Treatment Period		
		Daily (Day 1 up to EOT)	Additional Daily (Day 1 up to Day 8)	Weekly (± 3 days)	Other[b]	EOT/ Termination/ Early Withdrawal Visit[c]	Post-EOT Blood Culture	Weekly (± 3 days)	TOC Visit[d] (EOS)
Informed Consent[e]	X								
Review of Inclusion/Exclusion Criteria	X								
Medication and Medical History	X								
Body Temperature[f]	X	X				X		X	X
Physical Examination, including Vital Signs	X					X			X
Evaluate Signs/Symptoms of *S. aureus* Infection, including Metastatic Foci of Infection	X		X[g]	X[g]		X[g]		X[g]	X
Chest X-Ray or CT Scan (chest)[h]	X								
Blood Culture[i]	X[j]	X[k]					X[l]		
Urine Culture[bb]	X[aa]								
Infection Site Specimen Culture[m]	X								
Hematology, Serum Chemistry, Creatine Kinase	X			X[z]		X			
Urinalysis with Microscopy[bb]	X					X			
Additional Serum Creatinine, Creatinine Clearance[n]			X[o]		X[o]				

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

Procedure	Screening/ Enrollment[a]	Treatment Period					Post-Treatment Period		
		Daily (Day 1 up to EOT)	Additional Daily (Day 1 up to Day 8)	Weekly (± 3 days)	Other[b]	EOT/ Termination/ Early Withdrawal Visit[c]	Post-EOT Blood Culture	Weekly (± 3 days)	TOC Visit[d] (EOS)
Pregnancy Test[p]	X				X				X
Electrocardiogram (12-lead)[q]	X				X	X			
Randomization	X								
Study Drug Dosing[r]		X							
Infection Source Control[s]					X				
Classification of Infection Type[t]					X				
Echocardiography[u]					X				
Central Venous Ultrasonography[v]					X				
Recording of significant procedures (eg, surgical, radiographic)	X		X	X		X		X	X
Pharmacokinetic Blood Collection[w] *telavancin and vancomycin subjects only*					X				
Serum CRP	X			X	X	X			
Serum IL-10	X					X			
Obtain Urine for Renal Biomarker Quantification[bb]	X					X			
APACHE II Assessment[x]	X								
Concomitant Medications		X				X		X	X

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Table 1: Schedule of Study Procedures

Procedure	Screening/ Enrollment[a]	Treatment Period					Post-Treatment Period		
		Daily (Day 1 up to EOT)	Additional Daily (Day 1 up to Day 8)	Weekly (± 3 days)	Other[b]	EOT/ Termination/ Early Withdrawal Visit[c]	Post-EOT Blood Culture	Weekly (± 3 days)	TOC Visit[d] (EOS)
Assessment of Adverse Events[y]	X	X				X		X	X
Clinical Outcome Assessment						X			X

a Pretreatment (screening) evaluations will be performed within 48 hours before randomization unless otherwise specified. If the screening assessments and results are obtained within this 48-hour period, they will be considered valid screening evaluations and do not need to be repeated following ICF signature. Local laboratory test results will be used to determine a subject's eligibility for enrollment.

b Procedures to be completed at time points other than daily or weekly.

c End of therapy (EOT) visit occurs within 3 days after the last dose of study drug.

d Test of cure (TOC) visit: For subjects with uncomplicated bacteremia and assigned to receive 2 to 4 weeks (14-28 days) of treatment, their TOC is 38 (+/- 2) days after randomization regardless of the total duration of study drug therapy. For subjects with complicated bacteremia and assigned to receive 4 to 6 weeks of treatment (28 to 42 days), their TOC is 52 (+/- 2) days after randomization regardless of the total duration of study drug therapy. For subjects with endocarditis assigned to receive 6 weeks (42 +/-3 days) of treatment, their TOC is 52 (+/- 2) days after randomization regardless of the total duration of study drug therapy. The TOC visit is also the end of study (EOS).

e In the event that a subject is unable to give consent, when legally permitted, the subject's legally acceptable representative must do so.

f Obtain and record highest daily temperature and method of measurement on electronic case report form (eCRF). Use same method for consistency.

g Evaluate for metastatic *S. aureus* infection daily, up to Day 8. Prior to or on Day 8 a signs and symptoms worksheet will be completed to determine the infection type including metastatic disease (UCB, CB, RIE, LIE) and sent to the medical monitor to review. Subsequently, weekly worksheets noting signs and symptoms of potential metastatic *S. aureus* infection will be reviewed and completed by the physician investigator and forwarded to the medical monitor to optimize diagnosis and treatment of both the primary infection source and new metastatic foci of *S. aureus*. Additional procedures may include a physical exam, chest X-ray, ultrasonography, bone scan, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scan, and may be done at any time during the study, when clinically indicated, to evaluate extent of infection.

h Obtain chest x-ray or CT of chest within 3 days after the report of the QBC. If a chest x-ray or CT of chest is obtained during the screening period (within 48 hours prior to randomization), a repeat chest x-ray or CT does not need to be done.

i The investigator may initiate study treatment based on a single blood culture positive for *S. aureus* on Day -2 or -1. Perform culture and organism identification at the local or regional laboratory, as applicable. All *S. aureus* isolates should be sent to the central laboratory for organism identification and susceptibility testing. Record identification of all non-*S. aureus* isolates in the electronic case report form (eCRF).

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

j At baseline, a blood culture is to be obtained from a fresh venipuncture site. To be eligible for randomization, this blood culture must be positive for *S. aureus,* within 48 hours of randomization and is referred to as the QBC. All *S. aureus* isolates should be sent to the central laboratory for organism identification and susceptibility testing.

k Blood cultures will be obtained daily by fresh venipuncture during the treatment period until two successive blood cultures are negative for *S. aureus* (need not be consecutive calendar days) post-randomization. Blood cultures should be obtained at any time during the study when clinically indicated, eg, bacteremia is suspected. All *S. aureus* isolates should be sent to the central laboratory for organism identification and susceptibility testing.

l Follow-up blood cultures must be obtained at least 4 days after the EOT visit and results must be available prior to the TOC visit. These blood cultures consist of 2 samples (8-10 mL) from separate sites inoculated into 2 standard aerobic blood culture bottles. For subjects who are no longer hospitalized, this visit may be coordinated to occur when the subject returns for his/her weekly visit. For subjects not completing study treatment, two blood cultures from separate fresh venipuncture sites will be obtained at the early termination visit. All *S. aureus* isolates should be sent to the central laboratory for organism identification and susceptibility testing.

m Obtain specimen for culture when a primary source of bacteremia is identified. If there is no clinical evidence of the primary source of bacteremia, no culture is required. Any central or peripheral catheters present at the time of the bacteremia will be removed. Removed catheters can be replaced, but in the case of central catheters they cannot be replaced using wire-guided methods, or placed in the same site if there is clinical evidence of infection at the entry site.

n Creatinine clearance will be calculated by the central and local laboratories using the Cockcroft Gault Formula and actual body weight. For subjects on telavancin only, if dose adjustment is necessary due to renal impairment, per Table 3 in Section 5.2.1, the pharmacist will calculate creatinine clearance using the Cockcroft-Gault formula and ideal body weight (IBW). Use actual body weight if it is less than IBW.

o Obtain serum creatinine and creatinine clearance daily (sample will be sent to both the local and central lab), up to Day 8, while the subject is hospitalized. After Day 8, or if subject is discharged from the hospital to outpatient parenteral antibiotic therapy (OPAT) or home health care (HHC), serum creatinine and creatinine clearance will be obtained every 2 to 3 days (samples to be sent to central laboratory) while on study drug. On the days where the weekly safety lab coincides with the creatinine monitoring, serum creatinine and creatinine clearance will be tested using the weekly safety lab kit.

p Subjects may be enrolled into the study on the basis of a negative urine pregnancy test (local laboratory), pending the result of the serum pregnancy test. If the result of the serum test is subsequently positive, study drug must be discontinued, EOT evaluations performed, and an EOS visit scheduled. A urine pregnancy test (local laboratory) will be performed once per month (ie, in subjects treated for 6 weeks) as per local regulatory requirements.

q One 12-lead electrocardiogram (ECG) will be obtained at the prestudy treatment evaluation. If the QTc is >460 ms (using either the Bazett or Fridericia formula) at the screening ECG, the subject will not be entered into the study. Additional ECGs will be obtained at Week 3, 6, or at the Early Termination visit. Subject should be withdrawn from treatment if the QTc time is >500 ms or if the QTc time is ≥60 ms above baseline. Any other relevant ECG abnormalities noted at Week 3, 6, or unscheduled ECGs, should be classified as an AE and additional ECGs will be required weekly until the subject discontinues from the study. If feasible, every effort should be made to obtain duplicates of all ECGs. All original ECGs obtained for each time point (not photocopied) will be held with the study files for analysis in the event that a central reader is required.

r Daily dosing of study drug will be administered according to the infection classification. For uncomplicated bacteremia, subjects will receive a minimum of 2 weeks and maximum of 4 weeks (14 to 28 days) of therapy. For complicated bacteremia, subjects will receive a minimum of 4 weeks and a maximum of 6 weeks (28 to 42 days) of therapy. For endocarditis, subjects will receive 6 weeks (42 +/- 3 days) of therapy.

s Procedures to control or eliminate the infection source, eg, by removal of intravascular lines or drainage and debridement of the primary infection site, will be completed within the first 3 days of study drug treatment. All microbiological specimens must be cultured.

t Prior to or on Day 8 a signs and symptoms worksheet will be completed to determine the infection type including metastatic disease (UCB, CB, RIE, LIE) and sent to the medical monitor to review.

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

u Echocardiography (either TTE or TEE; TEE is strongly preferred) will be performed on or before Day 8. All echocardiograms will undergo blinded review by an independent echocardiography core laboratory.

v On or before Day 8, subjects with a central venous catheter (CVC) as the presumed source of the infection, should also undergo central venous ultrasound to evaluate for venous thrombosis associated with the central line.

w Pharmacokinetic (PK) samples will only be obtained from subjects on telavancin or vancomycin while in the hospital setting and as feasible in the outpatient setting.

For subjects receiving telavancin: Blood samples will be obtained for PK on Day 1: At 1 hour (+15 minute window), between 4 to 8 hours after the beginning of the infusion. On Day 2 prior to beginning the next infusion (within 30 minutes before dosing). On Days 3 and 5, predose (within 30 minutes before dosing). On Day 7, predose (within 30 minutes before dosing), and between 4 to 8 hours after the beginning of the infusion. On Day 14, predose (within 30 minutes before dosing). As feasible, following each change in telavancin dosing during the first 2 weeks of therapy due to a change in renal function classification: Predose (within 30 minutes before dosing), between 1 to 4 hours after the beginning of the infusion (sample must be collected following completion of the infusion), and 24 hours after the beginning of the infusion and prior to beginning the next infusion (within 30 minutes before dosing). These blood samples are in addition to scheduled samples. In the case where the additional sample coincides with a planned time point, then only one sample is to be drawn at that time.

For subjects receiving vancomycin: Blood samples will be obtained for PK on Day 1: at 1 hour after the beginning of the infusion (+15 minute window). On Day 3, predose (within 30 minutes before dosing). On Day 5, predose (within 30 minutes before dosing), and at 1, 5, 8, and 12 hours after the beginning of the infusion (+15 minute window). On Day 14, predose (within 30 minutes before dosing).

x The Acute Physiologic and Chronic Health Evaluation (APACHE) scoring system requires the input of many clinical variables, from which a severity score is derived. The resulting severity score is entered into a logistical regression equation, which predicts hospital mortality. Obtain within 24 hours prior to randomization.

y Additional information regarding renal AEs (eg, laboratory and radiographic results at the time of potential renal injury) will be obtained and recorded in the renal AE eCRF.

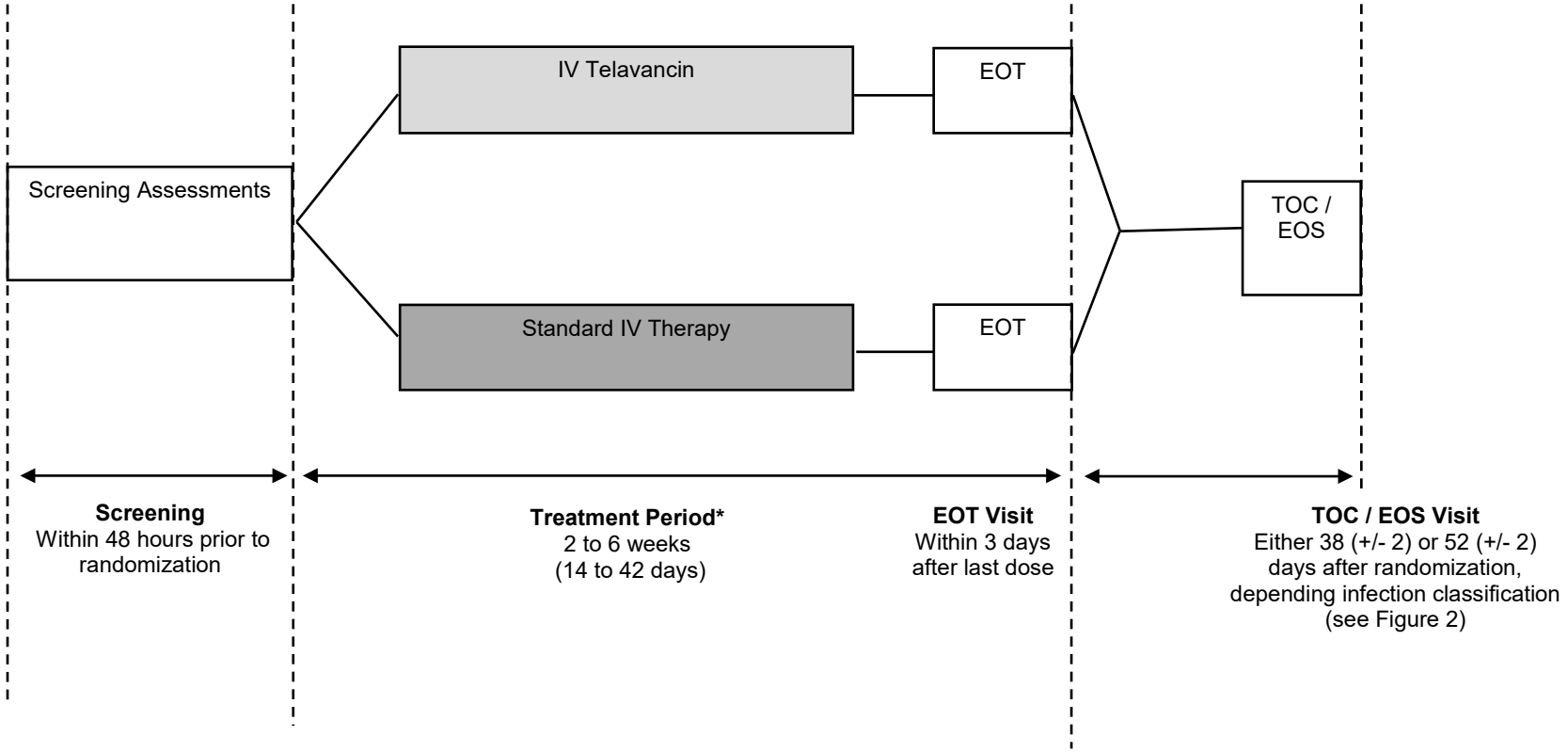
z Safety labs (hematology, serum chemistry, and creatine kinase) obtained at the completion of the first week should be obtained on Day 7 (+/- 1 day). Subsequent weekly safety labs should be obtained weekly (+/- 3 days).

aa Send only *S. aureus* isolates from the screening urine culture to the central laboratory.

bb Subjects on hemodialysis may have the urine assessments waived due to anuria.

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Figure 1: Study Diagram



* Minimum treatment period for: uncomplicated bacteremia is 2 weeks (14 days), 4 weeks (28 days) for complicated bacteremia and 6 weeks (42 +/-3days) for endocarditis

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Figure 2: Dosing Duration by Infection Classification

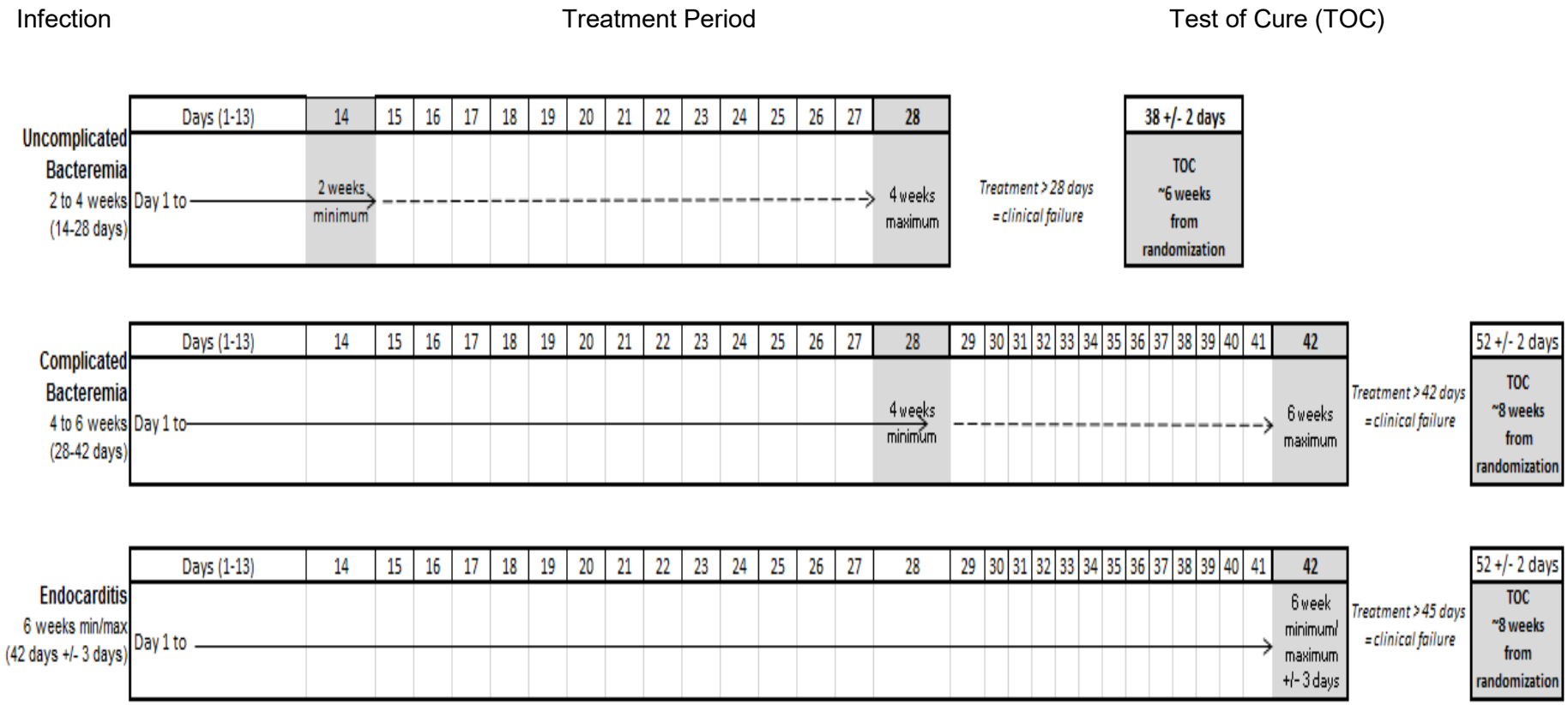


Figure 3: PK Collection Timepoints for Telavancin

Day	Telavancin PK collection
Day 1	1 hour (+15 min window) ***after*** *start of infusion*
	Between 4 to 8 hours ***after*** *start of infusion*
Day 2	Prior to start of the infusion (within 30 minutes ***before*** *dosing*)
Day 3	Predose (within 30 minutes ***before*** *dosing)*
Day 5	Predose (within 30 minutes ***before*** *dosing*)
Day 7	Predose (within 30 minutes ***before*** *dosing*)
	Between 4 to 8 hours ***after*** *start of infusion*
Day 14	Predose (within 30 minutes ***before*** *dosing)*
PK Collection for Every Telavancin Dose Change Due to Renal Function Classification (within first 2 weeks only, as feasible)	
Predose (within 30 minutes before dosing)	
Between 1 to 4 hours after start of infusion (sample must be collected following completion of the infusion)	
Prior to start of the next infusion (within 30 minutes ***before*** *dosing*)	

Figure 4: PK Collection Timepoints for Vancomycin

Day	Vancomycin* PK collection
Day 1	1 hour (+15 min window) ***after*** *start of infusion*
Day 3	Predose (within 30 minutes ***before*** *dosing)*
Day 5	Predose (within 30 minutes ***before*** *dosing*)
	1 hour (+15 min) after start of infusion
	5 hour (+15 min) after start of infusion
	8 hour (+15 min) after start of infusion
	12 hour (+15 min) after start of infusion
Day 14	Predose (within 30 minutes ***before*** *dosing)*

* Trough levels of vancomycin are determined by the hospital laboratory for use in adjusting vancomycin dosing will be recorded.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
APACHE	Acute Physiologic and Chronic Health Evaluation
aPTT	activated partial thromboplastin time
AT	All-Treated
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under the concentration versus time curve extrapolated to infinity
$AUC_{0\text{-}t}$	area under the plasma concentration versus time curve from time 0 to the last sample with measurable analyte concentration
BMI	body mass Index
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CB	complicated bacteremia
CE	clinically evaluable (analysis population)
CFR	(United States) Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL_p	plasma clearance
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CrCl	creatinine clearance
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
cSSSI	complicated skin and skin structure infection
CT	computed tomography
CVC	central venous catheter
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of therapy
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
HABP	hospital-acquired bacterial pneumonia
HEOR SAP	Health economics statistical analysis plan
HHC	home health care
HIV	human immunodeficiency virus
HR	heart rate
IB	investigator's brochure
IBW	ideal body weight
IL-10	interleukin-10
ICD	implantable cardioverter defibrillator
ICF	informed consent form
ICH	International Conference on Harmonization
IDMC	Independent data monitoring committee
IE	infective endocarditis
IEAC	independent efficacy adjudication committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intra-uterine device
IV	Intravenous
IXRS	interactive response system
LAR	legally authorized representative
LDH	lactate dehydrogenase
LIE	left-sided infective endocarditis
mAT	Microbiological all-treated (analysis population)
ME	Microbiological evaluable (analysis population)
MedDRA®	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-sensitive *Staphylococcus aureus*
NP	nosocomial pneumonia
OPAT	outpatient parenteral antibiotic therapy (facility)
PCN	Penicillin
PET	positron emission tomography
PI	principal investigator
PK	Pharmacokinetics
PT	prothrombin time
QBC	qualifying blood culture
QTc	corrected QT interval
REB	Research Ethics Board

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
RIE	right-sided infective endocarditis
RIFLE	Risk, Injury, and Failure; and Loss; and End-stage kidney disease
RR	respiratory rate
SAE	serious adverse event(s)
SA-RIE	right-sided infective endocarditis caused by *Staphylococcus aureus*
SAP	statistical analysis plan
SOP	standard operating procedure
S. aureus	*Staphylococcus aureus*
$t_{1/2}$	terminal elimination half-life
TEAE	treatment emergent adverse event(s)
TEE	transesophageal echocardiogram
T_{max}	time of maximum concentration
TOC	test of cure
TTE	transthoracic echocardiogram
UCB	uncomplicated bacteremia
ULN	upper limit of normal range
VABP	ventilator associated bacterial pneumonia
Vd_{ss}	volume of distribution at steady-state
VISA	vancomycin-intermediate *S. aureus*
WBC	white blood cell

1 INTRODUCTION

1.1 Background and Rationale

Bacteremia due to *S. aureus* is a frequently encountered serious infection that is often associated with infective endocarditis [1-3]. Treatment of bacteremia is challenging; infection metastasis and relapse are common, as is the involvement of antibiotic-resistant bacterial strains, including methicillin-resistant *S. aureus* (MRSA) [4]. In the treatment guidelines for MRSA bacteremia from the Infectious Diseases Society of America, only two agents are recommended: vancomycin, the traditional first-line therapy for MRSA infections, and daptomycin [5]. Both of these agents have recognized shortcomings. Vancomycin has limited tissue penetration, is slowly bactericidal [6], is suboptimal against methicillin-susceptible *S. aureus* (MSSA) [7, 8], and evidence suggests decreasing susceptibility among Gram-positive pathogens [7, 9, 10]. Resistance to daptomycin has more recently emerged, together with evidence suggesting that reduced susceptibility to vancomycin may also impact susceptibility to daptomycin [11, 12]. As such, there is a critical need for additional agents appropriate for the treatment of *S. aureus* bacteremia.

Telavancin is a rapidly bactericidal lipoglycopeptide antibiotic that is active against a range of clinically relevant Gram-positive pathogens, including MRSA. Telavancin exhibits concentration-dependent bactericidal effects via a dual mechanism of action (inhibition of bacterial cell wall synthesis and disruption of bacterial cell membrane barrier function), which may help to minimize the potential for the selection of resistance. In global surveillance studies, telavancin has demonstrated consistent in vitro microbiologic activity within the telavancin susceptible ranges against Gram-positive isolates, including MRSA, regardless of susceptibility to other agents or geographic region. Telavancin minimum inhibitory concentration (MIC) MIC_{50}/MIC_{90} values consistently show activity against *S. aureus* comparable or superior to other agents.

In vitro pharmacokinetic (PK)/pharmacodynamic models of simulated endocardial vegetations have demonstrated superior telavancin bactericidal activity against *S. aureus* strains compared with daptomycin and vancomycin. In vitro biofilm studies have demonstrated the potential efficacy of telavancin in the treatment of staphylococcal biofilm-associated infections [13]. Furthermore, studies using animal models of infection also have supported the potential for telavancin in the effective treatment of *S. aureus*

bacteremia and infective endocarditis. In murine models of bacteremia and rabbit models of infective endocarditis, telavancin has demonstrated greater efficacy than vancomycin [14].

The efficacy and safety of telavancin have been demonstrated in Phase 3 clinical trials for the treatment of subjects with complicated skin and skin structure infections (cSSSI) due to Gram-positive pathogens (ATLAS studies) and subjects with hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP) due to Gram-positive pathogens (ATTAIN studies). Telavancin, 10 mg/kg administered intravenously (IV) over 60 minutes, once every 24 hours for 7 to 14 days is the currently approved dosage for the treatment of adult patients with cSSSI caused by susceptible Gram-positive bacteria. The same telavancin dose, for a duration of 7 to 21 days, is the currently approved dosage for the treatment of adult patients with HABP/VABP caused by susceptible isolates of *S. aureus*, when alternative treatments are not suitable.

Limited data are available from post hoc analyses of subjects with concurrent bacteremia from these Phase 3 cSSSI and HABP/VABP studies. Of the 1784 subjects in the ATe population in the 2 cSSSI trials, 32 subjects had baseline *S. aureus* bacteremia: 21 (2.4%, including 13 with MRSA) subjects were treated with telavancin and 11 (1.2%, including 4 with MRSA) subjects were treated with vancomycin. In these bacteremic subjects, the clinical cure rate at test of cure (TOC) was 57.1% (12/21) for the telavancin-treated subjects and 54.6% (6/11) for the vancomycin-treated subjects. In subjects with Gram-positive bacteremic HABP/VABP in the ATTAIN studies, the clinical cure rates for telavancin and vancomycin were 46% (11/24) versus 37% (10/27), respectively. Moreover, only one telavancin-treated subject (1/34) compared with six vancomycin-treated subjects (6/39) had bacteremia that persisted beyond baseline cultures.

In a Phase 2 proof-of-concept study, comparing telavancin with standard therapy (vancomycin or anti-staphylococcal penicillin) for treatment of subjects with uncomplicated *S. aureus* bacteremia (the ASSURE study), compared with standard therapy, similar proportions of the clinically evaluable (CE) population (n = 17) were cured at a long-term follow-up visit (Day 84; 88% vs. 89%, respectively). However, the number of clinically evaluable subjects limits the strength of a conclusion regarding the comparative safety and efficacy of telavancin and standard therapy in this population.

In a retrospective case series, telavancin provided a favorable cure rate and rapid clearance of bacteremia in difficult-to-treat subjects with refractory MRSA bacteremia with or without infective endocarditis [15]. Additional case reports of subjects with vancomycin-intermediate *S. aureus* (VISA) or MRSA endocarditis have demonstrated successful treatment with telavancin [16, 17].

To explore means by which the telavancin risk-benefit profile could be improved the Sponsor recently performed additional integrated retrospective analyses of PK and outcomes data from the telavancin Phase 3 studies for cSSSI and HABP/VABP. Based on the results of the integrated retrospective data analyses, the Sponsor believes that a reduction in the telavancin dose could optimize the risk-benefit profile of telavancin for the treatment of bacteremia. In separate independent CART and logistic regression analyses of data from the Phase 3 studies, a telavancin exposure-response relationship with acute kidney injury was confirmed.

In the telavancin program a dose of 7.5 mg/kg was used in a limited number of patients with complicated skin and skin structure infections. (n=192). There were 4 studies that initially treated subjects with telavancin at a dose of 7.5 mg/kg IV once daily, including two phase 2 studies (Studies 202a, 202b) and two phase 3 studies, (0017 and 0018). In these four studies, the dose was subsequently amended. In the phase 2 studies the comparator consisted of either vancomycin or anti-staphylococcal penicillin. In the phase 3 studies, the comparator was vancomycin. Given the post-hoc nature of the comparisons between telavancin dose groups pre-and post-amendment and the paucity of data for patients dosed at 7.5 mg/kg, descriptive analyses were undertaken. In the pooled data from the 4 mentioned studies, no noticeable differences in the frequency of adverse events (AEs) between telavancin 7.5 mg/kg and 10 mg/kg were observed. However, the difference in sample size between the two telavancin doses (7.5 mg/kg, n=192 and 10 mg/kg, n=1029) compromises the ability to derive a definitive conclusion about AE rates, especially for events where the incidence was low.

The analyses support the conclusions that a dose reduction from 10 mg/kg to 7.5 mg/kg once daily would decrease the risk of nephrotoxicity and improve overall safety while having little to no impact on efficacy. Mortality was also examined in these analyses and despite small numbers and confounding factors, there was an exposure-response relationship in a subset of HABP/VABP subjects with creatinine clearance (CrCl) ≤50 mL/min. This risk may

also be decreased with the proposed dose reduction. Therefore, the Sponsor proposes to reduce the exposure of telavancin by incorporating the following three changes in the dose and dosing regimen: 1) decreasing the dose by 25% in all subjects; 2) decreasing the dose by 62% to 3.8 mg/kg from 10 mg/kg and altering the dosing schedule for severe renal impairment (creatinine clearance of 10 to <30 mL/min) to once daily rather than every 48 hours; and 3) recommending the dose not exceed 750 mg (or 560 and 380 mg in moderate or severe renal impairment) for subjects weighing greater than 100 kg. In addition, for subjects undergoing chronic hemodialysis, telavancin should be administered IV at a dose of 3.8 mg/kg (maximum dose of 380 mg) once daily by infusion over 60 minutes (following hemodialysis on hemodialysis days).

This study will be conducted in a population of subjects who are seriously ill with *S. aureus* bacteremia. Extra precautions have been built into the protocol to protect subject safety; however, by utilizing the proposed alterations in telavancin dose, the Sponsor believes that safety risks could potentially be reduced without loss of efficacy. This study will allow evaluation of the revised telavancin dose in a prospective, controlled fashion, and in an appropriate population of subjects.

Regarding the rationale for standard IV therapy as the comparator in this trial, in adult patients with MRSA bacteremia or infective native valve endocarditis, current recommendations include treatment with vancomycin or daptomycin. Vancomycin is recommended for empiric therapy for *S. aureus* bacteremia in healthcare settings with an elevated prevalence of MRSA. Guidelines recommend that vancomycin be administered at doses providing trough concentrations of 15 to 20 µg/mL, increasing the probability of optimal target serum concentrations and improving clinical outcomes of complicated infections. For institutions in which the preponderance of MRSA isolates have vancomycin MIC values >2 µg/mL, alternative agents, such as daptomycin, should be used [18]. Daptomycin is currently approved in the US at a dosage of 6mg/kg for the treatment of *S. aureus* bacteremia, including those with right-sided infective endocarditis, however, some experts recommend higher doses of up to 8 to 10 mg/kg [19-23]. For patients with methicillin-susceptible *S. aureus*, a β-lactam antibiotic with anti-staphylococcal activity (eg, nafcillin, oxacillin, cefazolin) is the recommended treatment.

Guidelines recommend treatment durations of at least 2 weeks for uncomplicated bacteremia (UCB), 4 to 6 weeks for complicated bacteremia (CB), and 6 weeks for infective

native valve endocarditis [18]. Although enriched for CB, it is anticipated that few patients enrolled may be deemed to suffer from UCB. As the final diagnosis for CB may take up to 8 days all efforts should be implemented to minimize the enrollment of patients with UCB. This includes monitoring strict adherence to the inclusion and exclusion criteria and discussion with the principal investigators to reinforce the intent of the protocol population.

To summarize, the use of telavancin for this study is supported by data from the post hoc analyses of subjects with bacteremia included in the Phase 3 studies of cSSSI and HABP/VABP, a Phase 2 proof-of-concept study of telavancin in subjects with uncomplicated *S. aureus* bacteremia, retrospective case series of subjects with refractory MRSA bacteremia, and case reports of subjects with VISA or MRSA endocarditis [15-17]. The available data describing telavancin for the treatment of bacteremia are limited, but are supportive of additional evaluation in larger, prospective studies including subjects with bacteremia due to *S. aureus* (specifically MRSA). Further prospective clinical studies are needed to assess the efficacy and safety of telavancin therapy in larger numbers of subjects with bacteremia and infective endocarditis.

1.2 Nonclinical Profile

A review of the nonclinical profile of telavancin can be found in the current version of the Investigator's Brochure (IB).

1.3 Clinical Experience

A description of the clinical experience with telavancin is provided in the current version of the IB and the Prescribing Information for VIBATIV® (telavancin).

The most common AEs occurring in ≥10% of telavancin-treated patients in Phase 3 studies of cSSSI were taste disturbance, nausea, vomiting, and foamy urine. Serious adverse events (SAE) were reported in 7% of patients treated with telavancin and most commonly included renal, respiratory, or cardiac events. Treatment discontinuations due to AE occurred in 8% of patients treated with telavancin, the most common events being nausea and rash. The incidence of AE indicative of renal impairment (increased serum creatinine, renal insufficiency, and renal failure) was 3% of telavancin-treated patients, and SAEs indicative of renal impairment occurred in 1% of telavancin-treated patients.

In Phase 3 studies of HABP/VABP, SAE were reported in 31% of patients treated with telavancin. Treatment discontinuations due to AE occurred in 8% of patients who received telavancin, with the most common events being acute renal failure and corrected QT interval (QTc) prolongation. Treatment-emergent AE that were reported in 5% or more of telavancin-treated patients included nausea, vomiting, and acute renal failure. The incidence of AE indicative of renal impairment (acute renal failure and increased serum creatinine) was 10% of telavancin-treated patients, and SAE indicative of renal impairment occurred in 2% of telavancin-treated patients.

1.4 Risks and Benefits

Telavancin is a lipoglycopeptide that has potent bactericidal activity against Gram-positive bacteria including clinically relevant Gram-positive pathogens: staphylococci (including methicillin-resistant and vancomycin-intermediate strains), streptococci (including multidrug-resistant pneumococci), enterococci (including many vancomycin-resistant strains), Gram-positive anaerobes such as clostridia (including *Clostridium difficile*), and other less commonly encountered pathogens. The bactericidal activity of telavancin results from a dual mode of action that includes inhibition of cell wall synthesis and disruption of bacterial plasma membrane function. Results from in vitro studies indicate that telavancin has a low potential to select for resistance. Importantly, development of resistance to telavancin in clinical studies has not been observed. Although some vancomycin-resistant enterococci (*vanA* genotype) have reduced susceptibility to telavancin, there is no known cross-resistance between telavancin and other classes of antibiotics. Organisms resistant to daptomycin or linezolid remain susceptible to telavancin at the proposed MIC breakpoints. In vivo pharmacology studies showed that telavancin is efficacious and demonstrates bactericidal activity in models of soft tissue (neutropenic murine thigh, murine subcutaneous infection), deep seated (rat and rabbit endocarditis), systemic (murine bacteremia) and lung (murine pneumonia) infections.

Telavancin (VIBATIV®) is approved in the United States for the treatment of adults with cSSSI and HABP/VABP caused by susceptible isolates of *Staphylococcus aureus;* in Canada for the treatment of adults with cSSSI; and in various countries in Europe for the treatment of adults with nosocomial pneumonia (NP), including ventilator associated pneumonia, known or suspected to be caused by MRSA. At the time of finalization of this

protocol amendment the medicinal product is currently approved in a total of 34 countries (US, Canada, Russia, and 31 countries in Europe via the centralized procedure).

In a Phase 2, randomized, double-blind, active-controlled, parallel-group, multicenter, multinational trial of telavancin (10 mg/kg IV once daily) or standard therapy (vancomycin 1 g every 12 hours IV or nafcillin, oxacillin, or cloxacillin 2 g every 6 hours IV) in adults with uncomplicated *S. aureus* bacteremia, similar proportions of the CE population (n = 17) were cured at a long-term follow-up visit (Day 84; 88% for telavancin vs. 89% for standard therapy). The conclusions that can be drawn from this study are limited owing to the low number of CE patients. Limited data are available from analyses of patients with bacteremia included in the Phase 3 studies. In the Phase 3 studies of cSSSI, the clinical cure rates for telavancin and vancomycin, respectively, were 55% versus 50% in the all-treated bacteremia group (n = 32) and 65% versus 83% respectively in the CE group (n = 23). In patients with Gram-positive bacteremic HABP/VABP in the Phase 3 studies of NP, the clinical cure rates for telavancin and vancomycin were 46% versus 37%, respectively (n = 51). Only one telavancin-treated patient compared with six vancomycin-treated patients had bacteremia that persisted beyond baseline cultures. A summary of known and potential risks to human subjects is provided in the IB in the Summary of Data and Guidance for the Investigator and the Prescribing Information [29].

2 OBJECTIVES

The primary objective of the study is as follows:

- To compare telavancin to standard intravenous therapy (ie, vancomycin, daptomycin, anti-staphylococcal penicillin, or cefazolin) clinical outcomes in the treatment of *S. aureus* bacteremia including *S. aureus* right-sided infective endocarditis (SA-RIE).

The secondary objectives of the study are as follows:

- To evaluate the safety and tolerability of telavancin compared with standard intravenous therapy in the treatment of *S. aureus* bacteremia, including SA-RIE.
- To evaluate the PK profiles of telavancin and vancomycin in subjects with *S. aureus* bacteremia, including SA-RIE.

3 STUDY DESIGN

3.1 Overview

This is a multicenter, randomized, open-label, noninferiority trial of telavancin versus standard IV therapy control (ie, vancomycin, daptomycin, or a β-lactam antibiotic with anti-staphylococcal activity [eg, nafcillin, oxacillin, cefazolin]) in the treatment of subjects with complicated *S. aureus* bacteremia and SA-RIE. The primary efficacy endpoint is clinical outcome at TOC, analyzed in subjects with a baseline diagnosis of UCB, CB, or right-sided infective endocarditis (RIE) in the microbiological all-treated (mAT) population. The baseline diagnosis and the clinical outcome will be assessed by a blinded Independent Efficacy Adjudication Committee (IEAC). Safety will be monitored by an Independent Data Monitoring Committee (IDMC).

Eligible subjects with confirmed *S. aureus* bacteremia will be randomized in a ratio of 1:1 to receive open-label telavancin or standard IV therapy. Randomization will be stratified by geographic region. Standard IV therapy, depending on the antibacterial susceptibility of the causative pathogen, will include vancomycin or daptomycin for subjects with known or suspected MRSA (daptomycin should be used for subjects with *S. aureus* with vancomycin MIC values >1 µg/mL); or a protocol-specified β-lactam antibiotic with anti-staphylococcal activity (ie, nafcillin, oxacillin, cloxacillin, or cefazolin) for subjects with known MSSA.

Subjects with a confirmed or suspected mixed polymicrobial infection with a Gram-negative pathogen requiring coverage with an antibiotic with Gram-negative activity at enrollment will be excluded from participation in the study. Subjects that develop an infection during study participation with a gram-negative pathogen may be allowed to continue on study after discussing the concomitant antibiotic treatment with the medical monitor.

Each subject must have at least one blood culture positive for S. aureus within 48 hours before randomization, referred to as the qualifying blood culture (QBC). The initial identification of *S. aureus* in the QBC can be done via standard culture identification methods or by use of a rapid diagnostic test. Use of a rapid diagnostic system, if available, is preferred, but not obligatory, for determination of *S. aureus* bacteremia. Regardless of method or the time that the blood sample was obtained, the identification of *S. aureus* bacteremia must be within 48 hours prior to randomization.

The study population will be enriched for subjects with CB by requiring subjects to have at least one risk factor for CB at enrollment. All subjects with CB will receive study drug for a minimum of 4 weeks and a maximum of 6 weeks (28 to 42 days) of therapy. Subjects with infective endocarditis, will receive 6 weeks (42 +/- 3 days) of therapy. Subjects with UCB will receive a minimum of 2 weeks and a maximum of 4 weeks (14 to 28 days) of therapy as per standard of care. As this protocol is designed to enhance the enrollment of patients with CB, all efforts should be implemented to minimize the enrollment of patients with UCB. This includes monitoring strict adherence to the inclusion and exclusion criteria and discussion with the principal investigators to reinforce the intent of the protocol population.

The calendar day of first study drug administration is designated as Day 1; subsequent calendar days are Days 2, 3, etc.

Procedures to control or eliminate the infection source, eg, by removal of intravascular lines or drainage and debridement of the primary infection site, will be completed within the first 3 days of study drug treatment.

Follow-up blood cultures will be performed daily until two successive post-randomization blood cultures are negative for *S. aureus.*

On or before Day 8, each subject must undergo echocardiogram (either transthoracic echocardiogram [TTE] or transesophageal echocardiogram [TEE]; TEE is strongly preferred) and will be evaluated by a physician investigator to determine the origin and extent of the *S. aureus* infection to establish the classification of infection type as one of the following:

- Uncomplicated bacteremia (UCB): A QBC, defined as a blood culture positive for *S. aureus* before randomization, no evidence of infective endocarditis, and all of the following:
  - Catheter-associated infection and removal of the catheter or cutaneous infection-associated infection and source control within 3 days after randomization.
  - A negative post-QBC blood culture drawn within 72 hours after start of study medication.
  - Defervescence within 3 days after start of study medication.
  - Absence of valvular findings on echocardiography predisposing to infective endocarditis.
  - No signs or symptoms suggestive of metastatic infection.

- Complicated bacteremia (CB): A QBC, defined as a blood culture positive for *S. aureus* before randomization, no evidence of infective endocarditis, and at least one of the following:
  - Follow-up post-QBC blood culture positive for *S. aureus* drawn after Day 3 and with known *S. aureus* identification on or before Day 8.
  - For subjects febrile at screening, persistence of fever on or beyond Day 3 after the start of study medication.
  - Evidence of metastatic infection (eg, septic arthritis, septic thrombophlebitis, deep tissue abscess).
  - Evidence of venous catheter line thrombosis or septic thrombosis associated with a venous catheter.

    NOTE: On or before Day 8, subjects with a central venous catheter (CVC) as the presumed source of the infection should also undergo central venous ultrasound to evaluate for venous thrombosis associated with the central line. Subjects who have documented central venous thrombosis, and therefore septic thrombophlebitis, should be classified as CB
- Right-sided infective endocarditis (RIE): Defined as having a QBC and Definite or Possible endocarditis according to Modified Duke Criteria [24] (Appendix 1) without predisposing abnormalities or active infection of mitral or aortic valve.
- Left-sided infective endocarditis (LIE): Defined having a QBC and Definite or Possible LIE according to Modified Duke Criteria [24] (Appendix 1).

On or before Day 8, subjects will be assigned to receive therapy based on the classification of infection type:

- For UCB, subjects will receive a minimum of 2 weeks and maximum of 4 weeks (14 to 28 days) of therapy.
- For CB, subjects will receive a minimum of 4 weeks and a maximum of 6 weeks (28 to 42 days) of therapy.
- For endocarditis, subjects will receive 6 weeks (42 days +/- 3 days) of therapy.

Prior to or on Day 8 a signs and symptoms worksheet will be completed to determine the infection type including metastatic disease (UCB, CB, RIE, LIE) and sent to the medical monitor to review. Subsequently, weekly worksheets noting signs and symptoms of potential metastatic *S. aureus* infection will be reviewed and completed by the physician investigator and forwarded to the medical monitor to optimize diagnosis and treatment of both the primary infection source and new metastatic foci of *S. aureus*.

Development of new signs or symptoms consistent with *S. aureus* infection will be assessed daily, during the hospital stay, or during the study drug treatment period as clinically

indicated, by clinical evaluation and other diagnostic modalities, eg, chest X-ray, ultrasonography, bone scan, computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET).

After Day 8, if signs and symptoms lead to a subsequent confirmed diagnosis of new metastatic foci, it will be criteria for clinical failure. Management of the subject (eg, discontinuation of study drug) will be at the discretion of the investigator based on his/her standard routine care.

Study visits for endpoint assessment will be conducted as follows:

- End of therapy (EOT) Visit: Within 3 days after the last dose of study drug
- Test of cure (TOC) Visit:
  - For subjects with UCB and assigned to receive 2 to 4 weeks (14 to 28 days) of treatment, their TOC is 38 (+/-2) days after randomization regardless of the total duration of study drug therapy
  - For subjects with CB and assigned to receive 4 to 6 weeks of treatment (28 to 42 days), their TOC is 52 (+/- 2) days after randomization regardless of the total duration of study drug therapy
  - For subjects with endocarditis assigned to receive 6 weeks (42 +/-3 days) of treatment, their TOC is 52 (+/- 2) days after randomization regardless of the total duration of study drug therapy

A post-EOT blood culture will be obtained at least 4 days after the EOT visit, and results must be available prior to the TOC visit. The results of this blood culture will be part of the assessment of clinical outcome at TOC.

Subjects who are discharged from the hospital during the treatment or follow-up period, will return to the hospital once per week for a study visit. After all the weekly visits are complete, the subject will also return to the hospital for the End of Therapy Visit, the Post-End of Treatment Visit, and the TOC visit. The TOC visit will occur based on infection classification as described above and is also the end of study (EOS).

3.2 Rationale for Study Design

This study is designed to evaluate the safety and efficacy of telavancin in subjects with *S. aureus* bacteremia by randomizing them to treatment with either telavancin or standard IV therapy. The study aim is to demonstrate that telavancin is noninferior to standard IV therapy in the treatment of *S. aureus* bacteremia including *S. aureus* right-sided infective endocarditis (SA-RIE). Standard IV therapy will be selected by the investigator depending

on known or suspected antibiotic susceptibility of the causative pathogen. Efficacy will be evaluated as clinical outcome at TOC visit. See Figure 1 for the study diagram. Safety and tolerability will be assessed throughout the study treatment period via laboratory measurements (eg, hematology, chemistry, and urinalysis) and monitoring of AE.

3.3 Selection of Dose and Duration of Treatment

3.3.1 Telavancin

A telavancin dose of 10 mg/kg administered over 60 minutes by intravenous infusion once every 24 hours for 7 to 14 days is the currently approved dosage for the treatment of adult patients with cSSSI caused by susceptible Gram-positive bacteria. The use of telavancin for this study is supported by data from a Phase 2 proof-of-concept study of telavancin in subjects with UCB, post hoc analyses of subjects with bacteremia included in the Phase 3 studies of cSSSI and HABP/VABP, a retrospective case series of bacteremia in difficult-to-treat subjects with refractory MRSA bacteremia, and case reports of subjects with VISA or MRSA endocarditis. Based on results of integrated retrospective analyses of the VIBATIV Phase 3 study data, the Sponsor believes that a reduction in the telavancin dose could optimize the risk-benefit profile of telavancin for the treatment of bacteremia. The Sponsor proposes to reduce the exposure of telavancin by incorporating the following three changes in the dose and dosing regimen: 1) decreasing the dose by 25% in all subjects; 2) decreasing the dose by 62% to 3.8 mg/kg from 10 mg/kg and altering the dosing schedule for severe renal impairment (creatinine clearance of 10 to <30 mL/min) to once daily rather than every 48 hours; and 3) recommending the dose not exceed 750 mg (or 560 and 380 mg in moderate or severe renal impairment) for subjects weighing greater than 100 kg.

For subjects with renal impairment, the telavancin dosage should be adjusted as described in Section 5.2.1.

Serum creatinine and CrCl will be obtained daily, up to Day 8, while the subject is hospitalized. After Day 8, or if subject is discharged from the hospital to outpatient parenteral antibiotic therapy (OPAT) facility or home health care (HHC), serum creatinine and creatinine clearance will be obtained every 2 to 3 days while on study drug. Close monitoring of renal function is being done in order to make appropriate dosage adjustments as described in Section 5.2.1, as well as monitoring for the need to discontinue study drug

due to renal dysfunction. If, in the opinion of the investigator, it is judged that development of or worsening of renal dysfunction is most likely secondary to the use of study drug. Examples of laboratory values often associated with clinically significant changes in renal function might include an increase from baseline in serum creatinine > 2 × value at enrollment; a serum creatinine of >1.5 mg/dL on two consecutive measurements if the baseline serum creatinine was within normal limits; or two or more post-baseline measurements of CrCl showing a ≥50% decline from baseline. In the absence of other more likely explanations for acute renal injury, and alternatives exist to treat the underlying infection, then study drug should be discontinued after consultation with the medical monitor.

Clinical practice guidelines recommend treatment durations of at least 2 weeks for UCB, 4 to 6 weeks for CB, and 6 weeks for infective native valve endocarditis [5]. The study population will be enriched for subjects with CB by requiring subjects to have at least 1 risk factor for CB at enrollment. All subjects with CB will receive study drug for 4 to 6 weeks (28 to 42 days), depending on extent of the infection. Uncomplicated bacteremia with risk factors for complicated disease, will receive 2 to 4 weeks (14 to 28 days) of therapy, and infective endocarditis will receive 6 weeks (42 +/- 3 days) of therapy. Cases with metastatic foci will receive 4 to 6 weeks, per the discretion of the investigator, depending on the location and extent of the metastatic *S. aureus* infection.

3.3.2 Standard Intravenous Therapy

Regarding the rationale for standard IV therapy as the comparator, in adult patients with bacteremia or infective native valve endocarditis, current recommendations include treatment with vancomycin or daptomycin. Vancomycin is recommended for empiric therapy for *S. aureus* bacteremia in healthcare settings with an elevated prevalence of MRSA. Guidelines recommend vancomycin to be dosed to provide trough concentrations of 15 to 20 µg/mL, increasing the probability of optimal target serum concentrations and improving clinical outcomes of complicated infections. For institutions in which the preponderance of MRSA isolates have vancomycin MIC values >2 µg/mL, alternative agents, such as daptomycin, should be used [18]. For patients with methicillin-susceptible *S. aureus*, an anti-staphylococcal PCN, such as nafcillin or oxacillin, is the preferred treatment with cefazolin as an alternative treatment [18].

Standard IV therapy will be selected by the investigator based on antibiotic susceptibility of the causative pathogen, and will include vancomycin or daptomycin for subjects with known or suspected MRSA (daptomycin should be used for subjects with MRSA with vancomycin MIC values >1 µg/mL); or. *S. aureus*, a β-lactam antibiotic with anti-staphylococcal activity (eg, nafcillin, oxacillin, cefazolin) is the recommended treatment for subjects with known MSSA.

- Vancomycin (recommended of dose of 15 mg/kg IV q12 hours); dose may be adjusted per local or regional product information/guidelines or local standard of care.
- Daptomycin (recommended dose of 6 mg/kg IV q24 hours); dose may be adjusted per local or regional product information/guidelines or local standard of care.
- Anti-staphylococcal PCN (eg, nafcillin, oxacillin or cloxacillin), recommended dose of 2 gm IV q4 hours or 12 gm IV continuous infusion over 24 hours); dose may be adjusted per local or regional product information/guidelines or local standard of care.
- Cefazolin (recommended dose of 2 gm IV q8 hours); dose may be adjusted per local or regional product information/guidelines or local standard of care.

All subjects with CB will receive study drug for 4 to 6 weeks (28 to 42 days), depending on the extent of the infection. Subjects with endocarditis will receive 6 weeks (42 +/- 3 days) of therapy; subjects with UCB may receive a minimum of 2 week and a maximum of 4 weeks (14 to 28 days) of therapy based on standard of care.

3.3.3 Switching to Another Intravenous Antibiotic Therapy

Switching to another protocol-permitted comparator IV therapy based on susceptibility of the pathogen is permitted prior to Day 8. Examples include switching from cefazolin to vancomycin for MRSA, switching from vancomycin to daptomycin for a vancomycin MIC >1 µg/mL, or switching from daptomycin to vancomycin if daptomycin non-susceptible and the vancomycin MIC is ≤1 µg/mL.

Subjects with a pathogen identified to be MRSA that is daptomycin non-susceptible and has a vancomycin MIC >1 µg/mL have no other protocol-permitted standard IV therapy options. The clinical outcome for these subjects will be classified as clinical failure.

Subjects should receive at least 3 days of therapy before it is determined the subject is not responding to therapy (eg, worsening signs and symptoms of *S. aureus* bacteremia). Subjects who, in the opinion of the investigator, must switch therapy based on failure to respond clinically will be classified as treatment failures. Protocol-permitted standard IV

therapy may be selected based on the subject's known medication allergies; however, switching IV antibiotic therapy as a result of an AE will result in the clinical outcome classified as clinical failure.

3.4 Study Endpoints

This study will evaluate the safety, efficacy, and PK of telavancin compared to standard IV therapy in the treatment of adults with *S. aureus* bacteremia and SA-RIE.

3.4.1 Safety Endpoints

Safety endpoints include AE, clinical laboratory results (including hematology, serum chemistry, creatine kinase, and urinalysis), vital signs, use of concomitant medical and physical examination. Additional information regarding renal AEs (eg, laboratory and radiographic results at the time of potential renal injury) will be obtained and recorded in the renal AE eCRF.

3.4.2 Primary Efficacy Endpoint

The primary efficacy endpoint is clinical outcome at TOC.

The efficacy endpoint of clinical outcome at TOC will be determined by the investigator and adjudicated by the blinded IEAC. Specific evaluability criteria (outlined in the statistical analysis plan [SAP]) will be applied to determine subject eligibility for each population.

Subjects who meet all of the following criteria of the composite endpoint will be classified as a clinical success (Table 2):

- Alive at TOC
- Resolution of all clinical signs and symptoms of the *S aureus* infection at TOC; excluding signs and symptoms more likely explained by an alternative diagnosis
- No evidence of microbiological persistence or relapse
  - Persistence defined as no successive days of sterile blood cultures by the eighth day of study drug
  - Relapse defined as all blood cultures negative for *S. aureus* for two successive days (need not be consecutive days) followed by a positive blood culture of the same organism before or at TOC

- No new foci of metastatic *S. aureus* infection after Day 8
  - Defined as any infection remote from the primary focus not present at the time of the classification of infection type (on or before Day 8), caused by (1) hematogenous seeding (eg, endocarditis or vertebral osteomyelitis) or (2) extension of infection beyond the primary focus (eg, septic thrombophlebitis or abscess); all cases of metastatic infection will be defined by either radiologic imaging, culture of *S. aureus* from a normally sterile site, or the use of a validated diagnostic criteria; embolic stroke will be defined as radiologic evidence of an acute thromboembolic event; the infection must be a result seeding or extension from the primary focus of *S. aureus* infection.

Subjects will be classified as a clinical failure if they meet one of the following: 1) who do not meet all of the criteria of clinical success; 2) Subject receives potentially effective non-study antibiotic up to TOC visit; 3) Subject switches study antibiotic due to lack of clinical response or an AE; 4) Subject discontinued study drug due to treatment-emergent, drug-related AE; 5) Subject required further antibacterial therapy for the *S. aureus* infection beyond the assigned treatment duration (exemption: oral prophylaxis); 6) New foci of metastatic *S. aureus* infection after Day 8.

Once assigned, on or before Day 8, to receive 2 to 4 weeks (14 to 28 days) for UCB, 4 to 6 weeks (28 to 42 days) for CB, or 6 weeks (42 +/-3 days) for endocarditis, any antibiotic treatment for *S. aureus* infection beyond the assigned treatment durations will be classified as a clinical failure. If the subject discontinues study drug prior to their assigned treatment duration, their TOC visit remains either 38 (+/- 2) days, 52 (+/-2) days, or 52 (+/- 2) days after randomization, respectively.

Subject outcomes will be classified as indeterminate if they discontinued the study prematurely for one or more the following reasons:

- Withdrew consent
- Discontinued study drug therapy against medical advice.
- Lost to follow-up

Note: Every effort should be made to retain each subject in the study. If therapy is withdrawn, all outcome data should be collected according to the protocol.

Once a subject is determined to be a clinical failure, all outcome data should be collected according to the Schedule of Study Procedures (Table 1); subjects must undergo the EOT, post-EOT blood culture, and TOC evaluations (Sections 6.2.5, 6.2.6, and 6.2.7,

respectively). Once the subject is classified as failure, the weekly assessments are not mandated unless the subject is still hospitalized. A blood culture obtained after EOT and before TOC is encouraged, but optional for cases of clinical failure.

Table 2: Clinical Outcome at TOC

Outcome	**Definition**
Clinical Success	*Must meet all of the following criteria:*
	• Subject alive at TOC • Resolution of all clinical signs and symptoms of the *S. aureus* infection at TOC (unless explained by a more likely alternative diagnosis) • No evidence of microbiological persistence or relapse • No new foci of metastatic *S. aureus* infection after Day 8
Clinical Failure	*Meets any of the following:*
	• Subject did not meet all the criteria for clinical success • Subject receives potentially effective non-study antibiotic up to TOC visit • Subject switches study antibiotic due to lack of clinical response or an AE • Subject discontinued study drug due to treatment-emergent, drug-related AE • Subject required further study antibacterial therapy for the *S. aureus* infection beyond assigned treatment duration (exemption: oral prophylaxis) • New foci of metastatic *S. aureus* infection after Day 8
Indeterminate	*Meets one or more of the following:*
	• Subject withdrew consent • Subject remains lost to follow-up • Subject discontinued study drug against medical advice

3.4.3 Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows (see Section 8.4.2):

- Clinical outcome (success or failure) at TOC by baseline diagnosis in the mAT and microbiological evaluable (ME) populations.
- Clinical response (success or failure) at EOT in the mAT and ME populations.
- Development of new metastatic foci of *S. aureus* infection after Day 8 in the mAT and ME populations.
- Duration of treatment with study medication by baseline clinical diagnosis in the mAT and ME populations.
- For subjects with a positive *S. aureus* blood culture on Day 1, time to all blood cultures negative for *S. aureus* for two days in succession (ie, clearance of

bacteremia) (does not have to be consecutive calendar days) in the mAT and ME populations; date will be first of the two days in succession.

- 28-day all-cause mortality for subjects with a baseline diagnosis of CB or RIE in the mAT and ME populations.
- Incidence of AEs, treatment-emergent AEs (TEAEs), SAEs, and deaths in the safety population.
- Incidence of key laboratory indices in the safety population to be further described in the SAP.

Definitions for additional efficacy endpoints will be as follows:

- Clearance of bacteremia is defined as occurring on the first date of all blood cultures negative for *S. aureus* for two successive days post-randomization; date of clearance will be the first of the two successive days.
- For subjects with a positive *S. aureus* blood culture on Day 1, the duration of *S. aureus* bacteremia is defined as the time (days) from randomization to all blood cultures negative for *S. aureus* for two successive days (post-randomization; date will be first of the two days in succession.
- 28-day all-cause mortality is defined as all deaths that occur during the study, regardless of cause, on or before Day 28.

In addition, analyses evaluating evidence of treatment-emergent resistance to telavancin, vancomycin, daptomycin, anti-staphylococcal PCNs, or cefazolin may be conducted.

NOTE: Echocardiograms (TTEs and TEEs) will undergo blinded review by an independent echocardiography core laboratory.

Exploratory analyses will be conducted to assess a variety of health utilization variables. Methods of analysis for these variables will be outlined in a separate health economics outcomes statistical analysis plan (HEOR SAP). The results of these analyses will be presented separately and not included in the clinical study report (CSR).

The study will also evaluate the safety and tolerability of telavancin compared with standard IV therapy in the treatment of *S. aureus* bacteremia and SA-RIE.

3.4.4 Pharmacokinetic Endpoints

Pharmacokinetic endpoints include AUC and C_{max} as measures of drug exposure. Additional information regarding the relationship between selected subject covariates and drug exposure may be generated.

3.5 Minimization of Bias

Study design measures used to minimize bias include treatment assignment by randomization. As described in Section 3.5.2, a blinded IEAC will review data from each subject to establish the diagnosis and clinical outcome at EOT and TOC. The Sponsor will remain blinded to the IEAC's adjudication results until after database lock.

3.5.1 Treatment Assignment

Subjects will be randomized to receive either telavancin or standard IV therapy in a ratio of 1:1, stratified by geographic region. Randomization will be generated using a centralized computer-generated block randomization schedule. The reference therapy (ie, standard IV therapy) will be selected by the investigator depending on known or suspected antibacterial susceptibility of the pathogen.

As a subject qualifies for the study, the investigator will notify the site pharmacist (or other authorized staff member), who will access a centralized interactive response system (IXRS) to obtain a treatment assignment.

3.5.2 Blinding

This is an open-label study. A blinded IEAC of clinical experts in acute care, hospital-based medicine will review the data from each subject to establish the diagnosis and outcome. The outcome of the primary composite endpoint will be assessed and determined by IEAC and the adjudication will be conducted without information regarding treatment assignments. Neither Sponsor employees nor study personnel will participate in the closed sessions where the committee members discuss the subject outcomes. The Sponsor will remain blinded to the IEAC's adjudication results until after database lock.

In addition, the preparation of reports for the IDMC will be conducted by an independent statistical group outside of the Sponsor.

4 STUDY POPULATION

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for enrollment into this study.

4.1 Inclusion Criteria

1. Male or female at least 18 years old at the time of consent.
2. Subject has signed an informed consent form. If a subject is unable to give consent, when legally permitted, consent must be obtained from the subject's legally acceptable representative.

   NOTE: Subject, or appropriate legal representative, must be able to communicate effectively with investigator and site staff.

3. At least one blood culture positive for *S. aureus* within 48 hours before randomization, referred to as the QBC.
4. In addition to the QBC, subject must have at least one of the following signs or symptoms of bacteremia:
   - Temperature ≥38.0°C
   - White blood cell (WBC) count >10,000 or <4,000 cells/μL, or >10% immature neutrophils (bands) regardless of total peripheral WBC count
   - Tachycardia (heart rate >90 bpm)
   - Tachypnea (respiratory rate >20 breaths/min)
   - Hypotension (systolic blood pressure <90 mmHg)
   - Signs and symptoms of localized catheter-related infection (tenderness and/or pain, erythema, swelling, purulent exudate within 2 cm of entry site)
5. Subject must, at enrollment, have either 1) known right-sided infective endocarditis by Modified Duke Criteria, 2) known CB, demonstrated as signs or symptoms of metastatic foci of *S. aureus* infection (eg, any infection remote from the primary focus caused by hematogenous seeding or extension of infection beyond the primary focus), or 3) known bacteremia with at least one of the following risk factors for CB [25-28]:
   - Any venous catheter considered to be the source of the infection, demonstrated by inflammation or purulent drainage from the catheter insertion site AND evidence of catheter-associated thrombosis upon removal

     NOTE: A peripheral venous catheter with just inflammation or purulent drainage from the catheter insertion site without evidence of thrombus is not consistent with CB.
   - A CVC considered to be the source of infection, demonstrated by inflammation or purulent drainage from the CVC insertion site or presence of thrombus on ultrasound

- A long-term intravascular catheter (eg, tunneled cuffed intravascular catheter or subcutaneous port catheter) considered to be the source of infection, demonstrated by inflammation or purulent drainage from the catheter insertion site or presence of thrombus on ultrasound
- New onset cardiac murmur consistent with tricuspid regurgitation
- Community onset bacteremia (eg, subject does not live in a healthcare facility)
- Pathogen known to be MRSA at enrollment
- Duration of symptoms ≥2 days at time of presentation (prior to start of antibiotic therapy)
- Skin exam findings suggesting acute systemic infection (ie, petechiae, vasculitis, infarcts, ecchymoses or pustules due to the infection)

6. Willing to receive intravenous antibiotics for the duration of treatment.

7. Expected survival of at least 3 months.

8. Female subjects must be non-pregnant and non-lactating. If a female subject is of childbearing potential, must have a documented negative pregnancy test at screening.

   NOTE: All females are considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 2 years) or documented to be surgically sterile (bilateral tubal ligation or total hysterectomy). A subject may be admitted to the study on the basis of a negative urine pregnancy test (local laboratory), pending the result of the serum pregnancy test.

9. If sexually active, must agree to use a highly effective method of birth control with partners of childbearing potential during the study and for 1 month after study drug dosing

   NOTE: A highly effective method of birth control is defined as one that results in a low failure rate (ie, < 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence, or a vasectomized partner. Male subjects must agree to use medically acceptable birth control for at least one month following last dose of study medication. A vasectomy or a condom used with a spermicide is a medically acceptable birth control method for males.

10. Considered likely to comply with the study procedures and to return for scheduled evaluations.

4.2 Exclusion Criteria

Subjects who satisfy any of the following criteria are not eligible for study enrollment:

1. Treatment regimen greater than 60 hours with any potentially effective (anti-staphylococcal) systemic antibiotic(s) within 7 days before randomization.

   NOTE: It is preferable to have no more than 48 hours of total prior antibiotic therapy within 7 days before randomization.

   EXCEPTION: Documented resistance to the prior systemic antibacterial therapy, confirmed by a microbiological laboratory report.

2. Requirement or anticipated requirement of non-study systemic antibiotics during the study
3. Presence of an infection source (eg, intravascular line, abscess, septic arthritis, infected prosthetic material, infected wound) that will not be managed or controlled (eg, removal or replacement of the infected line, drainage of abscess, aspiration or drainage of septic arthritis, removal or replacement of infected prosthesis, or debridement of infected wound) within the first 3 days of study drug treatment
4. Presence of prosthetic cardiac valve or cardiac device (eg, implantable cardioverter defibrillator [ICD]), permanent pacemaker, or cardiac valve support ring)
5. Known or suspected LIE at enrollment, according to Modified Duke Criteria (Appendix 1)

   NOTE: Right-sided infective endocarditis (RIE) is permitted. If the subject is diagnosed with LIE after enrollment, subject will be allowed to remain on study.

6. At the time of enrollment, known or highly suspected osteomyelitis, meningitis, or metastatic septic foci involving the central nervous system (CNS)

   NOTE: Investigators should use clinical judgment to determine whether additional imaging studies (eg, X-ray, computed tomography scan, magnetic resonance imaging) are indicated at screening to rule out the presence of osteomyelitis, meningitis, or metastatic septic foci in the CNS.

7. Known at the time of enrollment to have MRSA bacteremia that is non-susceptible to daptomycin AND has a vancomycin MIC $\geq$2 µg/mL
8. Confirmed evidence (identification or Gram stain) of a mixed polymicrobial infection with a Gram-negative pathogen that requires non-study antibiotic treatment with agent(s) that have activity against Gram-negative pathogens
9. Previous participation in an anti-infective study during the past 12 months
10. A history of significant hypersensitivity, allergy or intolerance to telavancin

    NOTE: Caution should be taken in subjects with a history of severe hypersensitivity reaction to vancomycin. If the pathogen is known MRSA, allergy to both vancomycin and daptomycin may require exclusion. If the pathogen is known MSSA, allergy to both anti-staphylococcal PCN/cephalosporin and daptomycin may require exclusion. Investigator discretion is advised on a case-by-case basis.

11. Solid organ transplantation or bone marrow transplantation within 6 months before randomization

12. Severe neutropenia, defined as an absolute neutrophil count (ANC) <500 cells per microliter, or expected development of severe neutropenia during study
13. Known or suspected human immunodeficiency (HIV) infection with a CD4+ T-cell count <200/μL within the previous 6 months
14. Subjects requiring concomitant administration of anti-coagulation therapy (eg, intravenous heparin sodium) AND requiring specific coagulation testing known to have interference by telavancin (prothrombin time [PT]/international normalized ratio, activated partial thromboplastin time [aPTT], or activated clotting time, or coagulation-based Factor X activity assay)

    NOTE: Although telavancin does not interfere with coagulation, it interferes with some assays used to monitor coagulation. The use of unfractionated heparin or a low molecular weight heparin AND testing using an Anti-Xa chromogenic testing assay would be permissible.
15. Severe liver disease, ie, Child-Pugh Class C (Appendix 2), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 10 times the upper limit of normal (ULN)
16. Requirement for acute renal replacement therapy; or acute kidney injury (AKI) defined as an acute decrease in CrCl to < 30 mL/min and at least one of the following:
    - ≥2x increase in serum Cr or 50% decrease in glomerular filtration rate (GFR) within the 2 weeks prior to enrollment (RIFLE stage 2 injury (Appendix 3)
    - Oliguria defined as urine output <0.5 mL/kg per hour for ≥12 hours at any time during screening

    NOTE: Chronic renal insufficiency with a stable CrCl <30 mL/min, including chronic hemodialysis, is permitted.
17. Shock or hypotension (supine systolic blood pressure <80 mm Hg) unresponsive to fluids or pressors within 24 hours prior to randomization
18. QTc >460 ms (using either the Bazett or Fridericia formula), congenital long QT syndrome, uncompensated or new onset heart failure, aortic stenosis, aortic insufficiency, or mitral insufficiency
19. Serum creatine kinase (CK) ≥2000 U/L
20. Breast-feeding or pregnant or intending to become pregnant (self or partner) at any time during the study
21. Any other condition that in the opinion of the investigator would jeopardize the safety or rights of a subject or would render the subject unable to comply with the protocol; or any other condition that in the opinion of the investigator may confound the data.

5 STUDY DRUGS

All study drug supplied by the Sponsor must be stored in a secure location accessible only to designated study personnel.

5.1 Description of Study Drugs

Descriptions of telavancin, including physical, chemical, and pharmaceutical properties, formulations and dosage forms, packaging and labeling, storage and handling, and preparation for administration, are provided in the study Pharmacy Manual. For standard IV therapy (ie, vancomycin, daptomycin, anti-staphylococcal PCN, cefazolin) sites should refer to the applicable approved country specific drug package inserts for descriptions of pharmaceutical properties, formulations, dosage forms, packaging, labeling, storage and handling as well as preparation and administration for the standard of care therapy administered to the subjects.

5.2 Dosage and Administration

Enrolled subjects will be randomized in a ratio of 1:1 to receive either open-label telavancin or standard IV therapy (ie, vancomycin, daptomycin, anti-staphylococcal PCN, or cefazolin). Standard IV therapy will be selected by the investigator based on known or suspected antibiotic susceptibility of the causative pathogen. Duration of therapy will be guided based on the initial diagnosis on or before Day 8. All subjects with CB will receive study drug for a minimum of 4 weeks and a maximum of 6 weeks (28 to 42 days) of therapy. Subjects with infective endocarditis, will receive 6 weeks (42 +/- 3 days) of therapy. Subjects with UCB will receive a minimum of 2 weeks and a maximum of 4 weeks (14-28 days) of therapy as per standard of care.

5.2.1 Telavancin

Telavancin should be prepared and administered as described in the Pharmacy Manual. For subjects with normal renal function, telavancin should be administered IV at a dose of 7.5 mg/kg, in either 5% dextrose injection (D5W), sterile water for injection, or 0.9% sodium chloride; in 100 to 250 mL over 60 (+/- 10) minutes, once every 24 hours.

Subjects with renal impairment, either at baseline or which develops during the course of study treatment, should have the dosage of telavancin modified, based on estimated creatinine clearance, as listed in Table 3.

The pharmacist will calculate the estimated creatinine clearance using the creatinine value provided by the local and/or central laboratory, the Cockcroft-Gault formula and ideal body weight (IBW). If the actual body weight is less than IBW, the actual weight will be used.

Calculation for IBW:

- If subject is male, then IBW(kg) = 50.0 + 0.9*[height(cm) – 152.0]
- If subject is female, then IBW(kg) = 45.5 + 0.9*[height(cm) – 152.0]

Table 3: Telavancin Dosage Adjustment in Subjects with Renal Impairment

Creatinine Clearance[a] (mL/min)	Telavancin Dosage Regimen	Maximum Daily Dose
>50	7.5 mg/kg every 24 hours	750 mg
30-50	5.6 mg/kg every 24 hours	560 mg
10 to <30	3.8 mg/kg every 24 hours	380 mg
Stable chronic hemodialysis[b]	3.8 mg/kg every 24 hours	380 mg

[a] For subjects receiving telavancin, the creatinine clearance for dosing should be calculated using the Cockcroft-Gault formula and ideal body weight (IBW). Use actual body weight if it is less than IBW.

[b] On days when subject receives hemodialysis, telavancin should be administered following completion of hemodialysis.

For subjects weighing more than 100 kg, the daily telavancin dose should not exceed 750 mg for those with normal renal function, 560 mg for those with moderate renal impairment, and 380 mg for subjects with severe renal impairment (creatinine clearance of 10 to <30 mL/min) or those undergoing chronic hemodialysis (Table 3).

5.2.2 Vancomycin

For subjects with known or suspected MRSA, vancomycin should be administered. The recommended dose of vancomycin is 15 mg/kg administered IV q12h (doses may be adjusted per local or regional product information/guidelines or local standard of care). For subjects with renal impairment, including those receiving chronic hemodialysis, vancomycin should be dosed per local or regional product information/guidelines or local standard of care.

5.2.3 Daptomycin

For subjects with known or suspected MRSA (and for subjects with a vancomycin MIC value >1 µg/mL), daptomycin should be administered. The recommended dose of daptomycin is 6 mg/kg IV q 24h by infusion over 30 minutes (doses may be adjusted per local or regional product information/guidelines or local standard of care). For subjects with renal impairment,

including those receiving chronic hemodialysis, daptomycin should be dosed per local or regional product information/guidelines or local standard of care. For patients with pneumonia and concurrent bacteremia, daptomycin should not be used.

5.2.4 Anti-Staphylococcal Penicillin

For subjects with known or suspected MSSA, an anti-staphylococcal PCN, also known as a penicillinase-resistant PCN, (eg, nafcillin, oxacillin, or cloxacillin) is the preferred therapy. The recommended dose is 2 gm IV q 4h, or 12 gm IV continuous infusion over 24 hours (doses may be adjusted per local or regional product information/guidelines or local standard of care). For subjects with renal impairment, including those receiving chronic hemodialysis, anti-staphylococcal PCNs should be dosed per local or regional product information/guidelines.

5.2.5 Cefazolin

For subjects with known or suspected MSSA, cefazolin is an acceptable alternative therapy. The recommended dose is 2 gm IV q8h (doses may be adjusted per local or regional product information/guidelines or local standard of care). For subjects with renal impairment, including those receiving chronic hemodialysis, cefazolin should be dosed per local or regional product information/guidelines.

5.3 Criteria for Hospital Discharge (Outpatient Study Drug Administration)

Subjects may be discharged from the hospital and study drug may be provided on an outpatient basis through an OPAT facility or HHC agency, prior to completing study drug, if the criteria listed below are met.

- All procedures required on or before Day 8 have been performed
- The Sponsor has approved use of the OPAT facility or HHC agency
- Investigator will obtain IRB approval for the use of OPAT or HHC agency and ensure the proper documentation/approval of such use in the ICF
- The subject is a good candidate for outpatient therapy per the investigator's judgment and is able to receive treatment daily in home or at an approved OPAT facility
- The subject has initially received study drug while hospitalized and has shown objective clinical improvement warranting study drug infusion continuation through an OPAT facility or HHC agency. Objective clinical improvement is defined as:

- All blood cultures negative for *S. aureus* for two successive days (need not be consecutive days) post-randomization
- Improvement (resolution not necessary) in all clinical signs and symptoms of *S. aureus* infection
- Afebrile (< 38°C; highest recorded daily temperature) for at least 24 hours
- Normalizing WBC count (WBC should not be trending upwards)

- The investigator or designee is capable of conducting all study assessments (Table 1), including face-to-face evaluations, at every time point required by the protocol while the subject is treated through a HHC agency or OPAT facility
- The OPAT and HHC personnel are trained in protocol procedures and training is documented in study files
- The investigator can ensure that appropriate safety monitoring will be implemented and all protocol-specified assessments and procedures will be conducted
- The investigator can ensure appropriate oversight and proper documentation of IP transfer, patient care and AE/SAE reporting
- The subject agrees to return to the primary investigative site for weekly visits, during treatment as well as post-treatment, and for EOT, post-EOT and TOC visits

5.4 Guidance to Investigators on Duration of Treatment

On or before Day 8, subjects will be assigned to receive study medication for a specified duration based on the classification of infection. Uncomplicated bacteremia will receive a minimum of 2 weeks and a maximum of 4 weeks (14 to 28 days), CB will receive 4 to 6 weeks (28 to 42 days) of therapy, and infective endocarditis will receive 6 weeks (42 +/- 3 days) of therapy. If possible, oral prophylaxis following primary therapy should be avoided during participation in the study.

5.5 Treatment Compliance

All study drug is to be administered by study personnel and documented in the case report forms.

5.6 Drug Accountability and Reconciliation

The investigator or designee is responsible for maintaining accountability records for all study drug(s) received from the Sponsor in accordance with applicable government regulations and study procedures. The accountability record will include entries for receipt, distribution or dispensing, and destruction of the material(s), as well as manufacturer and lot

number for all IV comparator medications. The IV comparator manufacturer and lot numbers will be entered into the electronic case report form. Unused and expired study drugs will be disposed of in accordance with written instructions from the Sponsor.

6 STUDY PROCEDURES

6.1 Schedule of Study Procedures

The schedule of study procedures is summarized in Table 1.

6.2 Procedures by Visit

The calendar day of first study drug administration is designated as Day 1; subsequent calendar days are Days 2, 3, etc. Written informed consent must be obtained prior to performing any protocol specific procedures.

6.2.1 Pretreatment Screening Evaluation

After providing full informed consent, subjects will undergo a medical screen to determine their eligibility for participation based on the criteria outlined in this protocol.

The following procedures will be performed within 48 hours before randomization unless otherwise specified. If the screening assessments and results are obtained within this 48-hour period, they will be considered valid screening evaluations and do not need to be repeated following ICF signature. Local laboratory test results will be used to determine a subject's eligibility for enrollment. Of note, subjects on hemodialysis may have the urine assessments waived due to anuria.

- Written informed consent (signed and dated) after the nature of the study has been explained and before any study procedure is performed (in the event that a subject is unable to give consent, when legally permitted, the subject's legally acceptable representative must do so).
- Confirm blood culture within 48 hours before randomization is positive for *S. aureus,* referred to as the QBC.
- All *S. aureus* isolates should be sent to the central laboratory for organism identification and susceptibility testing (refer to Central Laboratory Manual for instructions on shipping microbiology samples to the central laboratory). Record identification of all non-*S. aureus* isolates in the electronic case report form (eCRF).
- Medical history and medication history.
- Body temperature; obtain and record highest daily temperature and method of measurement on the eCRF. The same method for obtaining body temperature should be used for consistency.
- Physical examination, including vital signs.

- Obtain chest x-ray or CT of chest within 3 days after the report of the QBC. If a chest x-ray or CT of chest is obtained during the screening period (within 48 hours prior to randomization), a repeat chest x-ray or CT does not need to be done.
- Assessment of all signs and symptoms consistent with *S. aureus* infection.
    - Rigorous evaluation for evidence of metastatic foci of infection, as clinically indicated (eg, embolic phenomena to the skin, retina, lungs, bone or CNS; new heart murmur; new onset arthritis). Evaluations may include, but are not limited to, chest X-ray, ultrasonography, bone scan, CT, MRI and PET imaging.
    - Investigators should use clinical judgment to determine whether additional imaging studies (eg, x-ray, nuclear scan, CT or MRI) are indicated at screening to rule out the presence of osteomyelitis. If osteomyelitis is confirmed or highly likely by radiological tests, the subject must not be enrolled.
- Obtain and send blood and urine samples to the central laboratory for the following tests (refer to the Central Laboratory Manual for instructions on shipping samples to the central laboratory).
    - Hematology
    - Serum chemistry
    - Creatine kinase
    - C-reactive protein (CRP)
    - Serum interleukin-10 (IL-10)
    - Urinalysis
    - Quantification of prospective urinary biomarkers of renal function
- Obtain serum and urine for βhCG pregnancy test, if subject is female. Subjects may be enrolled into the study on the basis of a negative pregnancy urine test (local laboratory), pending the result of the serum pregnancy test (If the result of the serum test is subsequently positive, study drug must be discontinued, End of Therapy evaluations performed and an End-of-Study visit scheduled).
- Obtain one 12-lead electrocardiogram (ECG). If the QTc is >460 ms (using either the Bazett or Fridericia formula) at the screening ECG, the subject will not be entered into the study.
- Obtain a urine culture with an aseptic technique. If the subject has a urinary catheter, obtain the culture utilizing an aseptic needle stick through the catheter wall). All *S. aureus* isolates should be sent to the central laboratory for organism identification and susceptibility testing.
- Obtain specimen for culture when a primary source of bacteremia is identified (eg, pus from the entry site of the catheter, central line tip, purulent secretion from a wound, sputum). All *S. aureus* isolates should be sent to the central laboratory for

organism identification and susceptibility testing (refer to Central Laboratory Manual for instructions on shipping microbiology samples to the central laboratory). If there is no clinical evidence of the primary source of infection causing the bacteremia, no additional culture is required.

- Assessment of Acute Physiologic and Chronic Health Evaluation (APACHE) criteria (Appendix 4). Obtain within 24 hours prior to randomization.
- Confirm subject meets all inclusion criteria and no exclusion criteria.
- If the subject qualifies for the study, the IXRS will be contacted for assignment of study drug regimen, and the subject will be considered randomized in the study.
- Assessment of AE(s).

6.2.2 Daily Procedures

Day 1 procedures are to be completed after administration of the first dose of study drug.

The following procedures will be performed daily during the treatment period:

- Administration of study drug per protocol.
- Obtain and record highest daily temperature and method of measurement on the eCRF. The same method for obtaining body temperature should be used for consistency.
- Recording of all concomitant medications, including those used during procedures.
- Assessment of AE(s).
- Follow-up blood cultures will be performed daily, starting on Day 1, until two successive post-randomization blood cultures are negative for *S. aureus*.
  - Daily draws for blood culture consist of 2 samples from separate sites inoculated into 2 standard aerobic blood culture bottles.
  - Additional blood cultures should be obtained at any time during the study when clinically indicated (eg, bacteremia is suspected or subject has a fever spike).
  - Perform culture and organism identification at the local or regional laboratory, as applicable. All *S. aureus* isolates should be sent to the central laboratory for organism identification and susceptibility testing (refer to Central Laboratory Manual for instructions on shipping microbiology samples to the central laboratory).
  - For all non-*S. aureus* isolates record identification (genus and species) and susceptibility (if known) in the eCRF.
- For all subjects randomized to receive telavancin or vancomycin, obtain PK samples as noted in the Schedule of Assessments (Figure 3 and Figure 4) and detailed in Section 6.3.3.

- For subjects receiving vancomycin, trough levels of vancomycin as determined by the hospital laboratory for use in determining and adjusting the dosing amount will be recorded.

6.2.3 Additional Procedures On or Before Day 8

The following procedures will be performed on or before Day 8 while the subject is hospitalized:

- Echocardiography (either TTE or TEE; TEE is strongly preferred). All echocardiograms will undergo blinded review by an independent echocardiography core lab.
- For subjects presumed to have *S. aureus* bacteremia due to a CVC, obtain a central venous ultrasound to evaluate for venous thrombosis associated with the CVC.
- Within the first 3 days of starting study drug treatment, procedures to control or eliminate the infection source (eg, by removal of intravascular lines' drainage of abscesses, removal of infected prosthesis, or debridement of wounds), will be completed. Record any significant procedures, such as incision and drainage, debridement, suture removal, radiological procedures, surgery, etc.
  - Removed catheters can be replaced, but in the case of central catheters they cannot be replaced using wire-guided methods, or placed in the same site if there is clinical evidence of infection at the entry site.
  - All microbiological specimens must be cultured. All *S. aureus* isolates (obtained in the workup of *S. aureus* bacteremia) should be sent to the central laboratory for confirmation of organism identification and susceptibility testing (refer to Central Laboratory Manual for instructions on shipping microbiology samples to the central laboratory).
- Prior to or on Day 8 a signs and symptoms worksheet will be completed to determine the infection type including metastatic disease (UCB, CB, RIE, LIE) and sent to the medical monitor to review.
- For all subjects randomized to receive telavancin or vancomycin, obtain PK samples as noted in the Schedule of Assessments (Figure 3 and Figure 4) and detailed in Section 6.3.3.
- On Day 7 (+/- 1 day), obtain and send to the central laboratory blood samples for the following tests (refer to the Central Laboratory Manual for instructions on shipping samples to the central laboratory).
  - Hematology
  - Serum chemistry
  - Creatine kinase
  - CRP
- Assessment of all signs and symptoms consistent with *S. aureus* infection.

- Rigorous evaluation for evidence of metastatic foci of infection, as clinically indicated (eg, embolic phenomena to the skin, retina, lungs, bone or CNS; new heart murmur; new onset arthritis). Evaluations may include, but are not limited to, chest X-ray, ultrasonography, bone scan, CT, MRI and PET imaging.

- Obtain serum creatinine and creatinine clearance daily, up to Day 8, while the subject is hospitalized.

6.2.4 Weekly Procedures After Day 8

After Day 8, the following procedures will be performed each week (+/- 3 days) until TOC Visit:

- Obtain and record highest daily temperature and method of measurement on the eCRF. The same method for obtaining body temperature should be used for consistency.
- Recording of all concomitant medications, including those used during procedures.
- Assessment of AE(s).
- Assessment of all signs and symptoms consistent with *S. aureus* infection.
  - Rigorous evaluation for evidence of metastatic foci of infection, as clinically indicated (eg, embolic phenomena to the skin, retina, lungs, bone or CNS; new heart murmur; new onset arthritis). Evaluations may include, but are not limited to, chest X-ray, ultrasonography, bone scan, CT, MRI, and PET imaging.
- Weekly worksheets noting signs and symptoms of potential metastatic *S. aureus* infection will be reviewed and completed by the physician investigator and forwarded to the medical monitor to optimize diagnosis and treatment of both the primary infection source and new metastatic foci of *S. aureus*.
- Recording of any significant procedures such as incision and drainage, debridement, suture removal, radiological procedures, surgery, etc.
- For all subjects randomized to receive telavancin or vancomycin, obtain PK samples as noted in the Schedule of Assessments (Figure 3 and Figure 4) and detailed in Section 6.3.3.
- Obtain and send to the central laboratory blood samples for the following tests (refer to the Central Laboratory Manual for instructions on shipping samples to the central laboratory). Obtain weekly until EOT Visit.
  - Hematology
  - Serum chemistry
  - Creatine kinase
  - CRP

- After Day 8, while subject is hospitalized, obtain serum creatinine and creatinine clearance every 2 days while on study drug (local and central laboratory). After Day 8, or if subject is discharged from the hospital to outpatient parenteral antibiotic therapy (OPAT) or home health care (HHC), obtain serum creatinine and creatinine clearance every 2 to 3 days (central laboratory) while on study drug (on the days where the weekly safety lab coincides with the creatinine monitoring, a sample will be sent to both the local and central laboratory).
- For female subjects, a urine pregnancy test (local laboratory) will be performed once per month (ie, in subjects treated for 6 weeks) as per local regulatory requirements.
- A single 12-lead ECG will be obtained at Week 3 and Week 6. If the QTc time is >500 ms or if the QTc time is ≥60 ms above baseline, the subject should be withdrawn from treatment. Any other relevant ECG abnormalities noted at Week 3, 6, or unscheduled ECGs, should be classified as an AE and additional ECGs will be required weekly until the subject discontinues from the study. If feasible, every effort should be made to obtain duplicates of all ECGs. All original ECGs obtained for each time point (not photocopied) will be held with the study files for analysis in the event that a central reader is required.

6.2.5 End of Therapy Visit / Termination / Early Withdrawal

The following procedures will be performed within 3 calendar days after the last dose of study drug at the End of Therapy (EOT) Visit:

- Investigator evaluation of clinical response at EOT visit.
- Obtain and record highest daily temperature and method of measurement on the eCRF. The same method for obtaining body temperature should be used for consistency.
- Obtain and send to the central laboratory, blood and urine samples for the following tests (refer to Central Laboratory Manual for instructions on shipping samples to the central laboratory).
    - Hematology
    - Serum chemistry
    - Creatine kinase
    - CRP
    - IL-10
    - Urinalysis
    - Quantification of prospective urinary biomarkers of renal function
- Physical examination including vital signs.
- Assessment of all signs and symptoms consistent with *S. aureus* infection.

  - Rigorous evaluation for evidence of metastatic foci of infection, as clinically indicated (eg, embolic phenomena to the skin, retina, lungs, bone or CNS; new heart murmur; new onset arthritis). Evaluations may include, but are not limited to, chest X-ray, ultrasonography, bone scan, CT, MRI, and PET imaging.
- A single 12-lead ECG will be obtained at EOT or Early Termination prior to Week 6. Any clinically significant ECG abnormalities should be classified as an AE and reported accordingly.
- Recording of any significant procedures (performed from last intravenous treatment day to the time of the EOT Visit), such as incision and drainage, debridement, amputation, suture removal, etc.
- Record all concomitant medications.
- Assessment of AE(s).

6.2.6 Post-End of Therapy Blood Culture

The following must occur at least 4 days after the EOT visit and results must be available prior to the TOC visit. The results will be part of the assessment of clinical outcome at TOC. For subjects who are no longer hospitalized, this visit may be coordinated to occur when the subject returns for his/her weekly visit:

- Obtain follow-up blood culture specimen. These blood cultures consist of 2 samples (8-10 mL) from separate sites inoculated into 2 standard aerobic blood culture bottles. All *S. aureus* isolates should be sent to the central laboratory for organism identification and susceptibility testing. (NOTE: For subjects not completing study treatment, two blood cultures from separate fresh venipuncture sites will be obtained at the early termination visit.)

6.2.7 Test of Cure Visit / End of Study

The TOC visit is also the EOS visit. The following procedures will be performed at the TOC visit:

- Investigator evaluation of clinical outcome at TOC Visit.
- Obtain and record highest daily temperature and method of measurement on the eCRF. The same method for obtaining body temperature should be used for consistency.
- Physical examination including vital signs.
- Assessment of all signs and symptoms consistent with *S. aureus* infection.
  - Rigorous evaluation for evidence of metastatic foci of infection, as clinically indicated (eg, embolic phenomena to the skin, retina, lungs, bone or CNS; new

heart murmur; new onset arthritis). Evaluations may include, but are not limited to, chest X-ray, ultrasonography, bone scan, CT, MRI, and PET imaging

- Recording of any significant procedures performed since the EOT Visit to the time of the TOC Visit (eg, incision and drainage, debridement, amputation)
- Obtain serum and urine for βhCG pregnancy test, if subject is female.
- Record all concomitant medications
- Assessment of AE

6.3 Description of Study Assessments and Procedures

6.3.1 Efficacy Assessments

Efficacy assessments include evaluation of signs and symptoms consistent with *S. aureus* infection such as blood cultures, physical examination, and echocardiography (TEE, or TTE if TEE is not possible); and may also include, but are not limited to, chest X-ray, additional specimen cultures, ultrasonography, bone scan, CT, MRI, and PET scan.

6.3.2 Safety Assessments

6.3.2.1 Adverse Events

AEs will be reviewed and recorded from signing of the informed consent through the last day of the TOC visit. AE may be observed by the site study personnel or spontaneously reported by the subject.

All AEs must be recorded in the subject's case report form and, if applicable, reported as described in Section 7.

The investigator must take all therapeutic measures necessary for resolution of AE. Any medications necessary for the treatment of an AE must be recorded in the subject's CRF. Refer to Section 7.

6.3.2.2 Medical History

Complete medical history at the pretreatment screening evaluation will include evaluation for past and present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary, substance abuse, surgical history, previous *S. aureus* infections, or any other diseases or

disorders. If any worsening in severity or frequency occurs for an existing condition or a new event occurs after signing of the informed consent, this must be recorded as an AE.

6.3.2.3 Physical Examination

The physical examinations at the pretreatment screening evaluation will be performed by an appropriately qualified individual (eg, physician, nurse practitioner, physician's assistant or equivalent under the supervision of a physician), and will include examination of the following: general appearance; head, ears, eyes, nose, and throat; neck, skin; cardiovascular system; respiratory system; abdominal system; lymphatic system, dermatologic system, musculoskeletal system, and nervous system. Subsequent physical examinations will be abbreviated and symptomatic, largely focused on evaluation of AEs, if any, and any abnormalities identified on the screening examination.

6.3.2.4 Vital Signs

Vital signs assessments will include heart rate (HR), blood pressure (BP), respiratory rate (RR), and body temperature and will be obtained according to the schedule of assessments (Table 1).

6.3.2.5 Electrocardiogram

One ECG will be obtained at the prestudy treatment evaluation. If the QTc is >460 ms (using either the Bazett or Fridericia formula) at the screening ECG, the subject will not be entered into the study. Additional ECGs will be obtained at Week 3, 6, or at the Early Termination visit.

Subject should be withdrawn from treatment if, at any point in the study, the QTc time is >500 ms or if the QTc time is ≥60 ms above baseline (screening ECG).

Any other relevant ECG abnormalities noted at Week 3, 6, or unscheduled ECGs, should be classified as an AE and additional ECGs will be required weekly until the subject discontinues from the study.

If feasible, every effort should be made to obtain duplicates of all ECGs. All original ECGs obtained for each time point (not photocopied) will be held with the study files for analysis in the event that a central reader is required.

6.3.2.6 Laboratory Tests

Blood (for hematology, serum chemistry, CRP, and creatine kinase) and urine (for urinalysis and urine renal biomarkers) should be sent to a central laboratory according to the schedule of assessments (Table 1). Pretreatment screening blood samples for hematology and serum chemistry will also be sent to local laboratory and will be used to determine a subject's eligibility for enrollment.

6.3.2.6.1 Hematology

Hematology tests include the following: hematocrit; hemoglobin; WBC count, including differential count by microscopy with percentage of immature neutrophils (bands), mature neutrophils, and eosinophils; and platelet count.

6.3.2.6.2 Serum Chemistry

Serum chemistry tests include the following: potassium, magnesium, blood urea nitrogen (BUN), creatinine, albumin, total bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), ALT, and AST.

6.3.2.6.3 Additional Serum Creatinine and Creatinine Clearance

Serum creatinine and CrCl will be obtained daily while the subject is hospitalized up to Day 8. Sample will be sent to both the local and central laboratory. After Day 8, or if subject is discharged from the hospital to OPAT or HHC, obtain serum creatinine and creatinine clearance every 2 to 3 days (central laboratory) while on study drug (on the days where the weekly safety lab coincides with the creatinine monitoring, serum creatinine and creatinine clearance will be tested using the weekly safety lab kit).

6.3.2.6.4 Creatine Kinase (CK)

Serum creatine kinase (CK) will be obtained at screening, weekly while on study drug, and at the EOT visit.

6.3.2.6.5 C-Reactive Protein (CRP)

Serum C-reactive protein (CRP) will be obtained at screening, weekly while on study drug, and at the EOT visit.

6.3.2.6.6 Serum Interleukin-10 (IL-10)

Serum IL-10, an anti-inflammatory cytokine, will be obtained at screening, and at the EOT visit.

6.3.2.6.7 Pregnancy Test

For all female subjects, serum and urine β-human chorionic gonadotropin pregnancy tests will be conducted at screening visit, and serum pregnancy test at EOS visit as specified in (Table 1). Subjects may be enrolled into the study on the basis of a negative urine pregnancy test (local laboratory), pending the result of the serum pregnancy test. If the result of the serum test is subsequently positive, study drug must be discontinued, EOT evaluations performed, and an EOS visit scheduled. A urine pregnancy test (local laboratory) will be performed once per month (ie, in subjects treated for 6 weeks) as per local regulatory requirements.

6.3.2.6.8 Urinalysis and Urine Culture

Urinalysis tests include the following: presence of blood, bilirubin, urobilinogen, nitrite, and leukocytes, (if dipstick positive) microscopic examination of sediment; urine creatinine and urine microalbumin; and urine culture. Urine will also be collected for prospective assessment of urine renal biomarkers.

6.3.3 Pharmacokinetic Assessments

Pharmacokinetic (PK) samples will be collected while in the hospital setting and, as feasible, in the outpatient setting, from randomized subjects who receive telavancin or vancomycin. A total of 8 samples will be obtained per subject if no dose adjustment is made and sent to the central laboratory for analysis. For subjects receiving telavancin, an additional 3 samples will be obtained per subject each time a dose adjustment is made within the first two weeks of treatment, due to a change in renal functional classification and sent to the central laboratory for analysis. Samples should be collected from the opposite arm of the infusion site.

The following sample collection time points are relative to the active dose infusion on that day:

From all subjects randomized to receive telavancin, eight blood samples for PK assessment will be obtained as follows:

- On Day 1: At 1 hour (+15 minute window) and between 4 to 8 hours after the start of the infusion.
- On Day 2 prior to start of the infusion (within 30 minutes before dosing).
- On Days 3 and 5: Predose (within 30 minutes before dosing).
- On Day 7: Predose (within 30 minutes before dosing), and between 4 to 8 hours after the start of the infusion.
- On Day 14: Predose (within 30 minutes before dosing).
- As feasible, following each change in telavancin dosing during the first 2 weeks of therapy due to a change in renal function classification.
    - Predose (within 30 minutes before dosing), between 1 to 4 hours after the start of the infusion (sample must be collected following completion of the infusion), and 24 hours post the initial infusion and prior to the start of the next infusion (within 30 minutes before dosing).

      NOTE: These blood samples are in addition to scheduled samples. In the case where the additional sample coincides with a planned time point, then only one sample is to be drawn at that time. Blood samples should be collected at pretreatment and prior to the infusion (trough blood levels) on the day that PK samples are obtained.

From all subjects randomized to receive vancomycin, eight blood samples for PK assessment will be obtained as follows:

- On Day 1: At 1 hour (+15 min window) after the start of the infusion.
- On Day 3: Predose (within 30 minutes before dosing).
- On Day 5: Predose (within 30 minutes before dosing), and at 1, 5, 8, and 12 hours after the start of the infusion (+15 minute window).
- On Day 14: Predose (within 30 minutes before dosing).

For subjects receiving vancomycin, trough levels as determined by the hospital for use in determining the dosing amount will be recorded.

Additional details regarding PK sample collection will be provided in the central laboratory manual.

The following plasma PK parameters may be estimated:

- Time of maximum concentration (T_{max})
- Maximum observed plasma concentration (C_{max})

- Area under the plasma concentration versus time curve from time 0 to the last sample with measurable analyte concentration (AUC_{0-t})
- Area under the concentration versus time curve extrapolated to infinity (AUC_{0-inf})
- Terminal elimination half-life ($t_{1/2}$)
- Plasma clearance (CL_p)
- Volume of distribution at steady-state (Vd_{ss})

Pharmacokinetic parameters will be derived using noncompartmental and nonlinear mixed effect modeling methods, as appropriate.

6.4 Laboratory Test Interference

6.4.1 Coagulation Tests

Although telavancin does not interfere with coagulation, it interferes with certain tests used to monitor coagulation (Table 4), when conducted using samples drawn 0 to 18 hours after telavancin administration for subjects being treated once every 24 hours. Telavancin has the potential to prolong both PT and aPTT in vitro. The effect of telavancin on these coagulation tests is dose-dependent and varies according to the reagents used. The effects of telavancin on PT and aPTT are most likely because of in vitro interference with these assays, and do not reflect alterations in coagulation mechanisms in vivo. An increased bleeding risk has not been observed in toxicology studies or in large-scale clinical trials of telavancin. However, clinicians should be aware of the potential for interference by telavancin with routine coagulation assays resulting in apparent prolongations, specifically the PT and aPTT.

As noted in the FDA-approved prescribing information, use of intravenous unfractionated heparin sodium is contraindicated with telavancin administration because the aPTT test results are expected to be artificially prolonged for 0 to 18 hours after telavancin administration, and patients receiving this form of IV heparin may be in the titration phase where aPTT is obtained frequently until therapeutic levels are reached. However, in a study by Barriere et al. [30], telavancin at trough concentrations was not associated with a potentially significant or consistent increase in aPTT with any of the seven reagents tested. For subjects who require aPTT monitoring while being treated with telavancin, a nonphospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT monitoring may be considered. Blood samples

for coagulation tests affected by telavancin should be collected as close as possible prior to a patient's next dose of telavancin.

Regarding PT prolongation, in the study by Barriere et al. [30], telavancin at trough concentrations was associated with a potentially significant increase in PT with only one (HemosIL PT-Fibrinogen Recombinant) of the 16 reagents tested. Warfarin therapy may be monitored with a functional Factor X assay. As noted in the FDA-approved prescribing information, blood samples for coagulation tests affected by telavancin should be collected as close as possible prior to a patient's next dose of telavancin.

Blood samples for coagulation tests unaffected by telavancin may be collected at any time.

Table 4: Coagulation Tests Affected and Unaffected by Telavancin

Affected by Telavancin	Unaffected by Telavancin
Prothrombin time/international normalized ratio Activated partial thromboplastin time Activated clotting time Coagulation based factor X activity assay	Thrombin time Whole blood (Lee-White) clotting time Platelet aggregation study Chromogenic anti-factor Xa assay Functional (chromogenic) factor X activity assay Bleeding time D-dimer Fibrin degradation products

6.4.2 Urine Protein Tests

Proteinuria may be monitored by available quantitative urine protein assays that are not affected by telavancin (eg, microalbumin).

6.5 Prohibited Concomitant Medications

All concomitant medications administered should be recorded on the case report form.

The following concomitant medications are prohibited (see exclusionary criteria specified in Section 4.2):

- Potentially effective (anti-staphylococcal) non-study systemic antibacterials
- Agents containing cyclodextrin (intravenous itraconazole or voriconazole)
- Other investigational agents
- Intravenous unfractionated heparin sodium (refer to Section 6.4.1)

6.6 Restrictions

Not applicable.

6.7 Discontinuation

6.7.1 Subject Discontinuation

Study drug therapy may be discontinued at any time at the discretion of the investigator and in accordance with his or her clinical judgment. If study therapy is withdrawn, all outcome data should be collected according to the Schedule of Study Procedures (Table 1); subjects must undergo the EOT, post-EOT blood culture, and TOC evaluations (Sections 6.2.5, 6.2.6, and 6.2.7, respectively), including all safety and efficacy assessments, as outlined in the protocol. The Sponsor will be notified of all subject withdrawals.

Reasons for which the investigator or the Sponsor may withdraw a subject from study drug therapy include, but are not limited to, the following:

- AE
- Insufficient therapeutic effect (lack of efficacy) after 72 hours of IV study drug therapy
- Causative pathogen has developed a resistance to the administered study drug and no clinical improvement is observed
- Major violation of the protocol
- Pregnancy
- Need for prohibited concomitant medication
- Need for adjunctive antibiotic therapy or need for rescue antibiotic therapy due to failure to respond to study drug
- Termination of the study by the Sponsor
- Withdrawal of consent (subject's choice)
- Other
- After Day 8, if signs and symptoms lead to a subsequent confirmed diagnosis of new metastatic foci, it will be criteria for clinical failure. Management of the subject (eg, discontinuation of study drug) will be the discretion of the investigator based on his/her standard routine care.

Once a subject is determined to be a clinical failure, all outcome data should be collected according to the Schedule of Study Procedures (Table 1); subjects must undergo the EOT, post-EOT blood culture, and TOC evaluations (Sections 6.2.5, 6.2.6, and 6.2.7,

respectively). Once the subject is classified as failure, the weekly assessments are not mandated unless the subject is still hospitalized. A blood culture obtained after EOT and before TOC is encouraged, but optional for cases of clinical failure.

Any subject (or his or her legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. If a subject withdraws consent, all appropriate outcome and safety assessments at the time of study withdrawal should be obtained if possible. Assessments listed in the Schedule of Study Procedures (Table 1) for the EOT visit and EOS visit should be carried out, as applicable.

Every effort should be made to retain each subject as a participant in the study. If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If a subject withdraws before completing the study, the reason for withdrawal is to be documented on the CRF.

6.7.2 Subject Replacement

Discontinued subjects will not be replaced.

6.7.3 Study Discontinuation

The Sponsor reserves the right to discontinue this study at any time for any reason.

6.8 Pregnancy

If a female subject becomes pregnant during the study, the Sponsor's clinical study director (or designee) must be notified immediately and the subject will be withdrawn from the study. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7 ADVERSE EVENTS

7.1 Regulatory Definition of an Adverse Event

In the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), Section 1.2 defines an AE as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

7.2 Adverse Event Definition for the Purposes of This Study

For the purposes of this clinical study, AE will be defined as follows:

An AE is any untoward medical occurrence in a subject who has signed an informed consent form and is participating in a clinical investigation. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not considered related to the study drug (investigational product).

Preexisting events that increase in frequency or severity or change in nature during or as a consequence of participation in clinical studies will also be considered as AE. An AE may also include pre- or post-treatment complications that occur as a result of a protocol-mandated procedure (such as a biopsy).

Any medical condition or clinically significant laboratory abnormality with an onset date prior to the time the subject signed the informed consent form is considered to be preexisting and should be documented in the medical history CRF, if applicable for the study.

Whenever possible, the diagnosis (rather than a series of terms related to a diagnosis) should be recorded as the AE term.

An AE does not include the following:

- Worsening of the primary infection under study in this protocol (*S. aureus* bacteremia), such as the diagnosis of metastatic foci of *S. aureus* infection (eg, septic pulmonary emboli). These events will be captured in the assessment of clinical signs and symptoms of *S. aureus* bacteremia. EXCEPTION: Death due to progression of *S. aureus* bacteremia will be reported as an SAE.

- Medical or surgical procedures (such as surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an AE
- Preexisting diseases or conditions present or detected before signing an informed consent form that do not worsen
- Situations where an untoward medical occurrence has not occurred (such as hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of either study drug or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation

7.3 Assessment of Adverse Events

All AEs will be assessed by the investigator and recorded in the case report form, including the dates of onset and resolution, severity, relationship to study drug, outcome, and action taken with study drug.

Clinical severity should be recorded and graded using mild, moderate or severe as described below.

Mild = Awareness of signs or symptoms, but easily tolerated

Moderate = Discomfort sufficient to cause interference with usual activities

Severe = Incapacitation with inability to work or perform usual activities

The relationship to study drug therapy should be assessed using the following definitions:

- **Not Related:** Evidence exists that the AE has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Possibly/Probably Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

These criteria in addition to good clinical judgment should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

7.4 Serious Adverse Events

An SAE is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death (including death due to progression of *S. aureus* bacteremia)
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events)
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are as follows:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in hospitalization
    - Development of drug dependency or drug abuse

Additional Considerations for Serious Adverse Events

- Death is an outcome of an AE and not an AE in itself. In reports of death due to disease progression, where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study drug(s).
- All deaths, regardless of cause, must be reported for subjects if the death occurs while the subject is participating in the study.
- “Occurring at any dose” does not imply that the subject is receiving study drug at the time of the event; dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- “Life-threatening” means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- “Inpatient hospitalization” means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

- The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

7.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Abnormal laboratory findings (such as clinical chemistry, hematology, or urinalysis) or other abnormal assessments (such as X-rays or vital signs) that are associated with signs and/or symptoms or are considered clinically significant in the judgment of the investigator must be recorded as AEs or SAEs if they meet the definition of an AE (or SAE), as described in Sections 7.2 (Adverse Event Definition for the Purposes of This Study) and 7.4 (Serious Adverse Events).

If there are any AE questions, the investigator is encouraged to contact the Sponsor to discuss.

7.6 Serious Adverse Event Reporting

Any SAE that occurs after a subject signs an informed consent form through the End-of-Study (TOC visit) (or at the time a subject is determined to be ineligible to continue participation in the study, or who does not enroll in the study), regardless of causal relationship, must be reported to the Sponsor within 24 hours of the investigator's knowledge of the event. To report an SAE, complete and fax the SAE Report Form to the following:

Theravance Biopharma US, Inc. Clinical Drug Safety

Email: 0112_safety@theravance.com

For medical questions regarding an SAE, contact the Sponsor's medical monitor (or designee) by telephone as follows:

Medical Monitor Contact Information:

Gino Girardi, MD
Lead Medical Monitor, North America and Latin America
INC Research
Cell: +1 (919) 418-5164

Krzysztof Kacik, MD
Medical Monitor, Europe
INC Research
Office: + 48126462570
Cell: + 48602648836

For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents when requested. Additional information may be requested from the investigator to ensure the timely completion of accurate safety reports.

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the study drug and is unexpected/unlisted based on the current IB. In this case, all investigators will receive notification of the event. The investigator is responsible for notifying the Institutional Review Board or Ethics Committee and documenting the notification, as required by local regulatory authorities and in accordance with the local institutional policy.

7.7 Adverse Event Follow-up

A subject experiencing an AE or SAE will be followed by the investigator or his/her trained delegate(s) through the TOC visit or until the investigator and/or the Sponsor has determined that the AE or SAE has resolved or a stable clinical endpoint is reached, whichever is longer. The Sponsor may request follow-up of certain AE until resolution and documentation of assessments made during this period.

The investigator must take all therapeutic measures necessary for resolution of an SAE. Any medications necessary for the treatment of the SAE must be recorded in the concomitant medication section of the case report form.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size and Power

Assuming a population clinical cure rate of 70% for standard IV therapy and 72.5% for telavancin, a total sample size of 210 (105 per treatment group) is deemed sufficient (80% power) to demonstrate noninferiority based on a noninferiority margin of 15% at a one-sided significance level of 2.5%. This calculation does not take into account potential stopping for futility at the interim analysis. A total of 248 subjects will be enrolled to allow for exclusion of up to 15% of subjects from the primary analysis set due to an LIE diagnosis or not meeting the mAT population criteria.

8.2 General Considerations

All individual data will be listed as measured. All statistical summaries and analyses will be performed using SAS software (SAS Institute, Cary, North Carolina, USA).

Continuous data will be summarized using an 8-point descriptive summary (n, mean, standard deviation, median, interquartile range (IQR) [25% quartile, 75% quartile]), minimum and maximum unless otherwise stated. Categorical data will be summarized using the frequency of events and percentage of total events.

Any changes to the protocol-specified analyses will be pre-specified in the SAP prior to database lock.

8.3 Analysis Populations

Specific criteria for subject evaluability will be outlined in the SAP and, when applicable, programmatically applied.

8.3.1 Efficacy Analysis Populations

The AT population is defined as all randomized subjects who have received at least one dose of study drug and were enrolled after protocol Amendment 1. Subjects enrolled prior to Protocol Amendment 1 will be excluded from all efficacy analyses, because the dose of telavancin was decreased following Protocol Amendment 1. Analyses conducted based on the AT population will assign subjects according to their randomized treatments.

The mAT population includes subjects in the AT population who have a mono-microbial QBC positive for *S. aureus*.

The mAT subjects with a diagnosis of UCB, CB, or RIE will constitute the primary analysis population for efficacy.

The ME population is a subset of the mAT population and includes subjects who meet the following criteria:

1. Completed at least 80% of prescribed study medication for their baseline diagnosis
2. Did not miss more than 2 consecutive doses of study medication
3. Completed the TOC visit
4. Did not have any recorded major protocol deviations
5. If assessed as failure at TOC, received at least 2 days of study medication
6. If assessed as cure at TOC, received at least 5 days of study medication
7. Did not receive any prohibited concomitant, potentially effective antibiotic (other than study medication)

8.3.2 Safety Analysis Population

The safety population will be defined as all subjects from the AT population and subject assignment according to actual study treatments they receive.

8.3.3 Pharmacokinetic Analysis Population

The PK population will be defined as all subjects from the safety population who provide evaluable PK data from at least one postdose sample in plasma.

8.3.4 Examination of Subgroups

Additional efficacy evaluations, conducted for the primary and secondary efficacy endpoints, will include subset analyses by vancomycin MIC values (eg, MIC ≤1, or MIC >1), and by infection type (eg, UCB, CB, RIE and LIE).

In addition, evaluation of the primary and key secondary endpoints may be performed for the following subgroups/factors:

- Infection with MRSA
- Infection with MSSA
- Presence or absence of diabetes
- Subgroups defined by baseline renal function, as determined by baseline creatinine clearance
- Baseline modified APACHE II score (chronic health assessment not included in modified score)
- Subject age
- Geographic region

Details of subset analyses will be defined in the SAP. Subset analyses will proceed if it is deemed that a sufficient number of subjects are available to render a meaningful summary.

8.4 Analyses

8.4.1 Disposition, Demographics, Baseline Characteristics, and Exposure

Summaries will present, by treatment group, the number of subjects randomized; the number in each population; the number completing and discontinuing early from study; the reason for termination from study; race, age, sex, and baseline clinical characteristics; the number of days of study drug dosing, and reason for final discontinuation of study drug.

For analyses of demographics and other baseline characteristics, the mAT, ME, and safety populations will be prepared in separate tables.

8.4.2 Analysis of Efficacy

The primary efficacy endpoint is clinical outcome at the TOC visit (See Section 3.4.2). Specifically, clinical cure rate, defined as proportion of subjects with the clinical outcome of success, at TOC will be evaluated. The primary efficacy endpoint will be determined by the investigator and adjudicated by the IEAC blinded to treatment assignments.

In order to evaluate secondary efficacy endpoints described in Section 3.4.3, clinical cure rate at EOT, proportion of subjects with new metastatic loci of infection, and duration of treatment with study medication will be derived.

In addition, analyses evaluating evidence of treatment-emergent resistance to telavancin, vancomycin, daptomycin, anti-staphylococcal PCNs, or cefazolin may be conducted.

Exploratory analyses will be conducted to assess a variety of health utilization variables. Methods of analysis for these variables will be outlined in a separate HEOR SAP. The results of these analyses will be presented separately and not included in the clinical study report (CSR).

The primary analysis will be to first test the hypothesis of telavancin's clinical noninferiority to standard therapy, employing a noninferiority margin (the "Δ") of 15 percentage points on the difference of proportions scale, in the mAT subjects with a diagnosis of UCB, CB, or RIE. The null hypothesis is that telavancin is clinically inferior to standard therapy, where "clinically inferior" is defined as having a population clinical cure rate that is 15 percentage points (or more) lower than that for standard IV therapy. The alternative hypothesis is that telavancin is at least clinically noninferior to standard IV therapy, where "clinical noninferiority" is defined as having population clinical cure rates that differ by less than 15 percentage points. Expressed symbolically, the null hypothesis (H_0) and the alternative hypothesis (H_1) are as follows:

H_0: $\pi_{TLV} - \pi_{STD} \leq -15\%$

H_1: $\pi_{TLV} - \pi_{STD} > -15\%$

where π_{TLV} and π_{STD} denote the population clinical cure rates of telavancin and standard IV therapy, respectively.

Final testing will be conducted at a one-sided 2.5% significance level. Testing will be implemented by the construction of a two-sided 95% confidence interval (CI) on the treatment difference, $\pi_{TLV} - \pi_{STD}$.

If the lower confidence limit (CL_{LOWER}) is less than or equal to -15%, then the null hypothesis of inferiority will not be rejected. If $CL_{LOWER} > -15\%$, then the null hypothesis of clinical inferiority will be rejected in favor of the alternative hypothesis of clinical noninferiority.

If the above analysis concludes that telavancin is clinically noninferior to standard IV therapy, then a test for superiority will be conducted. The superiority analysis is to test the null hypothesis that telavancin is the same as (or worse than) standard IV therapy, against the alternative hypothesis that telavancin is superior to standard therapy, in the mAT subjects with a diagnosis of UCB, CB, or RIE. Expressed symbolically, the null and alternative hypotheses were as follows:

H_0: $\pi_{TLV} - \pi_{STD} \leq 0$

H_1: $\pi_{TLV} - \pi_{STD} > 0$

If the CL_{LOWER} of the previously described CI is zero or less, then the null hypothesis will not be rejected. If CL_{LOWER} is greater than zero, then the null hypothesis will be rejected in favor of the alternative hypothesis of superiority.

By the close-testing principle, no adjustment on the Type I error rate will be necessary for performing the noninferiority and superiority tests sequentially, because the two null hypotheses constitute a closed family, and the hypothesis of clinical inferiority (H0: $\pi_{TLV} - \pi_{STD} \leq -15\%$) implies the hypothesis of nonsuperiority (H0: $\pi_{TLV} - \pi_{STD} \leq 0$).

For the primary efficacy analysis, the point estimate and CI for the treatment difference will be calculated using the normal approximation to the binomial distribution without continuity correction. If any cell size is less than 10, as might have occurred during a subgroup analysis, the CI will be calculated using the method of Agresti and Caffo [31] to adjust for the sparse cell size.

Analysis of other endpoints focusing on incidence of occurrence (eg, development of new metastatic foci of infection) will be similar to the primary analysis of clinical outcome previously described.

Time-to-event endpoints, including 28-day all-cause mortality and time to two successive negative blood cultures, will be reported graphically using Kaplan-Meier survival curves and, as appropriate, treatment differences will be evaluated using log-rank tests, stratified by geographic region.

Additional supportive or exploratory analyses of the AT, mAT, ME, and safety populations will be described in the SAP.

8.4.3 Analysis of Safety

All safety endpoints will be evaluated for the safety population as defined in Section 8.3.2.

Unless specified otherwise, safety assessments will be summarized descriptively by treatment group. Safety endpoints to be summarized include vital signs, AE, clinical laboratory results (hematology, chemistry, and urinalysis).

Treatment-emergent AEs are defined as AE with onset on or after initiation of study drug. The number and percentage of subjects reporting TEAEs will be tabulated by Medical Dictionary for Regulatory Activities system organ class and preferred term, severity, and relationship to study drug. Serious TEAEs and TEAEs resulting in discontinuation of study drug will be summarized separately.

Additional summaries of AEs of special interest (eg, renal injury) may be prepared.

Concomitant medications will be mapped using the WHODRUG dictionary. The number and percentage of subjects taking each concomitant medication will be tabulated. Separate summaries of prior and concomitant antibiotics will be prepared.

Subject eligibility for enrollment will be made based on laboratory results performed at the study centers. Analysis of laboratory results will be based on those reported by the Central Laboratory. Continuous laboratory measurements will be descriptively summarized for observed values and changes from baseline. Categorical laboratory measurements will be summarized by the number and percentage of subjects with low, normal and high values. A shift table of laboratory measurements comparing pre- and post-treatment values relative to normal ranges (for example, normal to low, normal to normal, or normal to high) will also be summarized. Listing of laboratory results will flag values that are outside of normal range. Vital signs parameters will be summarized for observed values and changes from baseline.

8.5 Analysis of Pharmacokinetics

For subjects who receive telavancin or vancomycin and have at least one post-dose PK sample collected, plasma concentration profiles will be estimated.

Summary statistics for plasma telavancin and vancomycin concentrations (mean, standard deviation, median, minimum, maximum, number of subjects, and coefficient of variation) will be calculated for each predose time point.

For subjects with at least one post-dose PK sample collected, telavancin plasma concentration-time profiles will be estimated. Estimated PK parameters may include the following: T_{max}, C_{max}, $AUC_{o\text{-}t}$, $AUC_{o\text{-}inf}$, $t_{1/2}$, CL_p, and Vd_{ss}.

Noncompartmental and nonlinear mixed-effects modeling methods will be used for determination of PK parameters, as appropriate. All PK parameters will be presented as

individual listings and as summary statistics (mean, geometric mean, median, range, standard deviation, coefficient of variation, minimum, maximum, and number of subjects).

Plasma concentration data may also be analyzed using non-linear mixed effects PK modeling techniques. The following covariates will be obtained for each subject: height, weight, body surface area (BSA), body mass index (BMI), age, sex, and relevant laboratory tests that reflect the function of organs responsible for drug elimination. The relationship between these parameters and PK of the drug of interest will be examined using suitable statistical techniques and study designs. Reporting of any population PK analysis from this study will be reported separately.

8.6 Handling of Missing Data

Estimates of event rates (eg, the clinical cure rate) will be calculated relative to the number of subjects in the given analysis population. For example, any patient in the analysis population with an “indeterminate” or missing value for clinical outcome will be counted in the denominator when calculating clinical cure rate.

8.7 Multiple Testing: Order of Hypotheses

The primary analysis will test both clinical noninferiority and superiority of telavancin relative to standard IV therapy in the treatment of *S. aureus* bacteremia and SA-RIE. Both tests will be conducted at a one-sided 2.5% significance level. No adjustment of the Type I error rate is necessary for conducting these two tests sequentially as the process is supported by the closed-testing principle.

Secondary analysis hypotheses will be tested in hierarchical order at the two-sided 5% level of significance until a failure to reject occurs.

For all supportive analyses of the primary efficacy endpoint and secondary efficacy endpoints, p-values and confidence intervals will be reported at the two-sided 5% level, with no adjustment for multiplicity.

8.8 Interim Analysis

A single interim assessment allowing early stopping for futility will be conducted by the IDMC (see Section 8.10) based on the subjects who completed or discontinued from the study on or before October 31, 2017.

Conditional power to show non-inferiority under the current trend will be computed using the normal approximation to the non-inferiority test statistic.

The IDMC may recommend stopping for futility, if the conditional power is 50% or less. With this futility analysis, the overall power of the study is approximately 64%. Conditional power of 50% or less would be associated with the negative point estimate of the treatment difference $\pi_{TLV} - \pi_{STD}$.

Furthermore, the IDMC may recommend stopping the study if the point estimate of the treatment difference, $\pi_{TLV} - \pi_{STD}$ in the subset of subjects with CB or RIE is not positive.

8.9 Independent Efficacy Adjudication Committee

A blinded IEAC of clinical experts will review the data from each subject to establish the 1) classification of infection type, and 2) clinical outcome at TOC, on an on-going basis. The committee will perform adjudication of efficacy events without having access to the subjects' treatment assignments. A separate charter describes the blinding plan and the adjudication committee's activities.

8.10 Independent Data Monitoring Committee

An unblinded IDMC will act in an advisory capacity to the Sponsor to monitor subject safety and the efficacy of the study drug. The IDMC responsibilities will be defined in a charter and are as follows:

- Review the following documents before commencing activities as a IDMC: draft IDMC charter, investigator brochure, study protocols, blank informed consent form, blank case report forms and mockups of proposed data presentations
- Evaluate the progress of the study; timeliness and quality of the data; subject recruitment, accrual, and retention; risk versus benefit to subjects; and other factors that might affect the outcome of the study
- Consider relevant information that may have an impact on subject safety or the ethics of the study
- Make recommendations to the Sponsor concerning continuation, termination, or other modifications to the study based on their observations of the study and its data
- Conduct a review of interim analysis of safety and efficacy

A full IDMC charter will be prepared to govern the activities of the committee.

9 STUDY ADMINISTRATION

This study will be conducted in compliance with all applicable regulations.

9.1 Principal Investigator Responsibilities

Before beginning the study, the principal investigator (PI) at each site must provide to the Sponsor or its designee a fully executed and signed Form FDA 1572 and, if applicable, a financial disclosure form. For applicable studies, financial disclosure forms must also be completed for all subinvestigators who will be directly involved in the treatment or evaluation of research subjects in this study. (A subinvestigator is defined in ICH E6 as any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions [eg, associates, residents, research fellows].)

The PI will ensure the following:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- He or she will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- He or she has read and understands the information in the VIBATIV® (telavancin) Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments.
- If subjects are discharged to an OPAT facility or HHC agency, he or she will provide appropriate oversight and proper documentation of IP transfer, patient care, AE/SAE reporting, IRB approval for the use of OPAT or HHC agency and the proper documentation/approval of such use in the ICF
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC complies with the requirements of 21 CFR Part 56, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are

reported to the IRB/IEC. Additionally, he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

9.2 Institutional Review Board/Independent Ethics Committee

Before beginning study-specific research, the investigator will obtain written confirmation that the IRB, IEC, or Research Ethics Board (REB) is properly constituted and compliant with ICH and GCP requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to the Sponsor or its designee. The protocol, informed consent form (ICF), IB, use of OPAT or HHC agency, and any other appropriate written information provided to the subjects that the IRB/IEC/REB may require to fulfill its responsibilities will be submitted to the IRB/IEC/REB in advance of the study. The Sponsor or its designee must approve the ICF and all subject recruitment materials before they are submitted to the IRB/IEC/REB. The study will not proceed until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol and the ICF are obtained by the investigator and copies are received by the Sponsor or its designee. If possible, the approval document should refer to the study by study protocol title and the Sponsor's study number, identify the documents reviewed, and include the date of the review and approval. The written approval of the IRB/IEC/REB will be retained as part of the study file. The study may proceed before approval of consent forms and other study documents translated to a language other than the native language of the clinical site, provided that written IRB/IEC/REB approval of the translated documents is obtained before they are used. Any amendments to the protocol should be reviewed promptly.

The investigator must provide the appropriate periodic reports on the progress of the study to the IRB/IEC/REB and the Sponsor in accordance with local IRB/IEC/REB requirements and applicable governmental regulations, whichever is strictest.

9.3 Informed Consent

A properly written and executed ICF, in compliance with ICH E6 (GCP Guideline, Section 4.8), 21 CFR §50, and other applicable local regulations, will be obtained for each subject before enrollment of the subject into the study. The investigator will prepare the ICF or revise the template ICF and provide the documents to the Sponsor (or designee) for

approval before submission to the IRB/IEC/REB. The Sponsor and the IRB/IEC/REB must approve the documents before they are implemented.

If a legally authorized representative (LAR) provides informed consent on behalf of the subject, documentation will also be required to indicate the relationship of the LAR to the subject.

The investigator will provide copies of the signed ICF to each subject (or the subject's legally authorized representative) and will maintain the original in the subject's record file.

9.4 Data Recording and Quality Assurance

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used.

Electronic data capture (EDC) technology will be used for this study. All clinical information requested in this protocol will be recorded on the electronic case report forms approved by the Sponsor, or via other data collection methods, eg, electronic laboratory data transfer. Study site personnel will enter (in English) study data into the CRFs for each randomized subject. Training on the EDC application will be completed and documented before access to the EDC system is given.

In the event of a CRF data change (eg, correction of an error or addition of new information), corrections will be made to the CRF. Corrections to the CRFs, including the reason for change, will be automatically documented through the EDC system's audit trail.

The investigator is responsible for reviewing all CRFs, verifying them for accuracy, and approving them via an electronic signature. The investigator is designated as the signatory coordinating investigator.

An electronic copy of the CRF casebooks will be sent to the site for retention with other study documents after full completion of the study, ie, after database lock.

The investigator is responsible for maintaining accurate, authentic, complete, and up-to-date records for each subject. The investigator is also responsible for ensuring the availability of any original source documentation related to the study (including any films, tracings,

computer discs, tapes, and worksheets). In most cases the source is the subject's medical record. Data collected on the CRFs must match the source documents.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded in the CRF and for which the CRF will stand as the source document.

9.5 Document Retention

Until otherwise notified by the Sponsor, an investigative site must retain in a controlled manner all study documents required by the Sponsor and by the applicable regulations. The investigative site must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (eg, subject charts) and any original source documents that are electronic, as required by applicable regulations.

The investigator must consult a Sponsor representative before disposal of any study records and must notify the Sponsor of any change in the location or disposition of the study files. If an investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study documents, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian and must approve this transfer of responsibility.

9.6 Confidentiality

The investigator or designee must explain to each subject, before enrollment into the study, that, for evaluation of study results, the subject's confidential medical information obtained during the study may be shared with the study sponsor, regulatory agencies, and the institutional review board (IRB) or independent ethics committee (IEC). The investigator (or designee) is responsible for obtaining written permission to use confidential medical information in accordance with country-specific regulations (such as the Health Insurance Portability and Accountability Act in the United States) from each subject or, if appropriate, the subject's legally authorized representative. If permission to use confidential medical information is withdrawn, the investigator is responsible for documenting that no further data from the subject will be collected.

Subject medical information obtained during this study is confidential, and disclosure to unauthorized third parties is prohibited. The pertinent sections of data protection laws will be complied with in full. Study records containing subject information will only be identified by the subject identification number, subject initials, date of birth, and study number, and not by the subject's full name, except the subject consent form, which is archived at the study center only. The subject's name will not be used in any public report of the study.

During the course of the study, a confidential subject identification list will be maintained by the investigator and archived at the investigative site.

Before and during the conduct of the study, no study-related details may be disclosed, ie, placed on the internet, published, or otherwise publicized, or provided to a third party without prior written permission from the Sponsor. The policy for publication of data after completion of the study is described in Section 9.10 (Publication).

9.7 Access to Data and Documents

Upon receipt of the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Study data recorded on the CRFs must be verifiable to the source data. All original recordings, laboratory reports, and subject records generated by this study must be available to the Sponsor, representatives of the Sponsor, the IRB/IEC/REB, and applicable regulatory authorities, and they may be used for submission to regulatory authorities. In addition, all source data should be attributable (signed and dated), consistent with local medical practice. The investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representatives) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent.

9.8 Quality Control: Study Monitoring and Auditing

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP and standard operating procedures (SOPs) for compliance with applicable government regulations. The investigator agrees to allow these monitors direct access to the clinical data and supplies, dispensing, and storage areas and, if requested, agrees to assist the monitors. The investigator and staff are responsible for being present or

available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Members of the Sponsor's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA or other Regulatory Agencies, including IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the investigator should notify the Sponsor immediately. The investigator will ensure that the auditors have access to the clinical supplies, study site facilities, laboratory and all data (including original source documentation) and all study files are available, if requested.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an investigator, institution, institution staff, or representatives of the Sponsor will lead to prompt action by the Sponsor to secure compliance. Continued noncompliance may result in termination of the investigator's involvement in the study. The IRB/IEC/REB and relevant regulatory authority will be informed.

9.9 End of Study

For each participating European Union (EU) country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last patient for all centers in the respective country has occurred.

9.10 Publication

The Sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and presentation at seminars or conferences. The Sponsor will retain the ownership of the data collected in this study. The investigator will provide any proposed manuscript or abstract to the Sponsor before submission for publication or presentation of any results or data obtained in this study.

Additional details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Trial Agreement between the Sponsor and the investigator.

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11 APPENDICES

Appendix 1: Modified Duke Criteria for Endocarditis

Definition of infective endocarditis (IE) according to the proposed modified Duke criteria [24]:

Definite infective endocarditis

A. Pathologic criteria:
   (1) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
   (2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

B. Clinical criteria:[a]
   (1) 2 major criteria; or
   (2) 1 major criterion and 3 minor criteria; or
   (3) 5 minor criteria

Possible infective endocarditis

(1) 1 major criterion and 1 minor criterion; or
(2) 3 minor criteria

Rejected

(1) Firm alternate diagnosis explaining evidence of infective endocarditis; or
(2) Resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days; or
(3) No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days; or
(4) Does not meet criteria for possible infective endocarditis, as above

[a] See following table for definitions of major and minor criteria.

A. Major criteria

(1) Blood culture positive for IE

(2) Typical microorganisms consistent with IE from 2 separate blood cultures:
- Viridans streptococci, *Streptococcus bovis,* HACEK group, *Staphylococcus aureus;* or
- Community-acquired enterococci, in the absence of a primary focus; or
- Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
  - At least 2 positive cultures of blood samples drawn >12 h apart; or
  - All of 3 or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least 1 h apart)

(3) Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800

(4) Evidence of endocardial involvement

(5) Echocardiogram positive for IE defined as follows:
- Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
- Abscess; or
- New partial dehiscence of prosthetic valve

(6) New valvular regurgitation confirmed by echocardiogram

B. Minor criteria

(1) Predisposition, predisposing heart condition or injection drug use

(2) Fever, temperature >38°C

(3) Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions

(4) Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor

(5) Microbiological evidence: positive blood culture but does not meet a major criterion as noted above[b] or serological evidence of active infection with organism consistent with IE

[b] Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.

Appendix 2: Child-Turcotte-Pugh Chronic Liver Disease Score

Scoring for Child-Turcotte-Pugh classification of severity of cirrhosis [32]:

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/liter)	2 to 3 mg/dL (34.2 to 51.3 micromol/liter)	>3 mg/dL (>51.3 micromol/liter)
Albumin	>3.5 g/dL (35 g/liter)	2.8 to 3.5 g/dL (28 to 35 g/liter)	<2.8 g/dL (<28 g/liter)
Prothrombin time			
Seconds over control	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Liver Disease Classification by Total Child-Pugh Score:

- Mild liver disease: Childs-Pugh Score A (5-6)
- Moderate liver disease: Childs-Pugh Score B (7-9)
- Severe liver disease: Childs-Pugh Score C (10-15)

Appendix 3: RIFLE Criteria for Acute Kidney Injury

RIFLE is an acronym of Risk, Injury, and Failure; and Loss; and End-stage kidney disease. The RIFLE criteria consists of three graded levels of kidney dysfunction (Risk, Injury, and Failure), based upon either the magnitude of increase in serum creatinine or urine output, and two outcome measures (Loss and End-stage renal disease [ESRD]) [33].

Stage	GFR[a] Criteria	UO[b] Criteria
Stage 1: Risk	SCr[c] increased 1.5-2 times baseline or GFR decreased >25%	UO < 0.5 mL/kg/h < 6 h
Stage 2: Injury	SCr increased 2-3 times baseline or GFR decreased >50%	UO < 0.5 mL/kg/h >12 h
Stage 3: Failure	SCr increased >3 times baseline or GFR decreased 75% or SCr ≥4 mg/dL; acute rise ≥0.5 mg/dL	UO < 0.3 mL/kg/h 24 h (oliguria) or anuria 12 h
Loss of function	Persistent acute renal failure: complete loss of kidney function >4 weeks (requiring dialysis)	
ESRD[d]	Complete loss of kidney function >3 months (requiring dialysis)	

[a] GFR = glomerular filtration rate.

[b] UO = urine output.

[c] SCr = serum creatinine.

[d] ESRD = end-stage renal disease.

Appendix 4: APACHE II Assessment Criteria

The Acute Physiologic and Chronic Health Evaluation (APACHE) scoring system requires the input of many clinical variables, from which a severity score is derived [34]. The resulting severity score is entered into a logistical regression equation, which predicts hospital mortality.

The APACHE II Severity of Disease Classification System:

Physiologic Variable	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature – rectal (°C)	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
Mean Arterial Pressure (mm Hg)	≥160	130-159	110-129		70-109		50-69		≤49
Heart Rate	≥180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory Rate (non-ventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation (mm Hg) a. Fio_2 >0.5 use A-aDO_2 b. Fio_2 <0.5 us Pao_2	a ≥500	350-499	200-349		<200				
	b				>70	61-70		55-60	<55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum Sodium (mmol/l)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum Potassium (mmol/l)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum Creatinine (mg/dl, Double point score for acute renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	45-49.9	30-45.9		20-29.9		<20
White Blood Count (in 1000/mm^3)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow-Coma-Scale (GCS)	Score = 15 minus actual GCS								
Serum HCO_3 (venous, mmol/l, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15
A = Total Acute Physiology Score APS	Sum of the 12 individual variable points								
B = Age Points ≤44 years 0 points 45-54 years 2 points 55-64 years 3 points 65-74 years 5 points ≥75 years 6 points	**C = Chronic Health Points** If the patient has a history of severe organ system insufficiency or is immunocompromised, assign points as follows: a. For non-operative or emergency postoperative patients – 5 points b. For elective postoperative patients – 2 points								
APACHE II Score = Sum of A (APS points) + B (Age points) + C (Chronic Health points)									