Dalbavancin as an Option for Treatment of *S. aureus* Bacteremia (DOTS): A Phase 2b, Multicenter, Randomized, Open-Label, Assessor-Blinded Superiority Study to Compare the Efficacy and Safety of Dalbavancin to Standard of Care Antibiotic Therapy for the Completion of Treatment of Patients with Complicated *S. aureus* Bacteremia

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STATEMENT OF ASSURANCE

Each Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protections (OHRP) for federally-funded human subjects research. Each FWA will designate at least one Institutional Review Board (IRB)/Independent Ethics Committee (IEC) registered with OHRP, for which the research will be reviewed and approved by the IRB/IEC and will be subject to continuing review [45 CFR 46.103(b)]. The IRB/IEC designated under an FWA may include an institution's IRB/IEC, an independent IRB/IEC, or an IRB/IEC of another institution after establishing a written agreement with that other institution.

STATEMENT OF COMPLIANCE

The study trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
- International Conference on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
- Applicable Federal, State, and Local Regulations and Guidance

SIGNATURE PAGE

The signature below provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6 Good Clinical Practice (GCP) guidelines.

I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining the sponsor's approval and IRB/IEC approval, except when necessary to protect the safety, rights, or welfare of subjects.

Site Investigator Signature:

Signed: _____ Date: _____

Name

Title

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADL	Activity of Daily Living
AE	Adverse Event/Adverse Experience
AESI	Adverse Events of Special Interest
AUC	Area Under Curve
CNS	Central Nervous System
CE	Clinically Evaluable
CFR	Code of Federal Regulations
CI	Confidence Interval
CMS	Clinical Material Services
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DILI	Drug-Induced Liver Injury
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DOOR	Desirability of Outcome Ranking
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HEOR	Health Economics and Outcomes Research
HLGT	High Level Group Term

HIPAA	Health Insurance Portability and Accountability Act
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IE	Infective Endocarditis
IEC	Independent or Institutional Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
MedDRA®	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
mITT	Modified Intent to Treat
MM	Medical Monitor
MOP	Manual of Procedures
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
N	Number (typically refers to subjects)
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PCS	Potentially Clinically Significant
PID	Patient Identification
PD	Pharmacodynamic
PHI	Protected Health Information
PI	Principal Investigator

PK	Pharmacokinetics
PWID	Persons Who Inject Drugs
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
SAE	Serious Adverse Event/Serious Adverse Experience
SUSAR	Suspected Unexpected Serious Adverse Reaction
SD	Standard Deviation
SOC	Standard of Care
TOC	Test of Cure
ULN	Upper Limit of Normal
US	United States

PROTOCOL SUMMARY

Title:	Dalbavancin as an Option for Treatment of *S. aureus* Bacteremia (DOTS): A Phase 2b, Multicenter, Randomized, Open-Label, Assessor-Blinded Superiority Study to Compare the Efficacy and Safety of Dalbavancin to Standard of Care Antibiotic Therapy for the Completion of Treatment of Patients with Complicated *S. aureus* Bacteremia
Design of the Study:	Multicenter, randomized, open-label, assessor-blinded, superiority, active-controlled, parallel-group study
Study Phase:	2b
Study Population:	200 adult subjects (≥ 18 years old) diagnosed with complicated *S. aureus* bacteremia including definite or possible right-sided infective endocarditis (IE) treated with effective antibiotic therapy for at least 72 hours (maximum 10 days) and with subsequent clearance of bacteremia prior to randomization to study treatment
Number of Sites:	Approximately 20
Description of Study Product or Intervention:	• Dalbavancin 1500 mg intravenously (IV) over 30 (± 10) minutes on Day 1 and 1500 mg intravenously (IV) over 30 (± 10) minutes on Day 8 (if creatinine clearance ≥ 30 mL/min or if on regular hemodialysis or peritoneal dialysis) • Dalbavancin 1125 mg IV over 30 (±10) minutes on Day 1 and Dalbavancin 1125 mg IV over 30 (±10) minutes on Day 8 (if creatinine clearance < 30 mL/min and not receiving regular hemodialysis or peritoneal dialysis)
Study Objectives:	Primary:

- To compare the Desirability of Outcome Ranking (DOOR) at Day 70 of dalbavancin to that of standard of care antibiotic therapy used to consolidate therapy for the treatment of subjects with complicated *S. aureus* bacteremia in the intent-to-treat (ITT) population.

Secondary:

- To compare the clinical outcomes of dalbavancin with the standard of care antibiotic therapy at day 70 in the modified intent-to-treat (mITT) population.
- To compare the safety of dalbavancin with that of the standard of care treatment in the mITT.
- To compare each individual component of the DOOR outcome by treatment arm, in the ITT population.

Exploratory:

- To compare the clinical outcomes of dalbavancin with the standard of care antibiotic therapy at day 70 in the clinically evaluable (CE) population.
- To compare the DOOR endpoint of subjects on dalbavancin with that of subjects receiving standard of care antimicrobial therapy at day 42 in the ITT, mITT, and CE populations.
- To compare the clinical and microbiologic outcomes of dalbavancin with the standard of care antibiotic therapy at day 42 in ITT, mITT and CE populations.
- To compare clinical and microbiologic outcomes of dalbavancin with standard of care antibiotic therapy between clinically important subgroups, including a) those with MSSA versus MRSA; b) persons who inject drugs (PWID) vs non-PWID; c) those who received infectious disease consultation vs those who did not; d) underlying site of infection (endovascular, bone and joint, skin, pulmonary); e)

subjects with immune-suppression[1]; f) divided by duration of initial bacteremia in the ITT, mITT, and CE populations

- To compare Quality of Life (QoL) of subjects on dalbavancin with that of subjects receiving standard of care antibiotic therapy at Baseline, Day 42, and Day 70, in the ITT, mITT, and CE populations
- To characterize the population pharmacokinetic profile for dalbavancin administered via a 2-dose regimen (1500 mg on day 1 and day 8, renally adjusted when appropriate) in patients with *Staphylococcus aureus* bacteremia
- To assess patient-level and clinical covariates associated with dalbavancin pharmacokinetics in patients with *Staphylococcus aureus* bacteremia
- Examine the association between individualized plasma concentration profiles and clinical and microbiologic outcomes at day 42 and TOC
- Examine the association between individualized plasma concentration profiles and occurrence of adverse drug events, including AST/ALT elevations >3X upper limit of normal
- Examine the association between individualized plasma concentration profiles and late recurrence risk among the subset of patients with osteomyelitis and a 6 month follow-up visit

Duration of Individual Subject Participation:

Approximately 70 ± 7 days, with a late post-treatment follow-up visit for the subset of patients with osteomyelitis at 6 months

[1] Defined as: On chemotherapy or immunotherapy for active hematologic malignancy expected to cause ANC < 500 cells/mm^3 lasting > 7 days during the study period, chronic high dose oral steroids (equivalent of ≥ 20 mg prednisolone per day for or equivalent, for >2 weeks within the last month), HIV infection with a CD4 cell count < 100 cells/mm^3 based on last known measurement or patient-reported value

Estimated Time to Last Subject/Last Study Day:	Approximately 30 months, from site activation to the last subject's last study day.

Table 1: Treatment Arms

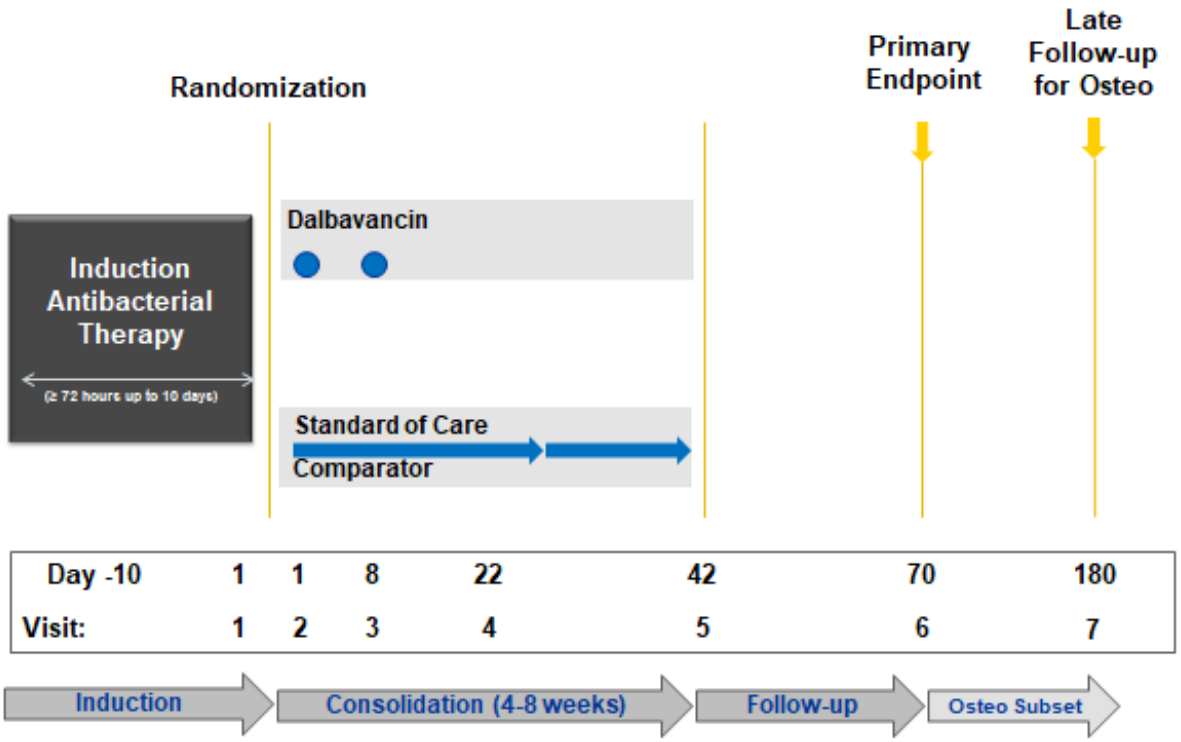
Dalbavancin	100 subjects	Dalbavancin 1500 mg IV over 30 (± 10) minutes on Day 1 and 1500 mg IV over 30 (± 10) minutes on Day 8, renally dose-adjusted to 1125 mg for subjects with CrCl <30 and not on dialysis
Standard of Care[a]	100 subjects	• Methicillin-sensitive *Staphylococcus aureus* (MSSA): nafcillin (2 g IV q4h × 4-6 weeks)[b] OR oxacillin (2 g IV Q4h x 4-6 weeks)[b] OR cefazolin (2 g IV q8h × 4-6 weeks) [b,c] • Methicillin-resistant *Staphylococcus aureus* (MRSA): vancomycin (dose per local standard of care × 4-6 weeks) OR daptomycin (6-10 mg/kg IV daily × 4-6 weeks)[c]

[a]Renally dose-adjusted as appropriate, per local standard of care

[b]As applicable per site standard of care, beta-lactams may be administered at an equivalent dose via continuous IV infusion (e.g., nafcillin 12g/24h IV continuous)

[c]If there are extenuating circumstances in which preferred standard of care antibiotics cannot be used, for example complex allergy history, then an alternative antibiotic may be used after discussion with the protocol PIs and DMID Medical Officer

Figure 1: Schematic of Study Design



1 KEY ROLES

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2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Background

Staphylococcus aureus bacteremia is a life-threatening infection with case fatality rates ranging from 15-50% (van Hal 2012). *S. aureus* bacteremia is also a leading cause of IE in industrialized nations (Tong 2015) and is associated with in-hospital mortality rates ranging from 16% to 25% (Thuny 2005, Murdoch 2009, Sy 2010, Selton-Suty 2012). Standard treatment of complicated *S. aureus* bacteremia and IE requires prolonged IV antibiotic therapy (4-6 weeks), typically necessitating placement of a central IV catheter, prolonged hospitalization, and home nursing or admission to a long-term care facility. Treatment is associated with high cost and healthcare burden, as well as complications such as catheter related bloodstream infections and catheter associated thrombosis (Keller 2018). Safe and effective alternative treatment strategies are needed.

Dalbavancin is a lipoglycopeptide that has potent activity against Gram-positive pathogens including MRSA (Table 2, Table 3). It is currently approved for treatment of acute bacterial skin and skin structure infection in the US and EU as a single dose or 2-dose regimen. A 2-dose, once weekly regimen can provide systemic therapy for 6 weeks, eliminating the need for a centrally placed catheter or prolonged IV access for antibiotic administration.

Table 2: Activity of Dalbavancin Against Gram-Positive Pathogens Collected in 2014 US Surveillance

		Dalbavancin MIC (µg/mL)			
Organism	N	Range	50%	90%	% Susceptible[a]
S aureus: all	1625	0.008 - 0.12	0.06	0.06	100
Methicillin-susceptible	875	0.008 - 0.12	0.06	0.06	100
Methicillin-resistant	750	0.008 - 0.12	0.06	0.06	100
Viridans group streptococci	220	≤ 0.002 - 0.12	0.015	0.03	100
Penicillin-nonsusceptible	46	0.004 - 0.06	0.015	0.03	100
S pyogenes	108	≤ 0.002 - 0.06	0.008	0.03	100
S dysgalactiae	75	≤ 0.004 - 0.12	0.015	0.03	100
E faecalis	151	0.02 - > 0.25	0.06	0.06	97.6

Bacterial pathogens frequently implicated as causative agents of IE include *S aureus* (including MRSA), *Streptococcus pyogenes,* viridans group streptococci, Group C and G streptococci, and *Enterococcus* spp.

IE = infective endocarditis; MRSA = methicillin-resistant *S aureus*; MIC = minimum inhibitory concentration

[a] Susceptible at ≤ 0.25 µg/mL

Source: Dalbavancin International (Two Continents) Surveillance Report for 2014, JMI Laboratories; Protocol 14-DUR-01, May 2015.

Table 3: Activity of Dalbavancin Against Gram –Positive Pathogens Collected in 2014 EU Surveillance

		Dalbavancin MIC (µg/mL)			
Organism	N	Range	50%	90%	% Susceptible[a]
S aureus: all	1625	0.004 - 0.12	0.06	0.06	100
Methicillin-susceptible	1209	0.015 - 0.12	0.06	0.06	100
Methicillin-resistant	416	0.004 - 0.12	0.03	0.06	100
Viridans group streptococci	213	≤ 0.002 - 0.12	0.015	0.03	100
Penicillin-nonsusceptible	57	≤ 0.002 - 0.06	0.015	0.03	100
S pyogenes	106	0.004 - 0.12	0.008	0.03	100
S dysgalactiae	94	≤ 0.002 - 0.12	0.015	0.03	100
E faecalis	305	0.03 - > 0.25	0.06	0.06	98.4

Bacterial pathogens frequently implicated as causative agents of IE include *S aureus* (including MRSA), *Streptococcus pyogenes,* viridans group streptococci, Group C and G streptococci, and *Enterococcus* spp.

IE = infective endocarditis; MRSA = methicillin-resistant *S aureus*; MIC = minimum inhibitory concentration

[a] Susceptible at ≤ 0.25 µg/mL

Source: Dalbavancin International (Two Continents) Surveillance Report for 2014, JMI Laboratories; Protocol 14-DUR-01, May 2015.

Dalbavancin appeared effective in rat and rabbit models of *S. aureus* IE (Candiani 1999, Lefort 2004). In the rat model of staphylococcal IE, dalbavancin was as effective as vancomycin and teicoplanin at reducing the bacterial load in the heart, but with a lower dose and less frequent dosing

intervals compared to standard of care (Candiani 1999). In a rabbit model of IE, dalbavancin given once daily (10 mg/kg for 4 days) or as a single dose of 40 mg/kg was effective against a strain of *S. aureus* with reduced susceptibility to vancomycin and teicoplanin (Lefort, 2004). Additionally, 5 Phase 2/3 clinical studies that evaluated the efficacy and safety of dalbavancin administered as a single dose or 2-dose regimen found that 100% of patients (55 of 55 evaluable subjects) with *S. aureus* bacteremia achieved clearance of bacteremia (Raad 2005, Dunne 2016, Boucher 2014, Selzter 2003, Jauregui 2005). Thus, dalbavancin may be a safe and effective alternative therapy for *S. aureus* bacteremia/IE, including highly antibiotic-resistant strains.

The safety profile of dalbavancin has been characterized for a total cumulative dose of 1500 mg, whether administered as a single dose or in split weekly doses (1000 mg on Day 1 followed by 500 mg on Day 8). Adverse reactions have been evaluated for 2473 patients treated with dalbavancin. Overall, the most common adverse reactions were nausea (4.7%), headache (3.8%), and diarrhea (3.4%). The median duration of adverse reactions was 3 days for patients receiving dalbavancin and 4 days for patients receiving a comparator. The safety database for the 3000 mg total dose includes 12 subjects from a Phase 1 study: 6 received a total of 3500 mg dalbavancin over 6 weeks (with a total of 2 mild adverse events), and 6 received a total of 4500 mg dalbavancin over 8 weeks (with total of 4 mild adverse events and 1 moderate adverse event). Elevations in ALT >3x the upper limit of normal have been reported, though at a frequency not significantly different than comparator arms in trials conducted to date. Per product insert, 4.9% (121/2473) subjects receiving dalbavancin experienced SAEs, with 2.6% (64/2473) discontinuing the medication as a result.

2.2 Scientific Rationale

2.2.1 Purpose of Study

The current standard of care for the antibiotic treatment of complicated bacteremia or IE uses a stepwise approach. The initial phase of treatment involves the initiation of empirical antibiotic therapy, definitive diagnosis (as per the modified Duke criteria), and the assessment of the need for early valve replacement, if applicable. Subsequent identification of the causative pathogen, including antibiotic susceptibility and MICs supports the choice of definitive antibiotic therapy and determination of the required duration of antibiotic treatment. Guidelines for the use of outpatient parenteral antibiotic therapy in the treatment of complicated bacteremia or IE similarly advocate that antibiotic therapy can be divided into an initial phase during which life threatening complications of complicated bacteremia or IE are likely to occur (approximately 14 days) and a completion phase of therapy (2 weeks to 6 weeks) (Holland 2018).

The proposed clinical study design of dalbavancin in the treatment of complicated bacteremia or IE is consistent with this standard of care. Specifically, prior to study eligibility, patients will receive pre-randomization antibiotic therapy pending a definitive diagnosis of complicated *S. aureus*

bacteremia or IE, as well as the resolution of bacteremia. Eligible patients will then be randomized into the study to complete their antibiotic therapy with either a 2-dose regimen of dalbavancin or the current standard of care with daily IV administration of antibiotic therapy for a total duration of 4 to 6 weeks (Baddour 2015) for most patients, and up to 8 weeks for patients with vertebral osteomyelitis/discitis.

The proposed clinical study design offers a number of advantages. First, it will support enrollment of patients with a confirmed diagnosis of complicated bacteremia or IE. Prior studies have been limited by the inability to confidently determine complicated vs uncomplicated status prior to randomization (Corey 2009). Second, the proposed study design addresses a true area of need in *S. aureus* bacteremia management and reflects the likely pattern of "real world" dalbavancin use by clinicians for the completion of systemic antibiotic therapy for complicated bacteremia or IE without the need for indwelling IV access to support daily therapy. This takes full advantage of the unusual PK profile of dalbavancin and the introduction of this therapy into clinical practice would potentially have a major impact on patient well-being and quality of life (QoL). In this study, presence or absence of these potential QoL effects will be assessed using an ARLG Bloodstream Infection QoL Measure developed specifically for this purpose (King 2020). Additionally, two previously validated measures (EQ-5D-5L, https://euroqol.org/eq-5d-instruments/sample-demo/ and the PROMIS Global Health short form, http://www.healthmeasures.net/administrator/components/com_instruments/uploads/Global%20Health%20Scale%20v1.2%2008.22.2016.pdf) will also be collected. Third, adequate treatment of complicated bacteremia or IE requires prolonged systemic antibiotic therapy to prevent relapse. Introduction of the 2-dose dalbavancin regimen may decrease the risk of relapse. Finally, the proposed design of this clinical study is consistent with antibiotic stewardship principles, reserving dalbavancin therapy for patients with fully characterized infections and pathogens.

2.2.2 Study Population

Approximately 200 eligible subjects will be enrolled to the study in the United States and Canada. Eligible subjects are adults who have been diagnosed with complicated bacteremia or right-sided IE due to *S. aureus*, have been treated with appropriate empiric/targeted antibiotic therapy, and in whom the blood cultures have become negative after at least 72 hours of initial antibiotic therapy (maximum 10 days). Subjects with uncomplicated bacteremia due to *S. aureus* will be excluded. More details regarding subject inclusion and exclusion criteria can be found in Section 5.1.

2.2.3 Selection of Dose

The dalbavancin dosing regimen consists of 1500 mg on Day 1 and 1500 mg on Day 8 for subjects with normal renal function or who are receiving dialysis, administered over 30 minutes by IV infusion. Patients with CrCl <30 who are not receiving dialysis will receive a reduced dose (1125mg on Day 1 and 1125 mg on Day 8). Based on a comparison to the updated nonclinical

pharmacokinetic (PK)/pharmacodynamics (PD) target of the area under the unbound drug concentration-time curve [fAUC]/MIC (Lepak 2015), this regimen is expected to provide sufficient therapeutic concentrations of free drug against *S. aureus* through Day 42.

Consistent with prior nonclinical investigation (Andes 2007), Lepak et al (Lepak 2015) found fAUC/MIC to be the most relevant PK/PD index in a neutropenic murine thigh infection model, with mean free drug daily area under the curve (AUC)/minimum inhibitory concentration (MIC)s for net stasis, 1log kill, and 2log kill of 27.1, 53.3, and 111.1, respectively. To justify the proposed dosing regimen, a target attainment analysis was conducted using the updated population PK model (Carrothers 2020). In the PK simulation, the proposed regimen was simulated using the Bayesian post hoc estimates of each of the 703 patients in the merged Phase 2/3 population PK dataset. As with previous target attainment analyses, free drug levels were assumed to be 7% of total drug concentrations. As a conservative assumption, the mean daily AUC for target attainment was calculated based on dalbavancin levels on Day 42. For the MIC, the dalbavancin *S. aureus* MIC_{90} of 0.06 mg/L was used. Results of this simulation analysis showed target attainments of > 99%, > 99%, and 90% for the net stasis, 1log kill, and 2log kill targets, respectively. For an even more conservative estimate, the US breakpoint for susceptibility of *S. aureus* to dalbavancin of 0.25 mg/L was also used: the 90% target attainment was achieved through Day 42 (stasis), Day 36 (1-log kill), and Day 28 (2-log kill) after clearance of bacteremia.

Simulations designed to evaluate plasma concentration-time profiles suggest that a 2-dose regimen of dalbavancin of 1500 mg given on Days 1 and 8 will provide plasma concentrations above the MIC_{99} of *S. aureus* for an average of 49 days after the start of therapy Figure 2.

Figure 2: Simulated Mean Plasma PK Profile for Dalbavancin (Source: Allergen data on file)

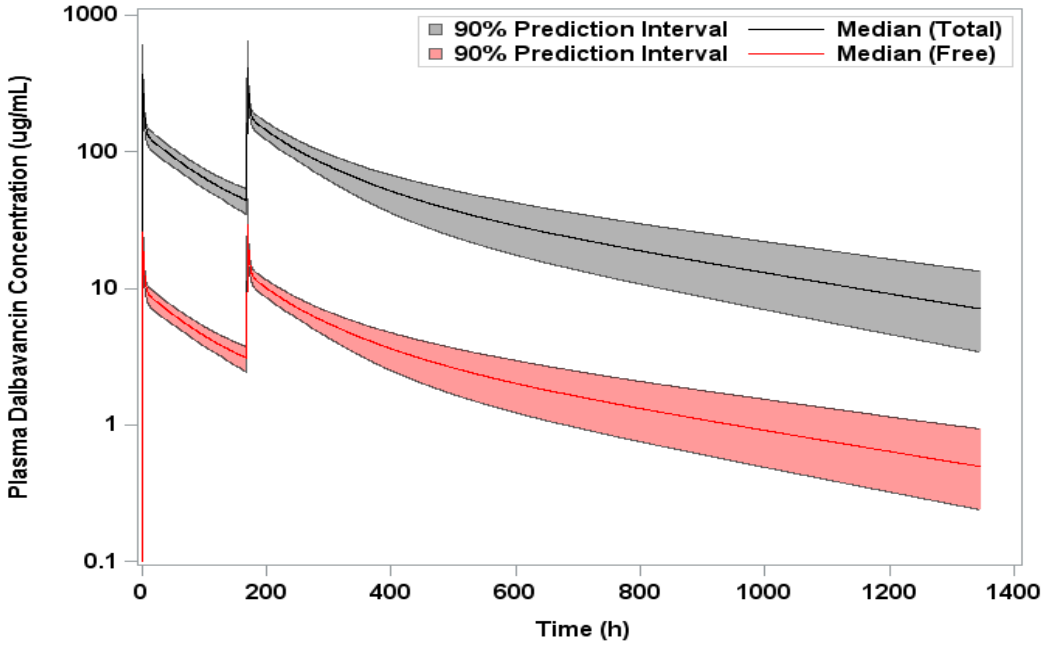
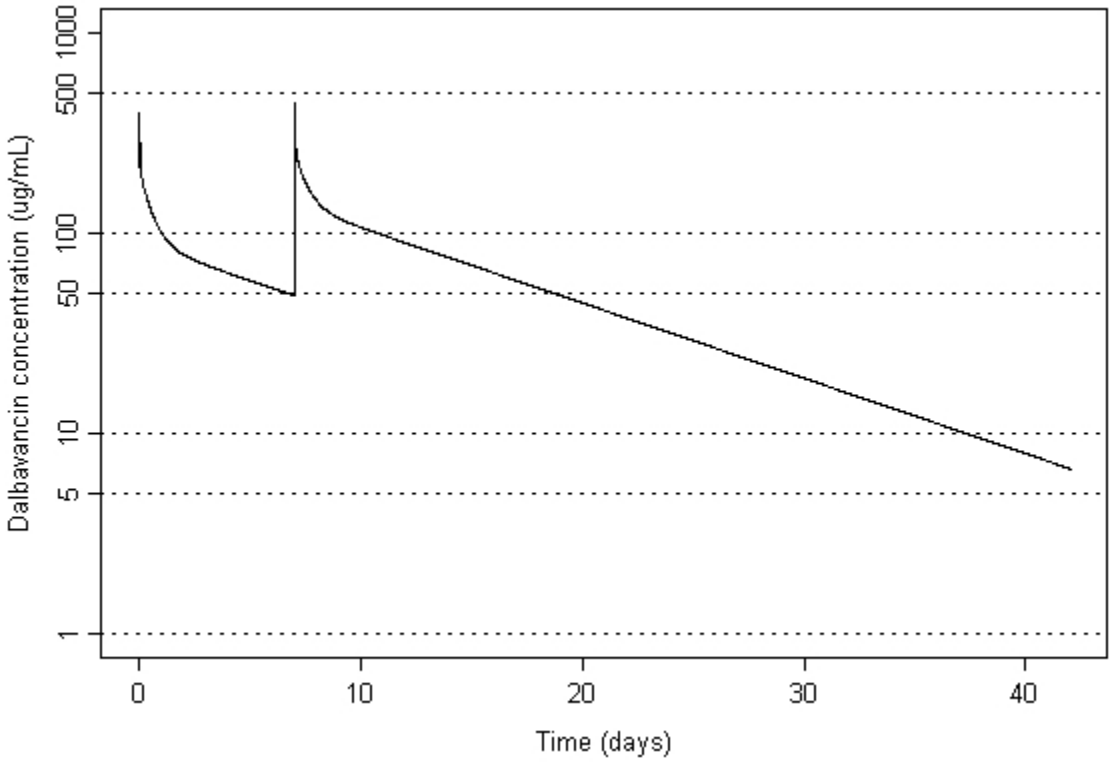


Figure 3 shows the time course of total dalbavancin concentration over the 6-week course of therapy for a typical patient. For this typical patient, Day 42 total drug concentration was 6.7 µg/mL [free drug = 7% × 6.7 = 0.47 µg/mL], which is greater than 7-fold the MIC_{90} value of 0.06 µg/mL for *S. aureus*, and > 15-fold the MIC_{90} value of 0.03 µg/mL for beta-hemolytic streptococci (Dalbavancin International [Two Continents] Surveillance Report for 2014) even at the end of a 6-week course of therapy.

Figure 3: Dalbavancin Concentration Time Course for a Typical Subject Under the Proposed Regimen (Source: Allergen data on file)



2.3 Potential Risks and Benefits

Dalbavancin is FDA-approved for the treatment of acute bacterial skin and skin structure infections caused by Gram positive organisms, though at lower doses than proposed for treatment of bacteremia here and has been the subject of one prior randomized controlled clinical trial for osteomyelitis using the same dosing regimen proposed in this study. Risk information is derived from both the product insert and previously conducted trials.

For those randomized to standard of care arms, the antistaphylococcal beta-lactams, cefazolin, vancomycin and daptomycin are all commonly used for treatment of *S. aureus* bacteremia and are associated with potential risks as well – outlined below from product inserts. These include risks associated with an indwelling vascular catheter, primarily secondary infections or thromboses. These also include the need for frequent blood draws to monitor for antibiotic toxicities.

2.3.1 Potential Risks

2.3.1.1 Dalbavancin

Hypersensitivity Reactions: Hypersensitivity reactions (both anaphylactic and limited cutaneous reactions) have been reported with glycopeptide antibiotics, including dalbavancin. Subjects will be excluded from this study if they report any history of anaphylactic reaction to glycopeptide antibiotics or dalbavancin.

Infusion-related Reactions: Rapid infusion of dalbavancin has been reported to cause flushing, urticarial, pruritic, or rash reactions resembling the "Red-Man Syndrome" described in association with vancomycin. Stopping or slowing the infusion typically resolves these reactions.

Central Nervous System Reactions: Headache has been infrequently reported with dalbavancin receipt (<4%).

Gastrointestinal: Nausea (4.7%) and diarrhea (<4%) have been infrequently reported with dalbavancin receipt (<4%).

C. difficile Infection: *C. difficile*-associated diarrhea has been reported with nearly all antibacterial agents, including dalbavancin.

Hepatic: Elevations of AST/ALT have been reported in clinical trials.

2.3.1.2 Cefazolin

Hypersensitivity Reactions: Anaphylaxis and a range of cutaneous drug eruptions have been reported with cefazolin.

Localized Reactions: Phlebitis has been rarely reported with cefazolin.

Nephrotoxicity: Elevations in BUN and creatinine, infrequently even acute renal failure, have been reported.

Gastrointestinal: Nausea, diarrhea and anorexia have been reported.

C. difficile Diarrhea: *C. difficile* diarrhea has been reported with nearly all antibiotics.

Hematologic: Neutropenia and thrombocytopenia have both been infrequently reported and are generally reversible upon discontinuation.

Hepatic: Transient elevations in AST/ALT have been reported.

2.3.1.3 Nafcillin

Hypersensitivity Reactions: Anaphylaxis and a range of cutaneous drug eruptions have been reported with nafcillin.

Localized Reactions: Phlebitis, sometimes even with skin sloughing, has been rarely reported with nafcillin.

Nephrotoxicity: Elevations in BUN and creatinine, infrequently even acute renal failure or acute interstitial nephritis, have been reported.

Gastrointestinal: Nausea, diarrhea and anorexia have been reported.

C. difficile Diarrhea: *C. difficile* diarrhea has been reported with nearly all antibiotics.

Hematologic: Neutropenia or even agranulocytosis has been reported with nafcillin and is generally reversible upon discontinuation.

Hepatic: Transient elevations in AST/ALT have been reported.

2.3.1.4 Oxacillin

Hypersensitivity Reactions: Anaphylaxis and a range of cutaneous drug eruptions have been reported with oxacillin.

Nephrotoxicity: Elevations in BUN and creatinine, infrequently even acute renal failure or acute interstitial nephritis, have been reported.

Gastrointestinal: Nausea, diarrhea and anorexia have been reported.

C. difficile Diarrhea: *C. difficile* diarrhea has been reported with nearly all antibiotics.

Hematologic: Neutropenia or even agranulocytosis has been reported with oxacillin and is generally reversible upon discontinuation.

Hepatic: Transient elevations in AST/ALT have been reported.

2.3.1.5 Vancomycin

Infusion Reactions: Rapid infusion of vancomycin has been reported to cause flushing, urticarial, pruritic, or rash reactions known as the “Red-Man Syndrome”. Stopping or slowing the infusion typically resolves these reactions.

Phlebitis and Localized Cutaneous Reactions: Vancomycin can be irritating to soft tissues, including causing thrombophlebitis at infusion sites. Inadvertent extravasation may result in localized pain, tenderness, or even necrosis.

Hypersensitivity Reactions: Hypersensitivity reactions including anaphylaxis have been reported with vancomycin.

Nephrotoxicity: When administered systemically, vancomycin can cause acute kidney injury. Risk of injury increases with supratherapeutic levels.

Ototoxicity: Hearing loss and tinnitus have been reported with vancomycin, reported mostly in patients with supratherapeutic levels, underlying hearing loss, or concomitant receipt of other ototoxic agents.

C. difficile Diarrhea: *C. difficile* associated diarrhea has been reported with the use of nearly all antibiotics.

Hematologic: Vancomycin has occasionally been associated with neutropenia or rarely thrombocytopenia. Cytopenias are usually reversible upon discontinuation.

2.3.1.6 Daptomycin

Hypersensitivity Reactions: Anaphylaxis and a range of cutaneous drug eruptions have been reported with daptomycin.

Myopathy/Rhabdomyolysis: Daptomycin has been reported to cause a myositis characterized by elevated creatine kinase levels, muscle pain, and muscle weakness. Risk may be increased upon co-administration with statins. Myopathy is generally reversible upon discontinuation.

Eosinophilic Pneumonia: Daptomycin has been rarely reported to cause eosinophilic pneumonia which may present with fever, dyspnea and pulmonary opacities.

Neuropathy: There are rare reports of peripheral neuropathy with daptomycin.

C. difficile Diarrhea: *C. difficile* diarrhea has been reported with nearly all antibiotics.

2.3.1.7 Risks Associated with Intravenous Access

The risks associated with peripheral IV placement are minimal and include minor bruising/bleeding, localized discomfort at the site, and rarely infection or a superficial clot.

The risks associated with peripherally inserted central venous catheters (PICC lines) or central lines include bleeding, discomfort at the site, deep venous thrombosis (blood clot), infection, rarely nerve injury or an irregular heartbeat.

2.3.2 Potential Benefits

Dalbavancin may or may not improve the clinical outcome of an individual subject who participates in this trial. There is potential benefit to society from their participation in this study resulting from insights gained about outcomes with dalbavancin among patients with *S. aureus* bacteremia. Since standard of care for complicated *S. aureus* bacteremia currently requires dosing via indwelling central venous access, with frequent dosing and prolonged duration of therapy, the potential benefit is the possible demonstration that a dalbavancin treatment strategy may avoid prolonged hospital stays and the need for central venous access.

3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES

3.1 Study Design Description

This clinical study will be a Phase 2b, multicenter, randomized, open-label, assessor-blinded, superiority study. The study will compare dalbavancin to standard of care antibiotic therapy for the completion of therapy in patients with complicated bacteremia or right-sided native valve IE caused by *S. aureus* who have cleared their baseline bacteremia.

Approximately 200 subjects will be randomized 1:1 to receive either dalbavancin or a standard of care antibiotic regimen that is based upon the identification and antibiotic susceptibility pattern of the baseline organism. Those randomized to the dalbavancin treatment group will receive 2 doses of dalbavancin IV 1 week apart (1500 mg on Day 1 and Day 8 after randomization, with renal dose adjustment if appropriate). Those subjects randomized to the standard of care antibiotic therapy treatment group will receive an antibiotic regimen considered to be standard of care based on the methicillin susceptibility pattern of the pathogen isolated at Baseline for a duration of 4 to 6 weeks.

Figure 1 provides a schematic of the study design. Study procedures are presented in Section 6. Detailed descriptions of each study visit can be found in Section 6.3.

3.2 Study Objectives

3.2.1 Primary

- To compare the Desirability of Outcome Ranking (DOOR) at Day 70 of dalbavancin to that of standard of care antibiotic therapy used to consolidate therapy for the treatment of subjects with complicated *S. aureus* bacteremia in the intent-to-treat (ITT) population.

3.2.2 Secondary

- To compare the clinical outcomes of dalbavancin with the standard of care antibiotic therapy at day 70 in the mITT population (see Section 10.5.1 for definitions of study populations).
- To compare the safety of dalbavancin with that of the standard of care treatment in the mITT population.
- To compare each individual component of the DOOR outcome by treatment arm, in the ITT population.

3.2.3 Exploratory

1. To compare the clinical outcomes of dalbavancin with the standard of care antibiotic therapy at day 70 in the CE population (see Section 10.5.1 for definition).
2. To compare the DOOR endpoint of subjects on dalbavancin with that of subjects receiving standard of care antimicrobial therapy at day 42, in the ITT, mITT and CE populations.
3. To compare the clinical and microbiologic outcomes of dalbavancin with the standard of care antibiotic therapy at day 42 in ITT, mITT and CE populations.
4. To compare clinical and microbiologic outcomes of dalbavancin with standard of care antibiotic therapy between clinically important subgroups, including a) those with MSSA versus MRSA; b) persons who inject drugs (PWID) vs non-PWID; c) those who received infectious disease consultation vs those who did not; d) underlying site of infection (endovascular, bone and joint, skin, pulmonary); e) subjects with immune-suppression[2]; f) divided by duration of initial bacteremia, in the ITT, mITT, and CE populations.
5. To compare Quality of Life (QoL) of subjects on dalbavancin with that of subjects receiving standard of care antibiotic therapy at Baseline, Day 42, and Day 70, in the ITT, mITT, and CE populations.
6. To characterize the population pharmacokinetic profile for dalbavancin administered via a 2-dose regimen (1500 mg on day 1 and 1500 mg on day 8; renally adjusted when appropriate) in patients with *S. aureus* bacteremia.
7. To assess patient-level and clinical covariates associated with dalbavancin pharmacokinetics in patients with *S. aureus* bacteremia.
8. Examine the association between individualized plasma concentration profiles and clinical and microbiologic outcomes at day 42 and TOC.
9. Examine the association between individualized plasma concentration profiles and occurrence of adverse drug events, including AST/ALT elevations >3X upper limit of normal.
10. Examine the association between individualized plasma concentration profiles and late recurrence risk among the subset of patients with osteomyelitis and a 6-month follow-up visit.

[2] Defined as: On chemotherapy or immunotherapy for active hematologic malignancy expected to cause ANC < 500 cells/mm^3 lasting > 7 days during the study period, chronic high dose oral steroids (equivalent of ≥ 20 mg prednisolone per day for or equivalent, for >2 weeks within the last month), HIV infection with a CD4 cell count < 100 cells/mm^3 based on last known measurement or patient-reported value

3.3 Study Endpoints or Outcome Measures

3.3.1 Primary

The **primary outcome** measure is the DOOR endpoint at day 70. The clinical components of the DOOR endpoint (success/failure and infectious complications) will be completed by an independent adjudication committee, blinded to treatment assignment. Day 70 was selected in this study as it occurs approximately 4 weeks after treatment completion for most patients, allowing time for detection of relapse.

There are 5 possible rankings in the DOOR endpoint:

Rank	Alive	How many of: 1) Clinical Failure 2) Infectious Complication 3) SAE, or AE leading to study drug discontinuation	QoL
1	Yes	0 of 3	Tiebreaker based on QoL score
2	Yes	1 of 3	
3	Yes	2 of 3	
4	Yes	3 of 3	
5	No (Death)	Any	

Rank 1: Alive without any of the following: (1) evidence of clinical failure; (2) an infectious complication; or (3) any SAE, or an AE leading to study drug discontinuation

Rank 2: Alive but with one of the following: (1) evidence of clinical failure; (2) an infectious complication; or (3) any SAE, or an AE leading to study drug discontinuation

Rank 3: Alive but with two of the following: (1) evidence of clinical failure; (2) an infectious complication; or (3) any SAE, or an AE leading to study drug discontinuation

Rank 4: Alive but with all of the following: (1) evidence of clinical failure; (2) an infectious complication; or (3) any SAE, or an AE leading to study drug discontinuation

Rank 5: Death

Clinical failure, infectious complications, and adverse events are each binary (yes/no) components of the DOOR endpoint.

For the primary endpoint, quality of life will be measured as a change from baseline QoL to day 70 QoL score, as assessed by the ARLG Bloodstream Infection QoL Measure (Appendix C).

Definitions for the DOOR endpoint:

Clinical Success: Resolution of clinical signs and symptoms of *S. aureus* bacteremia such that no additional antibiotic therapy is required or anticipated for its treatment.

Note that it is possible to achieve this overall Clinical Success status at Day 70 even if Infectious Complications have occurred prior to that time. For example, a patient who has a new metastatic focus of infection diagnosed after randomization, but who subsequently completes treatment and is felt to be cured at Day 70 would be considered a Clinical Success (and the Infectious Complication would result in a lower DOOR). That is, Clinical Success reflects the patient's overall status at the time of that assessment.

Clinical Failure: Absence of clinical success

Infectious Complications: occurrence of any of the following, between randomization and day 70:

- Endocarditis
- New evidence of metastatic foci of infection – e.g. osteomyelitis, visceral abscess, septic joint
- Relapse – isolation of baseline *S. aureus* pathogen from a blood culture drawn after randomization
- Readmission for subsequent care of indication under study
- Need for additional unplanned source control procedures – e.g. abscess debridement or drainage, cardiac valve replacement
- Change in antibiotic therapy due to inadequate clinical response. For any changes to study drug in the standard of care group, or when new antibiotics are started in either treatment group, the site PI will record the reason for the antibiotic change.

3.3.2 Secondary

The **secondary efficacy outcome** is as follows**.**

- Clinical efficacy, defined as none of: 1) Clinical failure; 2) Infectious complications; 3) All-cause mortality

The **secondary safety outcome** is as follows.

- Proportion of patients who have either 1) an SAE; or 2) an AE leading to study drug discontinuation

Each component of the DOOR will also be examined separately:

- clinical success
- infectious complications
- SAEs
- AEs leading to study drug discontinuation
- all-cause mortality

3.3.3 Exploratory

1. Clinical efficacy by treatment group in the CE population at day 70
2. DOOR endpoint by treatment group at day 42 in the ITT, mITT, and CE populations
3. Clinical and microbiologic outcomes by treatment group at day 42 in the ITT, mITT, and CE populations
4. Clinical and microbiologic outcomes by treatment group, within each subgroup of clinical interest, at day 42 and day 70 in the ITT, mITT, and CE populations. A microbiologic success will be defined as no post-randomization growth (e.g., no positive cultures) of the baseline pathogen from blood cultures or another sterile body site
5. QoL at Baseline, Day 42, and Day 70, which will be assessed using the ARLG Bloodstream Infection QoL Measure (Appendix C) as well as two additional comparator measures (EQ-5D-5L, https://euroqol.org/eq-5d-instruments/sample-demo/ and PROMIS Global Health short form, http://www.healthmeasures.net/administrator/components/com_instruments/uploads/Global%20Health%20Scale%20v1.2%2008.22.2016.pdf) in the ITT, mITT, and CE populations
6. Population mean PK parameter estimates and the magnitude of the associated inter individual variability for the 2-dose dalbavancin regimen in patients with *S. aureus* bacteremia.
7. Individual post hoc PK parameter estimates and calculated exposure measures for the 2-dose dalbavancin regimen in patients with *S. aureus* bacteremia.
8. Clinical and microbiologic response at day 42 and Day 70 according to individual plasma dalbavancin concentration curves.
9. Occurrence of grade 3 or higher adverse drug events, adverse events of special interest (AESIs), and occurrence of AST/ALT elevations >3x upper limit of normal (ULN) from first dose of dalbavancin through follow-up period.
10. Late recurrence within the osteomyelitis population will be defined by the presence of the following up to 6 months after randomization: progressive imaging changes along with isolation of *S. aureus* from blood, bone biopsy, associated fluid aspiration, or operative tissue culture.

4 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

4.1 Study Product Description

Dalbavancin is a lyophilized, white to off-white to pale yellow solid. It is a lipoglycopeptide synthesized from a fermentation product of *Nonomuraea* species. Dalbavancin is a mixture of five closely related active homologs (A_0, A_1, B_0, B_1, and B_2), shown in Table 4, below. The homolog B_0 is the major component of dalbavancin. The homologs share the same core structure and differ in the fatty acid side chain of the N-acylaminogluronic acid moiety (R_1) structure and/or the presence of an additional methyl group (R_2) on the terminal amino group, shown in Table 4 below. The B_0 INN chemical name is 5,31-dichloro-38-de(methoxycarbonyl)-7-demethyl-19-deoxy-56-O [2-deoxy-2-[(10-methylundecanoyl)amino]-β-D-glucopyranuronosyl]-38-[[3-(dimethylamino)propyl] carbamoyl]-42-O-α-D-mannopyranosyl-15-N-methyl(ristomycin A aglycone) hydrochloride. Please refer to the package insert and/or Investigator's Brochure for further details.

Table 4: Substitution Patterns for Dalbavancin API Homologs

Dalbavancin	R_1	R_2	Molecular Formula	Molecular Weight*
A_0	$CH(CH_3)_2$	H	$C_{87}H_{98}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1802.7
A_1	$CH_2CH_2CH_3$	H	$C_{87}H_{98}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1802.7
B_0	$CH_2CH(CH_3)_2$	H	$C_{88}H_{100}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1816.7
B_1	$CH_2CH_2CH_2CH_3$	H	$C_{88}H_{100}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1816.7
B_2	$CH_2CH(CH_3)_2$	CH_3	$C_{89}H_{102}N_{10}O_{28}Cl_2 \cdot 1.6\ HCl$	1830.7

*Anhydrous free base

4.1.1 Formulation, Packaging, and Labeling

Dalbavancin

Dalbavancin is supplied in clear glass vials as a sterile, lyophilized, preservative-free, white to off-white to pale yellow solid. Each vial contains dalbavancin HCl equivalent to 500 mg of dalbavancin.

Investigational dalbavancin vials will be labeled according to manufacturer or regulatory specifications and include the statement "*Caution: New Drug – Limited by Federal Law to Investigational Use*." The dispensed study product (IV bags) will be labeled with the cautionary statement "For Investigational Use Only."

The standard of care (SOC) antibiotics (Cefazolin, nafcillin, oxacillin, vancomycin, and daptomycin) will be prepared and labeled in accordance with the clinical site pharmacy's standard operating procedures (SOPs).

4.1.2 Product Storage and Stability

Dalbavancin

Unreconstituted dalbavancin for injection should be stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Reconstituted vials may be stored either refrigerated at 2°C to 8°C (36°F to 46°F), or at controlled room temperature 20°C to 25°C (68°F to 77°F). Do not freeze.

Once diluted into an intravenous bag , dalbavancin may be stored either refrigerated at 2°C to 8°C (36°F to 46°F), or at controlled room temperature 20°C to 25°C (68°F to 77°F). Do not freeze.

The total time from reconstitution to dilution to administration should not exceed 48 hours.

SOC Antibiotics: Cefazolin, nafcillin, oxacillin, vancomycin, and daptomycin

Store per manufacturer's instructions.

4.2 Acquisition/Distribution

Dalbavancin for injection will be supplied by Allergan, a subsidiary of AbbVie and will be obtained from the DMID Clinical Materials Services (CMS), Fisher BioServices, upon request by the study sites and approval by DMID.

SOC antibiotics (cefazolin, nafcillin, oxacillin, vancomycin, and daptomycin) specified for use in the study will be obtained locally by each participating site.

Any diluents or other vehicles for preparation of dalbavancin and SOC antibiotics for use in the study will also be obtained locally by each participating site.

4.3 Dosage/Regimen, Preparation, Dispensing and Administration of Study Intervention/Investigational Product

Dalbavancin Group

For subjects randomized to the dalbavancin treatment group, the dosage of dalbavancin administered will be determined based on individual estimated serum creatinine clearance (CrCl) levels and presence of regular hemodialysis or peritoneal dialysis as follows:

Subjects with CrCl ≥ 30 mL/min and subjects receiving regular hemodialysis or peritoneal dialysis will receive 1500 mg IV dalbavancin over 30 (± 10) minutes on Day 1 and on Day 8.

Subjects with CrCl < 30 mL/min who are not receiving regular hemodialysis or peritoneal dialysis will receive 1125 mg IV dalbavancin over 30 (± 10) minutes on Day 1 and on Day 8.

A repeat serum creatinine will be required within the 72 hours prior to the second (Day 8) dalbavancin dose. Whether creatinine clearance needs to be reassessed on Day 8 will be left to the clinical judgment of the study investigator. For example, a subject with stable renal function up to 72 hours before the second dalbavancin dose and no anticipated change to renal function may not require a repeat creatinine clearance measurement on Day 8. In contrast, if the subject had either fluctuating renal function or renal function near the threshold for dose adjustment, it would be entirely appropriate to repeat a creatinine measurement prior to the Day 8 dose.

If CrCl crosses the 30ml/min threshold in either direction after Day 1 but before the Day 8 dose, then the dose should be adjusted accordingly. That is, if a subject has CrCl ≥ 30 mL/min on Day 1 and received 1500mg IV dalbavancin, but the CrCl is < 30 mL/min on day 8then that subject will receive 1125mg IV for the Day 8 dose. If the CrCl improves to ≥ 30 mL/min between Day 1 and Day 8, then the dose will receive 1500mg IV dalbavancin for the Day 8 dose.

Standard of Care Group

Subjects randomized to the standard of care antibiotic therapy treatment group will receive an antibiotic considered standard of care, generally for a duration of 4 to 6 weeks (but up to a maximum of 8 weeks, which may be standard practice for vertebral osteomyelitis at some sites) and based on the results of antibiotic susceptibility testing for baseline pathogen. The site PI (or licensed sub-investigator listed on the Form FDA 1572), in agreement with the patient's treating clinician, will designate which antibiotic is considered the study drug for patients randomized to the standard of care group; this will generally be the antibiotic already being used to treat their infection. For example, a patient randomized to the standard of care group who is receiving vancomycin for treatment of bacteremia, would most likely continue to be treated with vancomycin and this would be designated as their study drug. If the treating clinician is changing the antibiotic regimen at the time of randomization, for example to an antibiotic that would be easier to administer in the outpatient setting, then that new antibiotic would be designated as the study drug.

Any changes to study drug (discontinuation or dose adjustment) will be captured and the reason for this change will be recorded, with the exception that vancomycin dose adjustments do not need to be captured.

For subjects randomized to standard of care antibiotic therapy, the counting of days for the duration of therapy may begin on the first day on which blood cultures are negative during the Induction Period.

Subjects randomized to the standard of care antibiotic therapy treatment group will receive the following antibiotic(s) shown in Table 5 for the specified duration based on baseline pathogen:

Table 5: Acceptable SOC Antibiotics

Baseline Pathogen	Standard of Care Therapy (doses may be adjusted for renal function)[b]
MSSA[a]	nafcillin (2 g IV q4h × 4-6 weeks[c])[e] OR oxacillin (2 g IV Q4h x 4-6 weeks[c])[e] OR cefazolin (2 g IV q8h × 4-6 weeks[c])[e]
MRSA	vancomycin (dose per local standard of care × 4-6 weeks[c])[d] OR daptomycin (6-10 mg/kg IV daily × 4-6 weeks[c])

IV = intravenous; qxh = every x hours; MRSA = methicillin--resistant *Staphylococcus aureus*; MSSA = methicillin--susceptible *Staphylococcus aureus*

[a] Vancomycin or daptomycin are also appropriate for patients with MSSA and anaphylactoid-type hypersensitivity to beta-lactams.

[b] If there are extenuating circumstances in which preferred standard of care antibiotics cannot be used, for example complex allergy history, then an alternative antibiotic may be used after discussion with the protocol PIs and DMID Medical Officer.

[c] Duration of antibiotics reflects usual standard of care for complicated SAB. It may be extended to a maximum of 8 weeks at the discretion of the treating clinician.

[d] Patients on vancomycin will have dose adjustment and monitoring based on local standard of care

[e] As applicable per site standard of care, beta-lactams may be administered at an equivalent dose via continuous IV infusion (e.g., nafcillin 12g/24h IV continuous).

Complete instructions for dosage, preparation, labeling, storage, stability, and administration for dalbavancin and SOC antibiotics are provided in the protocol-specific Manual of Procedures (MOP).

Regarding vancomycin dosing, dose adjustments and monitoring will be performed in accordance with local standard of care. Vancomycin monitoring may be performed by trough levels, area under the curve (AUC) based protocols, or other methods guided by sites' local standards. Because vancomycin dosing and monitoring is determined by these local standards of care, we will not require specific doses or levels to be recorded.

4.4 Pre-determined Modification of Study Intervention/Investigational Product for an Individual Subject

Dalbavancin dose will be modified per package insert for renal function only. Any contraindication to receipt of the second dose, including an allergic reaction, pregnancy or other adverse event (see individual halting rules in Section 8.5.2), should be discussed with the DMID Medical Officer.

Subjects with impaired renal function will have their dosage of standard of care antibiotic treatment adjusted as needed, based on local standard of care.

Any alteration in study drug therapy because of unusual clinical circumstances must be discussed with the DMID Medical Officer.

4.5 Accountability Procedures for the Study Intervention/Investigational Product(s)

Dalbavancin will be stored and shipped from the DMID contract Clinical Material Services (CMS) to the Clinical Sites. Once received, dalbavancin will be stored in and dispensed by the Investigational Pharmacy.

The Food and Drug Administration (FDA) requires accounting for the disposition of all investigational products. The Investigator is responsible for ensuring that a current record of product disposition is maintained and product is dispensed only at an official study site by authorized personnel as required by applicable regulations and guidelines. Records of product disposition, as required by federal law, consist of the date received, date administered, quantity administered, and the subject number to whom the drug was administered.

The Investigational Pharmacist will be responsible for maintaining accurate records of the shipment and dispensing of the investigational product. The pharmacy records must be available for inspection by the DMID monitoring contractors, and is subject to inspection by a regulatory agency (e.g., FDA) at any time. An assigned Study Monitor will review the pharmacy records.

Unused unreconstituted investigational product (dalbavancin) vials will be stored at 25ºC (77ºF); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) [see USP controlled room temperature] in the Investigational Pharmacy until clinical trial accountability is completed. At study termination, all unused investigational product will be disposed in accordance with the MOP following complete drug accountability and monitoring.

5 SELECTION OF SUBJECTS AND STUDY ENROLLMENT AND WITHDRAWAL

Subject Inclusion and Exclusion Criteria must be confirmed by a study investigator listed on the Form FDA 1572.

No exemptions are granted on Subject Inclusion/Exclusion Criteria in DMID-sponsored studies. Clarifications regarding applicability of specific inclusion and exclusion criteria may be discussed with a protocol clinician. Questions about eligibility will also be directed toward the DMID Medical Officer.

5.1 Eligibility Criteria

5.1.1 Subject Inclusion Criteria

A subject must meet all of the following criteria to be considered eligible for inclusion in the study:

1. Written informed consent obtained from the patient or legally authorized representative before the initiation of any study-specific procedures.
2. Patients ≥ 18 years old.
3. A diagnosis of complicated *S. aureus* (either MSSA or MRSA) bloodstream infection (see definition of uncomplicated bacteremia in Exclusion criterion #1).
4. Treated with effective antibiotic therapy for at least 72 hours (maximum 10 days)[3].
5. Subsequent defervescence for at least 24 hours and clearance of bacteremia from the qualifying pathogen (at Screening), with negative blood culture incubated for at least 48 hours.[4]
6. Provider willing to treat with either dalbavancin for two doses, or standard of care intravenous monotherapy for at least 4 and *no more than* 8 weeks from randomization.
7. Patients must be willing and able, if discharged, to return to the hospital or designated clinic for scheduled treatment, laboratory tests, or other procedures as required by the protocol.

[3] Ten consecutive days prior to randomization is the maximum allowed treatment duration. If a subject has received intermittent or incomplete therapy earlier in the treatment course for this episode of *S. aureus* bacteremia, then discuss with the protocol PI and DMID Medical Officer prior to enrollment.

[4] Two negative blood cultures incubated for 48 hours are preferred. However, if only a single blood culture set is drawn, no growth at 48 hours will be considered adequate to demonstrate clearance. If more than one culture set is drawn, *all* must show no growth at 48 hours to be considered evidence of clearance (e.g., 1 of 2 positive cultures would still be considered as ongoing bacteremia).

8. According to the site PI or sub-investigator assessment, patients must be expected to survive with appropriate antibiotic therapy and appropriate supportive care throughout the study.

5.1.2 Subject Exclusion Criteria

1. Uncomplicated bacteremia[5] (Appendix B).
2. Infectious CNS events, including septic emboli, ischemic or hemorrhagic stroke, epidural abscess, or meningitis (prior/unrelated CNS events are **not** exclusion criteria).
3. Known or suspected left-sided endocarditis or presence of a perivalvular abscess.
4. Planned right-sided valve replacement surgery in the first 3 days following randomization.
5. Presence of prosthetic heart valve, cardiac device[6] UNLESS removal is planned within 4 days post-randomization.
6. Presence of intravascular graft or intravascular material[7] UNLESS removal is planned within 4 days post-randomization.
7. Infected prosthetic joint or extravascular hardware UNLESS removal is planned within 4 days post-randomization OR hardware was placed >60 days before bacteremia and clinically appears uninfected.
8. Polymicrobial bacteremia unless the non-*S. aureus* organism is a contaminant [see Definitions (Appendix B)].[8]
9. Significant hepatic insufficiency (Child-Pugh class C or AST/ALT values >5x ULN at the time of randomization).
10. Immunosuppression.[9]

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[5] Uncomplicated *Staphylococcus aureus* bacteremia is defined as all of the following: exclusion of endocarditis by echocardiography; catheter-associated bacteremia and removal of catheter; no implanted prostheses; follow-up blood cultures drawn within 48 hours after initial set that do not grow screening pathogen and all follow-up blood cultures thereafter do not grow the screening pathogen; defervescence within 72 hours of initiating effective therapy; and no evidence of metastatic sites of infection. Any patient not meeting these strict criteria is considered to have *complicated* bacteremia and is eligible.

[6] Implantable cardioverter defibrillator (ICD), permanent pacemaker, valve support ring, ventricular assist device (VAD)

[7] Excluding cardiac stents, inferior vena cava filters in place for >6 weeks, vascular stents in place for >6 weeks, non-hemodialysis grafts in place >90 days, and hemodialysis grafts not used within the past 12 months and not previously infected. A fistula constructed from native veins or a biologic vascular graft (without synthetic graft material) does not count as intravascular graft/material.

[8] *Note:* If a gram-negative bacteremia or fungemia develops after the qualifying *S. aureus* blood culture, AND the patient does not have right-sided endocarditis, AND the infection can be treated with an antibiotic without efficacy against the patient's *S. aureus* isolate (e.g. aztreonam), then the patient may remain eligible. Discussion with the DMID Medical Officer is strongly encouraged.

[9] On chemotherapy or immunotherapy for active hematologic malignancy expected to cause > 7 days of ANC < 100 cells/mm^3, recent bone marrow transplant (in the past 90 days), solid organ transplantation within prior 3 months or receipt of augmented immunosuppression for rejection within 3 months, chronic granulomatous disease, HIV infection with a CD4 cell count < 50 cells/mm^3 based on last known measurement or patient-reported value.

11. History of hypersensitivity reaction to dalbavancin or other drugs of the glycopeptide class of antibiotics.
12. Treatment with either dalbavancin or oritavancin in the 60 days prior to enrollment.
13. Infection with *S. aureus* not susceptible to dalbavancin (dalbavancin mean inhibitory concentration [MIC] > 0.25 µg/mL) or vancomycin (vancomycin MIC > 2 µg/mL).
14. Planned treatment with concomitant systemic antibacterial therapy with potential efficacy against the patient's qualifying *S. aureus* isolate, other than that allowed in the protocol.
15. Pregnant/ nursing females.
16. Females of childbearing potential must have a negative pregnancy test[10] within 48h of randomization and use effective contraception for trial duration (Appendix B).
17. Other medical or psychiatric condition that may, in the judgment of the investigator, increase the risk of study participation or interfere with interpretation of study results.
18. Unwilling or unable to follow study procedures.
19. Treatment with an investigational drug within 30 days preceding the first dose of study medication.

5.2 Withdrawal from the Study, Discontinuation of Study Product, or Study Termination

5.2.1 Withdrawal from the Study or Discontinuation of the Study Product

Subjects may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled.

An investigator may also discontinue a subject from receiving the study product (i.e., dalbavancin or SOC antibiotic) for any reason. Follow-up safety evaluations for discontinued subjects will be conducted, if the subject agrees. If a subject withdraws or is withdrawn prior to completion of the study, the reason for this decision must be recorded in the case report forms (CRFs).

The reasons to withdraw from the study might include, but are not limited to, the following:

- Subject no longer meets eligibility criteria
- Subject withdraws consent

[10] If the serum pregnancy test results cannot be obtained before randomization, a urine pregnancy test may be used for enrollment.

- Subject lost to follow-up
- Subject becomes non-compliant
- Medical disease or condition, or new clinical finding(s) for which continued participation, in the opinion of the investigator might compromise the safety of the subject, interfere with the subject's successful completion of this study, or interfere with the evaluation of responses
- Study or site prematurely terminated by the sponsor for any reason

The reasons to discontinue study product (i.e., dalbavancin or SOC antibiotic) might include, but are not limited to, the following:

- Subject meets individual halting criteria (see Section 8.5.2)
- Subject becomes pregnant, if applicable
- Occurrence of an AE that, in the opinion of the investigator, warrants the subject's permanent discontinuation from IV study drug (i.e., dalbavancin or SOC antibiotic)
- Subject has an insufficient therapeutic response to study drug (i.e., lack of efficacy for SAB). A patient who does not show signs of improvement despite treatment with study drug for an appropriate length of time or a patient who shows signs of clinical worsening at any time may be prematurely discontinued from study drug therapy and treated with salvage therapy as directed by their treating clinician. These patients would still continue to be followed in the study unless withdrawn for another reason.

A subject who is prematurely discontinued from study drug or withdrawn from the study should have the assessments for Early Termination (ET) as detailed in the Schedule of Events (Appendix A). A clear description of reason for early withdrawal or discontinuation from study product (i.e., dalbavancin or SOC antibiotic) must be documented. The reasons for early withdrawal or premature discontinuation from study drug will be reflected on the relevant disposition page of the electronic case report form (eCRF).

The investigator should be explicit regarding study follow-up (e.g. safety and efficacy follow-up) that might be carried out despite the fact the subject will not receive further study product. If the subject consents, every attempt will be made to follow all AEs through resolution or through the end of the study, whichever occurs first. The procedures that collect safety data for the purposes of research must be inclusive in the original informed consent.

The investigator will inform the subject that already collected data will be retained and analyzed even if the subject withdraws from this study.

5.2.2 Subject Replacement

Subjects who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the informed consent form (ICF) and administration of the study product will not be replaced. Subjects who withdraw, or are withdrawn from this study, or are lost to follow-up after randomization but before administration of the study product will not be replaced.

5.2.3 Study Termination

The sponsor reserves the right to terminate the study in its entirety or at a specific study center before study completion.

If the study is prematurely terminated by the sponsor, any regulatory authority, or the investigator for any reason, the investigator will promptly inform the currently enrolled study subjects and assure appropriate therapy or follow-up for the subjects, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB/IEC.

6 STUDY PROCEDURES

The study schedule is outlined below and in the Schedule of Events (Appendix A). The descriptions of the procedures to be performed at each visit are provided below.

6.1 Induction Period: Visit 0 (Pre-screening, Day -10 to Day 1)

During the pre-screening period (Visit 0), chart review may be performed to determine if a patient is potentially eligible for the study. No study-related procedures will be requested or performed prior to obtaining informed consent:

- Confirm the subject is potentially eligible for the study based on chart review of inclusion/exclusion criteria

6.2 Screening: Visit 1 (Day -1 to Day 1)

- Obtain informed consent
- Obtain medical and surgical history, to include targeted/pertinent medical and surgical history only
- Collect medication history (from 30 days prior to ICF signing; extended review specifically for dalbavancin or oritavancin receipt in the prior 60 days given long half-lives of these two drugs)
- Review and record relevant medical events that occurred during the induction period. Examples include source control procedures [see Definitions (Appendix B)], vascular access procedures [see Definitions (Appendix B)], and complications of pre-randomization antibiotic therapy.
- Collect blood samples for hematology, serum chemistry laboratory assessments, and coagulation lab tests (PT/PTT and /or INR), if not already complete per standard of care within 48 hours prior to randomization (see Section 7.2.1)
- Record most recent vital signs (blood pressure, respiration rate, pulse rate, and temperature); these must be performed within 48 hours prior to randomization
- Perform physical examination (see Section 7.1.1)
- Perform pregnancy test for women of childbearing potential (see definition in Appendix B) within 48 hours of randomization; ensure test is negative before randomization. If the serum test results cannot be obtained before randomization, a urine pregnancy test may be used for enrollment.

- Collect results of echocardiography to evaluate for endocarditis; perform an echocardiogram if it has not already been done as part of standard of care for this episode of bacteremia/endocarditis. Either a transthoracic or transesophageal echocardiogram is acceptable.
- Review concomitant medications
- Review and record any concomitant nondrug interventions (e.g., procedures performed with a goal of source control).

6.3 Open-label Treatment Period, Planned Study Visits

6.3.1 Baseline (Randomization): Visit 2 (Day 1)

After a subject signs the ICF at the Screening Visit, any additional evaluations required to confirm eligibility will be performed (see Section 6.2). Subjects that do not meet all eligibility criteria after signing informed consent, for example due to an abnormal laboratory result, will be considered screen failures. Subject eligibility should be confirmed (or reconfirmed) within a maximum of 24 hours prior to randomization.

Once eligibility is confirmed, the subject may be randomized. Enrollment of subjects will be done online using the enrollment module of Advantage eClinical. Subjects will be randomized to receive either a 2-dose regimen of dalbavancin, or to completion of 4 to 6 weeks (maximum of 8) of standard of care antibiotic therapy in a 1:1 allocation ratio based on the randomization schedule further described in Section 10.3.1.

The Baseline Visit (Visit 2) will be conducted within a maximum of 10 days of effective antibiotic therapy for the qualifying bloodstream infection, after having confirmed defervescence for at least 24 hours and clearance of bacteremia from the qualifying pathogen, with negative blood culture incubated for at least 48 hours. Study procedures will be reviewed with the patient and the caregiver, if applicable.

At Baseline (Visit 2), the following procedures will be performed:

- Review medical and surgical history.
- Review concomitant medications (medications post first dose of study product).
- Collect QoL data.
- Randomization.
- Measure vital signs (blood pressure, respiration rate, pulse rate, and temperature).
- Perform targeted physical examination, focused on changes from screening.

- Administer IV dalbavancin or standard of care antibiotic therapy according to randomization as outlined in Section 4.3. The provider should designate which antibiotic is assigned as the study drug for patients randomized to standard of care group.
- Document study drug administration.
- For subjects receiving dalbavancin, collect blood samples for pharmacokinetic parameters prior to first dose, at end of infusion (+10 minutes), 6 (+/- 2) hours post end of dose, 12 hours (+/- 4) hours post end of dose, 24 (+/- 6) hours post end of dose, with documented draw time and date for each sample.
- Review and record AEs/SAEs/AESIs after study product (i.e., dalbavancin or SOC antibiotic) administration.
- Review and record any concomitant nondrug interventions (e.g., procedures performed with a goal of source control).

6.3.2 Visit 3 (Day 8 ± 1 day)

At Visit 3 the following procedures will be performed:

- Review and record AEs/SAEs/AESIs.
- Measure vital signs and perform targeted physical exam focused on changes from baseline, for patients who remain in the hospital or are receiving care at a location where research personnel can provide an in-person assessment (e.g. at an infusion center). Patients in the standard of care group who have been discharged from the hospital may have their symptoms assessed by telephone. If assessed by telephone, then all assessments for this visit will be done by phone and absence of vital signs/physical exam will not be a protocol deviation.
- For subjects receiving dalbavancin, collect blood samples for pharmacokinetic parameters prior to 2nd dose of dalbavancin on day 8 (+/- 1 day) with documented draw time and date.
- For subjects receiving dalbavancin, a serum creatinine assessment is required within 72 hours prior to the administration of the second dalbavancin dose. Whether a serum creatinine must be repeated on Day 8 will be at the discretion of the site investigator based upon stability of the serum creatinine in the preceding 72 hours and whether the serum creatinine is near the threshold where dose adjustment would be necessary (e.g., near 30 mL/min).
- Review concomitant medications.
- Review and record any concomitant nondrug interventions (e.g. procedures performed with a goal of source control).

- Document study drug administration.
- Collect QoL data.

6.3.3 Visit 4 (Day 22 ± 2 days)

At Visit 4 the following procedures will be performed:

- Review and record AEs/SAEs/AESIs.
- Measure vital signs (blood pressure, respiration rate, pulse rate, and temperature) and perform targeted physical examination, focused on changes from prior examinations.
- Collect blood samples for hematology and serum chemistry.
- For subjects who received dalbavancin, collect blood samples for pharmacokinetic parameters if feasible on day 22 (+/- 2 days) with documented time of draw and date.
- Review concomitant medications.
- Review and record any concomitant nondrug interventions (e.g. procedures performed with a goal of source control).
- Administer IV standard of care antibiotic therapy according to randomization as outlined in Section 4.3 and document compliance.
- Collect QoL data.

6.3.4 Visit 5 (Day 42 ± 3 days)

At Visit 5, the following procedures will be performed:

- Review and record AEs/SAEs/AESIs.
- Update medical history.
- Measure vital signs (blood pressure, respiration rate, pulse rate, and temperature) and perform targeted physical examination, focused on changes from prior examinations.
- Collect blood samples for hematology and serum chemistry.
- For subjects who received dalbavancin, collect blood samples for pharmacokinetic parameters if feasible on day 42 (+/- 3 days) with documented time of draw and date.
- Review concomitant medications.

- Review and record any concomitant nondrug interventions (e.g., procedures performed with a goal of source control).
- Administer IV standard of care antibiotic therapy according to randomization as outlined in Section 4.3 and document, if ongoing.
- Complete investigator assessment of efficacy.
- Collect QoL data.

6.3.5 Test of Cure: Visit 6 (Day 70 ± 7 days)

It is preferred that this visit be performed in-person, however a telephone visit is an acceptable alternative. If performed by telephone, then the subject should be asked about new symptoms (e.g. fever, pain) in lieu of a physical exam.

At Visit 6 (Day 70), the following procedures will be performed:

- Review and record AEs/SAEs/AESIs.
- Update medical history.
- Measure vital signs (blood pressure, respiration rate, pulse rate, and temperature) for patients with in-person visit.
- Perform targeted physical examination, focused on changes from prior examinations.
- For subjects who received dalbavancin, collect blood samples for pharmacokinetic parameters if feasible on day 70 (± 7 days) with documented time of draw and date.
- Review concomitant medications.
- Review and record any concomitant nondrug interventions (e.g., procedures performed with a goal of source control).
- Complete investigator assessment of efficacy.
- Collect QoL data.

6.3.6 Visit 7 (Day 180 ± 14 days – only for subjects with osteomyelitis)

Visit 7 will only be performed for subjects with osteomyelitis present at baseline assessment in order to determine long-term recurrence risk. As with visit 6, an in-person visit will be preferred however a telephone alternative will also be considered acceptable. If performed by telephone, the subject should be asked about specific symptoms (fever, back pain), resumption/continuation/repeat treatment with antibiotics for *S. aureus* osteomyelitis, or surgical intervention for osteomyelitis.

At Visit 7 (Day 180), the following procedures will be performed:

- Measure vital signs (blood pressure, respiration rate, pulse rate, and temperature) for patients with in-person visit.
- Perform targeted physical examination, focused on changes from prior examinations (especially point tenderness to spine or presence of neurologic deficits).
- Complete investigator assessment of efficacy.
- Collect QoL data.
- Review concomitant medications and concomitant nondrug interventions that are related to the treatment of osteomyelitis.

6.3.7 Final Study Visit

- For subjects without osteomyelitis, the final study visit will be Visit 6 (Day 70 ± 7 days) as above. For subjects with osteomyelitis, the final study visit will be Visit 7 (Day 180 ± 14 days) as above.

6.3.8 Early Termination Visit

In circumstances where a subject withdraws from the study or discontinues the study product (i.e., dalbavancin or SOC antibiotic) early, an Early Termination Visit will be performed, which include the following procedures:

- Review and record AEs/SAEs/AESIs.
- Update medical history.
- Measure vital signs (blood pressure, respiration rate, pulse rate, and temperature) and perform targeted physical examination, focused on changes from prior examinations.
- If clinically indicated, blood cultures should be collected at time of treatment discontinuation or for determination of treatment failure.
- Review concomitant medications.
- Review and record any concomitant nondrug interventions (e.g., procedures performed with a goal of source control).
- Complete investigator assessment of efficacy.
- For subjects who received dalbavancin, collect blood samples for pharmacokinetic parameters if feasible with documented time of draw and date.

- Collect QoL data.

6.4 Unscheduled Study Visits

An unscheduled study visit may be initiated by the subject/subject's LAR or investigator, if a subject is not improving on therapy, has a grade 3 and above AE or an SAE, or for any other reason. In addition, the reason for the visit will be documented, including who initiated the visit, what complaints the subject/subject's LAR has, and/or what concerns the primary medical team or site investigator have. Clinical outcome and any safety assessments will be documented.

Assessments to be completed at unscheduled study visits should include:

- Review and record AEs/SAEs/AESIs.
- Update medical history.
- Measure vital signs (blood pressure, respiration rate, pulse rate, and temperature) and perform targeted physical examination, focused on changes from prior examinations.
- Review concomitant medications.
- Review and record any concomitant nondrug interventions (e.g., procedures performed with a goal of source control).

6.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or protocol-specific Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions should be developed by the site and implemented promptly. It is the responsibility of the site Principal Investigator and other study personnel to use continuous vigilance to identify and report protocol deviations. All individual protocol deviations will be addressed in subject study records. All protocol deviations, either individual, product, or site-specific will be collected and the record stored in a sponsor-determined location. Protocol deviations must be sent to the IRB/IEC on which it relies per its guidelines as well as to the sites' local IRB/IEC if required. The site Principal Investigator and other study personnel are responsible for knowing and adhering to the requirements of their local IRB/IEC as well as the requirements of the IRB/IEC on which it relies.

Inability to draw pharmacokinetic samples will *not* be considered a violation of protocol, as pharmacokinetic sampling is being conducted for exploratory purposes only and does not alter in any way the planned treatment course for subjects.

7 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

7.1 Clinical Evaluations

7.1.1 Research Procedures

- Medical and Surgical History: includes targeted/pertinent medical and surgical history only.
- Medication History: from 30 days prior to signing the ICF, and 60 days for any prior lipoglycopeptides (oritavancin or dalbavancin) as reported by patient.[11]
- Vital Signs: Vital sign measurements will be documented at every in-person visit. The parameters are blood pressure (BP), respiration rate, pulse rate, and temperature. It is recommended that heart rate and BP readings be taken after the patient has been sitting for at least 5 minutes.
- Physical Examination: A physical examination (including general appearance, examination of head, eyes, ears, nose, throat, neck, skin, heart, lungs, abdomen, neurologic system, musculoskeletal system, extremities, height, and body weight) will be done at Screening (Visit 1). Physical examinations should be performed by a professionally trained physician or health professional licensed to perform physical examinations. Body weight and height will be measured at Screening (Visit 1). If height or weight is not obtainable (e.g., patient is immobilized), the last known or stated height and weight may be used. At subsequent visits, a targeted physical exam should focus on changes from prior exams and on the evaluation of newly reported symptoms.
- Echocardiograms: A transthoracic echocardiogram will be performed, or if clinically indicated, a transesophageal echocardiogram will be performed, unless one has been performed as standard of care for this episode of bacteremia/endocarditis. The overall interpretation and determination of the clinical significance of echocardiography findings will be the responsibility of the investigator, and the findings of all echocardiograms will be recorded in the patient's eCRF.
- Quality of Life Instruments: The following three QoL measures will be administered:

[11] As patients may receive medication prescriptions from multiple sources, patient-reported medications are intended to serve as the primary source for concomitant medications. For sites that have the ability to cross-query reported medications against prescription or medication administration records, this can be used as a secondary source but is not required.

- The ARLG Bloodstream Infection QoL Measure (Appendix C) is a 41-item questionnaire covering multiple domains of QoL.
- The EQ-5D-5L (https://euroqol.org/eq-5d-instruments/sample-demo/) is an instrument that comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as an overall self-rated health on a vertical visual analogue scale.
- The PROMIS Global Health short form (http://www.healthmeasures.net/administrator/components/com_instruments/uploads/Global%20Health%20Scale%20v1.2%2008.22.2016.pdf) is a 10-item instrument that assesses general health and five primary domains (physical function, fatigue, pain, emotional distress, and social health).

7.1.2 Assessment of Concomitant Medications/Treatments Other Than Study Product

Patient-reported medication history during the 30 days prior to ICF signing will be recorded at Screening (Visit 1) in the eCRF.[12] Thereafter, any changes in concomitant medications or new medications added will be recorded in the eCRF.

While most systemic medications taken by the subject, other than study drug, are considered concomitant medications and should be recorded, the following specific exceptions do *not* need to be recorded:

1. Topical medications (eye drops, ear drops, intranasal drops or sprays, dermatologic treatments, topical lidocaine)
2. Vitamins and supplements (e.g., vitamins, minerals, herbal supplements, dietary supplements, iron/ferrous sulfate, magnesium, calcium, electrolyte replacements)
3. Symptomatic care medications (e.g., antipyretics such as ibuprofen or acetaminophen, antihistamines, decongestants, non-steroidal anti-inflammatory drugs [NSAIDs])
4. Gastrointestinal agents (prokinetic agents, laxatives, stool softeners, gastrointestinal stimulants, antacids)
5. Nicotine replacement products (e.g., patches, lozenges, gums, nasal sprays)
6. Heparin flushes (e.g., as used for vascular access flushes)

All relevant concomitant systemic medications from Screening (Visit 1) through Day 70 ± 7 days (Visit 6) must be recorded in the subject's medical record and on the eCRFs. Specific dosages or

[12] As patients may receive medication prescriptions from multiple sources, patient-reported medications are intended to serve as the primary source for concomitant medications. For sites that have the ability to cross-query reported medications against prescription or medication administration records, this can be used as a secondary source but is not required.

dose changes for concomitant medications do not need to be recorded in the eCRFs. After Visit 6, for subjects with osteomyelitis, who are followed until Day 180 ± 14 days (Visit 7), the only concomitant medications that must be recorded are new antibiotics that are prescribed for the treatment of osteomyelitis. At each visit the investigator will obtain information on any therapeutic interventions (e.g., drug and nondrug therapy or surgery) provided. Subjects may not participate in any other antibiotic treatment trials or interventional studies involving non-FDA approved investigational products concomitantly while in this study.

Concomitant systemic antibacterials (other than dalbavancin or comparator study drug) for adjunctive therapy of the subject's *S. aureus* bacteremia are prohibited during the study, up to Day 70. This includes concomitant treatment with an aminoglycoside.

Patients who require additional therapy due to inadequate clinical response will be assessed as having lack of efficacy of study drug.

- Where possible, antibiotic treatment of intercurrent infections should be done with antibiotics that are not active against the patient's *S. aureus* isolate. Discussion with the DMID Medical Officer is encouraged before or within 24 hours of initiation of concomitant antibiotics for another indication. Exceptions include: Vancomycin oral 125 mg up to 500mg every 6 hours may be used in both treatment groups for the treatment of *Clostridium difficile* infections and may be continued as required throughout the duration of the study. The sponsor will not provide oral vancomycin.
- Metronidazole IV or oral 500 mg every 8 hours may be used in both treatment groups for the treatment of *C. difficile* infections and may be continued as required throughout the duration of the study. The sponsor will not provide metronidazole.
- Other antibacterials that do not achieve therapeutic levels in the serum (e.g., nitrofurantoin) may be considered. Consultation with the DMID Medical Officer is advised before use of these antibiotics.

7.1.3 Assessment of Subject Compliance with Study Intervention/Investigational Product/Investigational Device

Dalbavancin will be administered under the supervision of investigative site personnel, and infusion date, start, and stop time will be documented in the eCRF, as well as any infusion interruptions.

7.1.4 Non-Research Standard of Care

If clinically indicated, any surgical or non-surgical procedures required to achieve infection source control should be performed for patients enrolled in either treatment group. The necessity and timing of any such procedures will be decided upon by the patient's treating physicians. Procedures frequently required for source control in *Staphylococcus aureus* bacteremia may include

debridement of osteomyelitis, removal of indwelling vascular access device, prosthetic devices or materials, incision and drainage of any abscesses, or heart valve replacement.

7.2 Laboratory Evaluations

7.2.1 Clinical Laboratory Evaluations

The following laboratory evaluations will be evaluated during the study, per the schedule of events (Appendix A)

- Hematology: absolute and differential white blood cell (WBC) count, erythrocyte count, hemoglobin, hematocrit, and platelet count..
- Coagulation lab tests (PT/PTT and/or INR).
- Chemistry: sodium, potassium, calcium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total protein, alkaline phosphatase, albumin, total bilirubin, AST, and ALT.
- If clinically indicated, blood cultures should be collected at the time of treatment discontinuation or for determination of treatment failure. Blood cultures should be repeated every 24-48 hours upon knowledge of a positive result from any visit until clearance of bacteremia is confirmed. When blood cultures are required, 2 sets of blood samples (1 aerobic and 1 anaerobic bottle) should be obtained from 2 separate venipuncture sites.
- Culture, organism identification, and susceptibility testing will be conducted at the local laboratory. All pathogens will be tested for susceptibility; microbiological specimens and isolates will be collected, processed, and stored in accordance with local procedures.
- Pregnancy test (urine or serum).

7.2.2 Research Assays

Dalbavancin Concentration Measurements: Venous blood samples for PK analyses will be collected at Visit 2 (Day 1), Visit 3 (Day 8 ± 1 day),Visit 4 (Day 22 ± 2 days), Visit 5 (Day 42 ± 3 days), Visit 6 (Day 70 ± 7 days), or any early termination (ET) visit as outlined in Section 6 and Appendix A. The actual date and time of each blood sample collection will be recorded in the subjects' source document and the eCRF. Blood collected will be processed for plasma separation at the study site's laboratory; subsequent PK analyses will be performed on the plasma samples at a central laboratory. PK sample collection, labeling, processing, storage, and shipment instructions will be provided in the MOP.

7.2.2.1 Laboratory Specimen Preparation, Handling, and Storage

Plasma PK specimens will be processed and stored in a -70ºC or below freezer until time of shipment to the central PK laboratory for analysis. Detailed instructions for the preparation, handling, and storage of plasma PK specimens are detailed in the study MOP including aliquots of specimens, temperature requirements, where they will be stored, and how they will be labeled.

7.2.2.2 Laboratory Specimen Shipping

Plasma PK samples will be shipped on dry ice to the central PK laboratory. Samples will be shipped in compliance with the International Air Transport Association (IATA) regulations. Instructions for the shipment of specimens are outlined in the study MOP.

8 ASSESSMENT OF SAFETY

8.1 Assessing and Recording Safety Parameters

This study will assist in determining the safety of dalbavancin compared to that of standard of care for the treatment of complicated *S. aureus* bacteremia. Safety will be assessed by the frequency of SAEs, AESIs, and the frequency of AEs leading to study drug discontinuation in each treatment arm.

8.1.1 Adverse Events (AEs)

ICH E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs of grade 3 or higher including lab abnormalities (per CTCAE table, version 5.0, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf) will be captured on the appropriate data collection form and eCRF. All AEs, regardless of grade, leading to study drug discontinuation will be captured on the appropriate data collection form and eCRF. AESIs of all grades will also be captured (see Section 8.2.1). Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product (i.e., dalbavancin or SOC antibiotic) and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator), date of resolution, seriousness and outcome. AEs and AESIs that meet reporting criteria and occur during the trial collection and reporting period will be documented appropriately regardless of relationship and will be followed through resolution or through the end of the study, whichever occurs first. Resolution of an AE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

For the purpose of the site's data collection responsibilities, any untoward event that was reported from the time of first study drug dose (i.e., dalbavancin or SOC antibiotic) after randomization at the Baseline Visit (Visit 2) until study Visit 6 is to be considered an AE.

Examples of AEs are as follows:

- Changes in the general condition of the patient from baseline

- Subjective symptoms offered by or elicited from the patient
- Objective signs observed by the investigator or other study center personnel
- All diseases that occur after administration of study drug at the Baseline Visit, including any change in severity or frequency of pre-existing disease
- All clinically significant abnormalities in laboratory values or clinically significant physical findings that occur during the study collection and reporting period. However, a single abnormal laboratory result does not automatically indicate progression of a chronic condition. For example, a transient spike in blood glucose level for a subject with diabetes is not reported as an AE.

Please note that hospital admissions and/or medical/surgical procedures scheduled prior to study drug administration but occurring during the study should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

Any medical condition that is present at the time of signing of ICF when the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded in source documents as an AE. In this trial, only Grade 3 and higher AEs, AEs of any grade leading study drug discontinuation, and AESIs will be captured in the eCRF.

Any abnormal test result that is determined to be an error does not require reporting as an AE. Additional diagnostic testing or medical/surgical interventions that occur as a result of an AE due to an abnormal laboratory test finding should be noted in the eCRF, if it meets protocol-specified reporting criteria.

8.1.1.1 Adverse Events Grading

All AEs (laboratory and clinical symptoms) will be graded for severity (per CTCAE table, version 5.0, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf) and assessed for relationship to study product (i.e., dalbavancin or SOC antibiotic) as outlined below. AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF. Changes in the severity of an AE will be documented in the source documents at the site to allow an assessment of the duration of the event at each level of intensity.

Severity of Event:

AEs will be assessed by the investigator (those with the training and authority to make a diagnosis and listed on the Form FDA 1572) using the CTCAE, version 5.0

(https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf). The investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate source documentation. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 8.1.2). Severity will be assessed according to CTCAE, version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf), which follows the following general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (ADL).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Relationship to Study Product: The assessment of the AE's relationship to study product (i.e., dalbavancin or SOC antibiotic) will be done by a licensed study investigator indicated on the Form FDA 1572 and the assessment will be part of the documentation process. Whether the AE is related or not, is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

In a clinical trial, the study product must always be suspect. The relationship to study product (i.e., dalbavancin or SOC antibiotic) will be assessed for AEs using the terms related or not related:

- Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.2 Serious Adverse Events (SAEs)

An AE or suspected adverse reaction is considered a serious adverse event (SAE) if, in the view of either the site principal investigator or sponsor, it results in any of the following outcomes:

- Death,

- A life-threatening adverse event[1],
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

[1] Life-threatening adverse event. An AE is considered "life-threatening" if, in the view of either the site principal investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

SAEs will be:

- Assessed for severity and relationship to study product (i.e., dalbavancin or SOC antibiotic) and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 or by the Institution as the site Principal Investigator or Sub-Investigator.
- Recorded on the appropriate SAE data collection form and eCRF.
- Followed through resolution by a licensed study physician (for IND studies, a physician listed on the Form FDA 1572 as the site Principal Investigator or Sub-Investigator).
- Reviewed and evaluated by DMID, the DSMB (periodic review unless related), and the IRB/IEC.

8.2 Specification of Safety Parameters

Safety will be assessed by the frequency and severity of AEs, AESIs, and SAEs.

Safety will be assessed using descriptive statistics of AEs, vital signs, and laboratory tests by treatment group. For each safety parameter, the last assessment made before the first dose of study product will be used as the baseline for all analyses of that safety parameter.

8.2.1 Adverse Events of Special Interest (AESIs)

Adverse events of special interest (AESIs) are AEs that are common and known to occur following administration of study product (i.e., dalbavancin or SOC antibiotic). AESIs that are related to study product (i.e. dalbavancin or SOC antibiotic) will be collected after first dose of study product (i.e., dalbavancin or SOC antibiotic) is given and until final study visit. AESIs will be recorded on the eCRF and entered into the EDC. AESIs will include any CTCAE grades of allergic reaction, catheter-related infection, vascular access complication, infusion site extravasation, infusion-related reaction, alanine aminotransferase increases, aspartate aminotransferase increases, and acute kidney injury.

If an intravascular catheter related complication is related to the catheter or vascular access device itself and not to study medication being administered (e.g., catheter-associated thrombosis or catheter-associated infection), this should still be recorded as an adverse event of special interest but can be marked as not related to study drug.

8.3 Reporting Procedures

8.3.1 Reporting Serious Adverse Events

SAEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Any AE that meets a protocol-defined serious criterion that is judged to be <u>related</u> to either study product (i.e., dalbavancin or SOC antibiotic) must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group, at the following address:

DMID Pharmacovigilance Group

Clinical Research Operations and Management Support (CROMS)

6500 Rock Spring Dr. Suite 650

Bethesda, MD 20817, USA

SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)

SAE FAX Number: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)

SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, select SAE data fields must also be entered into the data coordinating center (DCC) database system, regardless of relationship to study product (i.e., dalbavancin or SOC antibiotic). Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The DMID Medical Monitor and DMID Clinical Project Manager will be notified of the related SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

SAEs that that are judged to be **not related** to study product (i.e., dalbavancin or SOC antibiotic) will be captured on the appropriate data collection form and eCRF, but do not require separate reporting to the DMID Pharmacovigilance Group.

At any time after completion of the study, if the site principal investigator or appropriate sub-investigator becomes aware of an SAE that is suspected to be related to dalbavancin that occurred during the subject's participation in the study, the site principal investigator or appropriate sub-investigator will report the event to the DMID Pharmacovigilance Group.

8.3.2 Regulatory Reporting for Studies Conducted Under DMID Sponsored IND

Following notification from the site Principal Investigator or appropriate sub-investigator, DMID, as the IND sponsor, will report any suspected unexpected serious adverse event. DMID will report an SAE as a Suspected Unexpected Serious Adverse Reaction (SUSAR) only if there is evidence to suggest a causal relationship between the study intervention and the SAE and based on whether that event is listed in the investigator brochure. DMID will submit an IND safety report to the FDA and will notify all participating site Principal Investigators (i.e., all Principal Investigators to whom the sponsor is providing drug under its IND(s) or under any Principal Investigator's IND(s) of potential serious risks from clinical studies or any other source, as soon as possible. DMID will report to the FDA any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. If the event is not fatal or life-threatening the IND safety report will be submitted within 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to the FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All SAEs designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

8.3.3 Reporting of Pregnancy

Female subjects of childbearing age who become pregnant during the study prior to day 8 will not receive the second dose of dalbavancin (if randomized to the dalbavancin group) and will be followed for pregnancy outcome. Pregnancy occurring during a subject's participation in the study must be recorded in the database within 5 days of site awareness, on the Pregnancy Report form. The report will include pregnancy outcome (e.g., any premature terminations, elective or therapeutic, any spontaneous abortions or stillbirths), as well as the health status of the mother and child, including date of delivery and infant's sex and weight. Any subject with a positive pregnancy test, who has received study product(s), will be followed through eight (8) weeks post-live delivery or elective or natural termination of the pregnancy, whichever occurs first. If the database is locked at time of pregnancy, a supplemental report will be generated and completed after birth, which will be appended to the database. Any occurring AEs or SAEs that occur to the mother or fetus will be recorded in the eCRF in the database and on the SAE Report form.

The site is responsible for notifying the IRB/IEC on which it relies of any pregnancies in accordance with their policies as well as notifying their local IRB/IEC of any pregnancies in accordance with local policies.

8.4 Type and Duration of Follow-up of Subjects after Adverse Events

AEs will be assessed, and AEs that are CTCAE grade 3 and higher, as well as all AESIs, will be followed from initial recognition of the AE until resolution or through the end of the study, whichever occurs first.

SAEs will be followed up through resolution even if duration of follow-up goes beyond the protocol-defined follow-up period (test of cure).

Resolution of an AE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

8.5 Halting Rules

8.5.1 Study Halting Criteria

The halting rules outlined below will be used to evaluate whether it is safe to proceed with dosing or whether the study should be suspended for further safety evaluation.

If any of the halting rules below are met, further enrollment will be halted pending DSMB review of safety data and recommendations. The continuation of the administration of dalbavancin (the second dose) or switch to SOC will be at the site PI discretion.

- More than one subject **death** (e.g., 2 or more deaths) during participation in the study that is **suspected to be related** to the treatment with **dalbavancin**. Note that mortality among patients with *S. aureus* bacteremia is not uncommon, and deaths that are not directly and solely related to dalbavancin will not by themselves trigger this halting rule.
- Five or more subjects in the study are suspected with development of drug induced liver injury (DILI) that are assessed as **related** to **dalbavancin.**
- Five or more subjects in the study experience a Grade 4 **related** to **dalbavancin** AEs (laboratory or systemic) that are coded in the same HLGT per MedDRA classification.

8.5.2 Individual Halting Rules

A subject will be discontinued from further dosing in either treatment group if any of the following criteria are met:

- An individual infusion must be stopped if a drug-related hypersensitivity (grade 2 or higher) to dalbavancin or standard of care study drug is suspected, including anaphylaxis. Note that dalbavancin infusion can cause reactions that resemble "Red-Man Syndrome," including flushing of the upper body, urticaria, pruritus, and/or rash. Stopping or slowing the infusion may result in cessation of these reactions and this reaction is not by itself a reason to discontinue dalbavancin for an individual subject.
- New onset of illness or condition that meets exclusion criteria, at the investigator's discretion
- The treatment of any subject may be stopped for SAEs, clinically significant adverse events, including severe laboratory abnormalities that indicate to the Investigator that continued dosing is not in the best interest of the patient.

8.6 Safety Oversight

8.6.1 Data and Safety Monitoring Board (DSMB)

Safety oversight will be conducted by a DSMB that is an independent group with expertise to interpret data from this study and will monitor subject safety and advise DMID. The DSMB members will be separate and independent of study personnel participating in the study and should not have scientific, financial, or other conflict of interest related to this study. DSMBs must consist of at least three voting members, including a biostatistician experienced in statistical methods for clinical trials and a clinician with relevant expertise.

The DSMB will operate under the rules of a DMID-approved charter that defines the data elements to be assessed and the procedures for data reviews and will be written at the organizational meeting of the DSMB. Procedures for DSMB reviews/meetings will be defined in the charter. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs. The DSMB will review SAEs on a regular basis and ad hoc during this trial. The DMID Medical Monitor will be responsible for reviewing SAEs in real time.

As defined in the charter, the DSMB will review data at specified times during the course of the study for subject and overall study progress and will conduct ad hoc reviews as appropriate when a halting rule is met or for immediate concerns regarding observations during this study.

The DSMB will conduct the following meetings:

- Organizational meeting
- Data review meeting for safety
- Every year
- An Interim analysis for futility after at least approximately 50% of subjects have completed the study
- Ad hoc meetings will occur when a halting rule is met, or when DMID or the DSMB chair has immediate concerns regarding observations during the trial
- Final review meeting will occur 6-8 months after the clinical database is locked to review cumulative safety and efficacy data. The final CSR, if available, will be provided for this review. The DSMB may be asked to provide recommendations in response to DMID's questions.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs. The DSMB will review grouped data in the closed session only. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study treatments), and to continue, modify, or terminate this trial.

9 HUMAN SUBJECTS PROTECTION

9.1 Institutional Review Board/Independent Ethics Committee

Each site principal investigator will obtain IRB approval for this protocol to be conducted at his/her research site(s) and send supporting documentation to the DMID before initiating recruitment of subjects. The investigator will submit applicable information to the IRB/IEC on which it relies for the review, to conduct the review in accordance with 45 CFR 46, ICH E6 GCP, and as applicable, 21 CFR 56 (Institutional Review Boards) and 21 CFR 50 (Protection of Human Subjects), other federal, state, and local regulations. The IRB/IEC must be registered with OHRP as applicable to the research. DMID must receive the documentation that verifies IRB/IEC-approval for this protocol, associated informed consent documents, and upon request any recruitment material and handouts or surveys intended for the subjects, prior to the recruitment and enrollment of subjects.

Any amendments to the protocol or consent materials will be approved by the IRB/IEC before they are implemented. IRB/IEC review and approval will occur at least annually throughout the enrollment and follow-up of subjects and may cease if annual review is no longer required by applicable regulations and the IRB/IEC. The investigator will notify the IRB/IEC of deviations from the protocol and reportable SAEs, as applicable to the IRB/IEC policy.

Each institution engaged in this research will hold a current FWA issued by the Office of Human Research Protection (OHRP) for federally funded research.

A single IRB of record, (WIRB Copernicus Group), will be accountable for compliance with regulatory requirements for this multi-centered study, at participating sites. A formal Reliance Agreement will be required between the single IRB and participating sites. The formal Reliance Agreement will set forth the specific responsibilities of the IRB and each participating site. Participating sites will then rely on the IRB of record to satisfy the regulatory requirements relevant to the IRB review. The participating sites will maintain essential required documentation of IRB reviews, approvals, and correspondence, and must provide copies of any agreements and essential documentation to the DMID or regulatory authorities upon request.

9.2 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained and documented. Subjects will receive a concise and focused presentation of key information about the clinical trial, verbally and with a written consent

form. The explanation will be organized, and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

An investigator or designee will describe the protocol to potential subjects face-to-face. The key information about the purpose of the study, the procedures and experimental aspects of the study, risks and discomforts (including the PK sampling plan for subjects receiving dalbavancin), any expected benefits to the subject, and alternative treatment will be presented first to the subject.

Subjects will also receive an explanation that the trial involves research, and a detailed summary of the proposed study procedures and study interventions/products. This will include aspects of the trial that are experimental, the probability for random assignment to treatment groups, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or to the embryo or fetus, if the subject is or may become pregnant, that are currently unforeseeable), the expected duration of the subject's participation in the trial, alternative procedures that may be available and the important potential benefits and risks of these available alternative procedures.

Subjects will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. Subjects will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Subjects will be informed of the anticipated financial expenses, if any, to the subject for participating in the trial, as well as any anticipated prorated payments, if any, to the subject for participating in the trial. They will be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project.

Information will also include the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. The subjects will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the subject is otherwise entitled.

The extent of the confidentiality of the subjects' records will be defined, and subjects will be informed that applicable data protection legislation will be followed. Subjects will be informed that the monitor(s), auditors(s), IRB, NIAID, and regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the subject is authorizing such access.

Subjects will be informed that records identifying the subject will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the subject's identity will remain confidential. Subjects will

be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Subjects will be allowed sufficient time to consider participation in this research trial, and have the opportunity to discuss this trial with their family, friends or legally authorized representative, or think about it prior to agreeing to participate.

Informed consent forms will be IRB-approved and subjects will be asked to read and review the consent form. Subjects must sign the informed consent form prior to starting any study procedures being done specifically for this trial.

Once signed, a copy of the informed consent form will be given to the subject(s) for their records. The subject(s) may withdraw consent at any time throughout the course of the trial. The rights and welfare of the subject(s) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Study personnel may employ recruitment efforts prior to obtaining study consent if a patient-specific screening consent is on record or if the IRB has agreed that chart review is allowed without a fully executed screening consent. In cases where there is not a patient-specific screening consent on record, site Clinical staff may pre-screen via chart review and refer potential subjects to the Research staff. Research staff would obtain written consent per the standard informed consent process before conducting protocol-specific screening activities.

New information will be communicated by the site principal investigator to subjects who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated and subjects will be re-consented per IRB requirements, if necessary. Subjects will be given a copy of all informed consent forms that they sign.

9.2.1 Other Informed Consent Procedures

Use of a Legally Authorized Representative (LAR)

Potential subjects for this study are adults but may be unable to provide legally effective informed consent due to their health status (*i.e*., dementia, intubated, sedated). The subjects may be enrolled in the study if consent is obtained from the LAR. The investigator will be familiar with the IRB/IEC policy on which he/she relies regarding the priority list of LAR and whether enrollment in a study is permitted by an advanced directive *(e.g*., living will, durable power of attorney for proxy consent). Additionally, subjects will be informed about the study to the extent compatible with the person's understanding, and enrollment declined if the subject refuses participation.

If a LAR originally provides legally effective informed consent and the subject's condition improves, the subject will also be informed about the study as soon as is feasible and will be re-consented. The subject may continue in the study only if the subject's consent is provided.

9.3 Exclusion of Women, Minorities, and Children (Special Populations)

Children will be excluded from this trial. Management algorithms for *S. aureus* bacteremia are different in children and their participation would thus not be appropriate.

9.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, subject's clinical information, and all other information generated during participation in the study. No information concerning the study or the data generated from the study will be released to any unauthorized third party without prior written approval of the DMID and the subject. Subject confidentiality will be maintained when study results are published or discussed in conferences. The study monitor or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

All records will be kept locked and all computer entry and networking programs will be carried out with coded numbers only and with password protected systems. All non-clinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number.

9.5 Certificate of Confidentiality

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the Federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent the subject from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the

subject's consent, information that would identify the subject as a participant in the research project regarding matters that must be legally reported including: child and elder abuse, sexual abuse, or wanting to harm themselves or others.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains.

9.6 Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for the research tests, procedures, and study product while taking part in this trial. Procedures and treatment for clinical care may be billed to the subject, subject's insurance or third party. Subjects may be compensated for their participation in this trial. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval.

If it is determined by the site principal investigator that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating site. No financial compensation will be provided to the subject by the NIAID, NIH to the subject for any injury suffered due to participation in this trial.

10 STATISTICAL CONSIDERATIONS

This is a phase 2b, multicenter, open-label, randomized, assessor-blinded, superiority study comparing a 2-dose dalbavancin regimen to standard of care therapy for the treatment of complicated bacteremia caused by *S. aureus*. Participants will be followed for 70 days, except for the subset with osteomyelitis who will be followed for 180 days.

On the basis of the intention-to-treat (ITT) principle, the primary outcome will be analyzed on the ITT set (defined as all participants as randomized regardless of whether they received the randomized treatment). A sensitivity analysis will be conducted using the modified ITT (mITT) population - defined as all participants who received at least one dose of study drug. Additionally, as one of the secondary assessments, we will compare the individual components of the DOOR outcome by treatment arm within the ITT population.

The secondary efficacy assessment, a non-inferiority analysis of overall clinical success rates by treatment group, will be conducted on the mITT population.

The secondary safety assessment will analyze rates of SAEs or of AEs leading to study drug discontinuation on the mITT population.

For all tests, *P* values will be two-sided with alpha < 0.05 level of significance. All reported confidence intervals will be two-sided 95%.

The outcomes could be missing for subjects who withdraw from the trial. The reasons for withdrawal will be reported and compared qualitatively by groups. The effect that any missing data might have on results will be assessed via sensitivity analysis. If the pattern of missing data is different to that envisaged at the design stage, further sensitivity analyses will be provided that are tailored to the missing data pattern observed.

The statistical analysis plan, which includes more technical and detailed elaboration of the principal features stated in the protocol, will be prepared separately.

10.1 Study Hypotheses

The primary objective is to compare the Desirability of Outcome Ranking (DOOR) at day 70 for dalbavancin versus standard of care antibiotic therapy for the treatment of complicated *S. aureus* bacteremia, conducted as a superiority assessment within the intention to treat population. We hypothesize that dalbavancin will have a higher DOOR relative to standard of care (e.g., the probability of a randomly selected patient having a better DOOR if assigned to receive dalbavancin versus standard of care (plus half the probability of a tied DOOR) is >50%). The null hypothesis would be no significant difference in DOOR between dalbavancin versus standard of care.

The key secondary objective will assess traditional clinical efficacy examining composite occurrence of clinical failure, infectious complications, or mortality as a non-inferiority comparison within the intention to treat population. We hypothesize that dalbavancin will have a non-inferior clinical efficacy rate relative to standard of care within a 20% absolute margin. The null hypothesis would be that dalbavancin has an inferior clinical efficacy relative to standard of care. The selection of a 20% non-inferiority margin is in line with previously published SAB trials, including the registrational trial of daptomycin versus standard of care (Fowler et al 2006). The protocol for an upcoming trial of ceftobiprole versus daptomycin includes a similar margin constructed around the particular context of SAB, noting that a non-inferiority margin of 20% includes more than half of the anticipated benefit of active-control treatment relative to untreated subjects (Hamed et al 2020). Additional secondary objectives will include a safety assessment and evaluation of the individual components of the primary DOOR outcome. Safety will be assessed by comparing the occurrence of serious (grade 3 or worse) adverse drug events between the dalbavancin and standard of care arms within the safety population. Each of the components of the DOOR outcome will be compared between the dalbavancin arm and standard of care arm within the ITT population.

10.2 Sample Size Considerations

The study is powered for a superiority comparison based on the primary objective, a comparison of DOOR outcomes. The probability of a subject from the dalbavancin arm having a superior DOOR ranking relative to a subject from the standard of care arm will be calculated along with a 95% confidence interval. Superiority will be considered to have been achieved if the 95% confidence interval for probability of having a superior DOOR ranking with dalbavancin does not cross 50%. If the confidence interval crosses 50% however, the null hypothesis cannot be rejected.

Sample size was calculated on the basis of the primary hypothesis. Assuming a 65% probability of a better DOOR in the dalbavancin treatment group versus the standard of care treatment group, with a 90% power and alpha=0.025 (by one-sided Wilcoxon rank sum test), 78 participants would be required in each treatment group. To allow for some inflation assuming around 12% of missing data or other study imperfections, using the method in Lachin (1981), we plan to recruit 100 per arm (200 subjects in total). Sample size was calculated using nQuery (MTT1-1 Module) (Version 8, Statistical Solution Ltd).

10.3 Treatment Assignment Procedures

10.3.1 Randomization Procedures

Once consented and upon entry of demographic data and confirmation of eligibility for the trial, the subject will be enrolled. Enrollment of subjects will be done online using the enrollment module of

Advantage eClinical. Subjects will be randomized 1:1 to dalbavancin or standard of care. Randomization will be stratified based on screening pathogen, MSSA vs. MRSA.

The list of randomized treatment assignments will be prepared by statisticians at the DCC (The Emmes Company). Emmes will assign each subject a treatment code and treatment assignment from the list after demographic and eligibility data have been entered.

Instructions for use of the enrollment module are included in the Advantage eClinical User's Guide. Manual back-up procedures and instructions are provided for use in case the site temporarily loses access to the internet or the online enrollment system is unavailable.

10.3.2 Masking Procedures

Study subjects and treating physicians will not be masked to treatment, as this is an open label study. Treatment group will be masked for study adjudicators.

10.4 Planned Interim Analyses

The DSMB will review interim reports of efficacy by treatment strategy. There will be one formal interim analysis of futility after approximately 50% of subjects have completed the trial. The statistical methods for the interim analysis will be fully specified in advance in a statistical analysis plan (SAP), to be prepared by a statistician, and summarized briefly in Section 10.4.2 below.

10.4.1 Interim Safety Review

The DSMB will evaluate safety at pre-specified intervals and at least yearly; however, ongoing review and summary of subject safety will occur to allow for early detection of a safety signal that may result from an AE or lack of efficacy of study drug. The DSMB will advise DMID on whether to continue, modify, or terminate the trial based on a risk-benefit assessment.

10.4.2 Interim Futility Review

A single interim analysis will be performed after approximately 50% of subjects have completed the trial. The interim futility analysis will consist of a quantitative evaluation of potential effect sizes and associated precision using a predicted intervals and predicted interval plots (PIPS) approach. Briefly, predicted intervals for both primary DOOR and secondary clinical failure outcomes will be modeled under a range of assumptions including: 1) the trends in outcomes observed at interim analysis continue to end of study, 2) the alternative hypothesis is true, 3) the null hypothesis is true, and 4) best and worst case scenarios for remaining outcomes. By relying on prediction intervals, no statistical hypothesis testing is required and no power is lost at interim analysis.

10.5 Final Analysis Plan

Results from primary and secondary endpoint analyses may be distributed by the SDCC to key study team members (protocol PIs, protocol statisticians, and other necessary study team members) after database lock and prior to the generation of all the CSR Tables, Listings, and Figures. These analyses may be used by the company collaborator for planning subsequent trials or by the lead principal investigator for manuscript and abstract development while the CSR is being finalized.

10.5.1 Study Populations

Five populations will be considered in the statistical analysis of the study:

1. *Screened Population*: The screened population will consist of all patients who undergo the Screening Visit (Visit 1) and receive a Patient Identification (PID) number.
2. *Intent-to-Treat/Randomized Population*: The intent-to-treat (ITT) population will consist of all randomized patients regardless whether or not they received study treatment.
3. *Safety Population*: The safety population will consist of all randomized patients who received at least 1 dose of study drug. Patients will be analyzed based on the treatment received.
4. *Modified Intent-to-Treat Population*: The modified intent-to-treat (mITT) population will consist of all patients in the ITT population who received at least one dose of study drug.
5. *Clinically Evaluable Population*: The CE population will consist of all patients in the mITT population who met criteria for clinical evaluability. Patients will be considered clinically evaluable if they have a primary outcome assessment and do not have missing data or major protocol violations that prevent the adjudication committee from evaluating their outcomes.

An independent, blinded adjudication committee will be used to review the data from each patient to establish the baseline diagnosis, final diagnosis, and final outcome (including DOOR outcome and its individual components), including reasons for treatment failure. This committee will consist of 3-4 infectious disease experts with no relevant conflicts of interest.

10.5.2 Patient Disposition

The number of subjects in four of the study populations (ITT, Safety, mITT, and CE) will be summarized by treatment group and study center; the screened population will only be summarized by study center.

Screen failures (i.e., patients screened but not randomized) and the associated reasons for failure will be tabulated overall. The number and percentage of subjects who complete the treatment period (up to Day 42) and of subjects who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for the ITT population. The reasons for premature discontinuation as recorded on the termination pages of the eCRF will be summarized (number and percentage) by treatment group for all randomized subjects, along with the number of subjects completing each visit.

10.5.3 Demographics and Other Baseline Characteristics

Demographic parameters (i.e., age, race, ethnicity, sex, weight, height, body mass index) and other baseline characteristics will be summarized by treatment group for the Safety and ITT populations. Continuous variables will be summarized by number of subjects and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects. The number and percentage of subjects with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized by treatment group for the ITT population.

Prior medication is defined as any medication taken before the date of the first dose of study product. Concomitant medication is defined as any medication started on or after the date of the first dose of study product.

Both prior and concomitant medication use will be summarized by the number and proportion of subjects in each treatment group receiving each medication within each therapeutic class for the safety population. If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject would be counted only once for the coded drug name or therapeutic class.

10.5.4 Extent of Exposure and Treatment Compliance

Exposure to study product for the safety population will be summarized for treatment duration, calculated as the number of doses of dalbavancin received for patients in the dalbavancin group, and by start and stop dates for standard of care antibiotics. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) will be presented by treatment group.

10.5.5 Efficacy Analysis

10.5.5.1 Primary Efficacy Analysis

The primary efficacy endpoint is the DOOR outcome at Day 70 post study entry (test of cure) in the ITT population. The clinical components of the DOOR outcome (survival, clinical success/failure, and infectious complications) will be determined by the blinded clinical adjudication committee (on a rolling basis). The DOOR probability is calculated, using the equation:

$$\text{DOOR probability} = \Pr[DOOR_D > DOOR_{SOC}] + \tfrac{1}{2}\Pr[DOOR_D = DOOR_{SOC}],$$

where $DOOR_D$ and $DOOR_{SOC}$ are the DOOR outcomes for dalbavancin and standard care groups, respectively, and $\Pr[DOOR_D > DOOR_{SOC}]$ is the probability of a DOOR from dalbavancin exceeding a DOOR from standard care and $\Pr[DOOR_D = DOOR_{SOC}]$ is the proportion of two DOOR outcomes being same. Pathogen (MSSA versus MRSA), which is considered in the permuted block randomization as a strata, will be incorporated into the calculation of the DOOR probability and its

corresponding 95% confidence interval (the stratified analysis). In addition, the DOOR probability and 95% confidence interval without strata will be calculated.

As a secondary analysis of the primary outcome will be:

i. DOOR distribution by groups
ii. Cumulative difference in DOOR categories for dalbavancin vs. Standard Care
iii. Point estimate and confidence interval of difference in mean partial credit vs. Standard Care
iv. Expected DOOR distribution for Standard Care and the expected numbers gained loss in each category with treatment

The same analysis above will be repeatedly conducted on the DOOR outcome at Day 42.

As an explanatory analysis of the primary outcome, in addition to pathogen (MSSA vs. MRSA), baseline covariate-adjustment analysis and subgroup analysis will be conducted.

10.5.5.2 Secondary Efficacy Outcomes

As the secondary efficacy outcomes, each component of the DOOR will also be examined separately: clinical success, infectious complications, SAEs, AEs leading to study drug discontinuation, all-cause mortality. Descriptive statistics, including number and percentage for the categorical variables, will be provided by groups.

Clinical failure at Day 70 will be analyzed using generalized estimating equations (GEE) assuming an unstructured correlation structure, including clinical failure at Day 42 (explanatory analysis time point). The difference in proportions of clinical failure between the two groups at Day 70 will be calculated with the corresponding 2-sided 95% confidence interval. As a sensitivity analysis, generalized linear mixed model (GLMM) approach will be used to analyze clinical failure.

10.5.5.3 Additional Efficacy Parameters

1. QoL score – QoL will be assessed using the ARLG Bloodstream Infection QoL Measure for the primary and exploratory endpoints (Appendix C). Two additional comparator measures (EQ-5D-5L, https://euroqol.org/eq-5d-instruments/sample-demo/ and PROMIS Global Health short form, http://www.healthmeasures.net/administrator/components/com_instruments/uploads/Global%20Health%20Scale%20v1.2%2008.22.2016.pdf) will also be collected and will be used in exploratory analyses only.
2. Desirability of Outcome Ranking (DOOR) (Evans 2015) endpoint results at Day 42.

For the additional efficacy endpoints, descriptive statistics will be provided by treatment group. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values by treatment group. Categorical variables will be summarized by number and percentage of patients by treatment group. For QoL measures, the descriptive statistics will be presented by item as well.

Descriptive statistics for the DOOR endpoint will be provided by treatment group and summarized by number of patients and mean, SD, median, minimum, and maximum values; p-values will be determined using the Wilcoxon-rank sum test for continuous variables.

10.5.6 Safety Analyses

Safety analyses will be based on the safety population. Safety will be assessed using descriptive statistics of AEs, vital signs, and laboratory tests by treatment group. For each safety parameter, the last assessment made before the first dose of study product will be used as the baseline for all analyses of that safety parameter.

10.5.6.1 Adverse Events

An AE (classified by preferred term) that occurs during the treatment period will be considered a treatment-emergent AE if it was not present before the first dose of study product or was present before the first dose of study product and increased in severity during the treatment period.

The number and percentage of patients reporting treatment-emergent AEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and causal relationship to the study product. If more than one AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by causal relationship to the study product.

The distribution of treatment-emergent AEs and AESIs by severity and causal relationship to the study product will be summarized by treatment group.

The incidence of common (≥ 2% of patients in any treatment group) treatment-emergent AEs, on-therapy SAEs, AESIs, and AEs leading to premature discontinuation of the study product will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for the study product. In addition, the incidence of fatal on-therapy SAEs (i.e., events that caused death) will be summarized separately by treatment group and preferred term. An SAE will be defined as an on-therapy SAE if it occurred during or after the first infusion of study product.

Listings will be presented for subjects with SAEs, AESIs, subjects with AEs leading to discontinuation, and subjects who die (if any).

10.5.6.2 Clinical Laboratory Parameters, and Vital Signs

Descriptive statistics for clinical laboratory values and changes from the baseline values at each assessment time point will be presented by treatment group for each clinical laboratory parameter.

Descriptive statistics for vital signs (e.g., pulse rate, systolic and diastolic BP) and changes from baseline values at each visit and at end of study will be presented by treatment group.

The number and percentage of subjects with potentially clinically significant (PCS) post-baseline clinical laboratory values will be tabulated by treatment group. The criteria for PCS laboratory values will be detailed in the statistical analysis plan. The percentages will be calculated relative to the number of subjects with available non-PCS baseline values and at least 1 post-baseline assessment. The numerator will be the total number of subjects with available non-PCS baseline values and at least 1 PCS post-baseline value. A supportive listing of subjects with PCS post-baseline values will be provided, including the PID number, study center number, and baseline and post-baseline values. A listing of all AEs that occur in subjects who have PCS laboratory values or vital signs will also be provided.

10.5.6.3 Exploratory Dalbavancin Plasma Pharmacokinetic Analyses

A range of exploratory analyses related to dalbavancin pharmacokinetics will be conducted among the subset of subjects receiving dalbavancin (n=100). The methodology used to evaluate PK parameters will be described in detail in the PK Plan and is reviewed briefly below.

Pharmacokinetic Analysis

Dalbavancin concentration-time data will be visualized using box and whisker plots, with investigation of any outliers for erroneous time or concentration data entry. Queries will be generated to resolve potential erroneous time or concentration data point entries due to transcription or measurement errors. Individual concentration-time plots will be generated on linear and semi-log scales to inform potentially optimal models for analysis.

Non-Compartmental Pharmacokinetic Analysis

Non-compartmental analysis (NCA) will serve as the initial approach to generate base PK parameter estimates for dalbavancin concentration-time data. These analyses will be conducted using an appropriate statistical package (e.g., Phoenix WinNonlin v8.2 or higher). This descriptive analysis will allow for comparison to previously published data. The following PK exposures for concentration-time data will be calculated as appropriate and if possible depending upon samples collected: plasma concentration prior to dose, maximum plasma concentration (C_{max}) after the first dose on Day 1, time to C_{max} (T_{max}), plasma concentration on Day 8 [C_{8day}], plasma concentration on day 22 (C_{22day}), concentration on day 42 (C_{42day}), concentration on day 70 (C_{70day}), area under the plasma concentration-time curve (AUC) from days 0-8 ($AUC_{0\text{-}8days}$), AUC from days 0-22 ($AUC_{0\text{-}22days}$), AUC from days 0-42 ($AUC_{0\text{-}42day}$), days 0-70 ($AUC_{0\text{-}70days}$), AUC from days 8-22 ($AUC_{8\text{-}22days}$), AUC from days 22-42 ($AUC_{22\text{-}42day}$), AUC from days 42-70 ($AUC_{42\text{-}70day}$), AUC to the last quantifiable sample ($AUC_{0\text{–}last}$), and AUC to infinity ($AUC0\text{–}\infty$).

Population Pharmacokinetic Analysis

Population Pharmacokinetic Analysis. Population pharmacokinetic analysis provides a platform to identify patient covariates which can help explain a portion of the interindividual variability in

selected PK parameters. The non-linear mixed effects modeling software NONMEM Version 7.3 or higher (ICON Development Solutions, Ellicott City, MD) will be used to develop the population PK model for dalbavancin concentrations in plasma. The first-order conditional estimation method with interaction (FOCEI) will be utilized; other estimation methods such as expectation-maximization (e.g., SAEM) will also be considered.

Structural PK model base development to model the plasma dalbavancin concentration-time data will be initiated using a linear three-compartment model with zero-order infusion as has been used previously (https://www.ncbi.nlm.nih.gov/pubmed/31087630). Other model modifications will be considered as necessary. Between-subject variability associated with model parameters and differing residual error structures will be tested. Model development will be guided by goodness of fit plots, plausibility of parameter estimates, reduction in inter-individual variability for structural and residual error parameters, as well as objective function and shrinkage values.

Upon selection of an appropriate base structural PK model, covariate effects (e.g., age, gender, body size descriptors, creatinine clearance, albumin and IV drug use status) will be evaluated using stepwise forward selection followed by stepwise backward elimination processes. Model validation will be assessed through visual predictive checks as well as bootstrapping. A listing of the individual PK parameters derived using the final population PK model will be provided for each patient. The steady-state volume of distribution (V_{ss}) will be calculated as the sum of the central (V_c) and peripheral volume terms (V_{p1} and V_{p2}). The alpha-phase half-life ($T_{1/2,\alpha}$) beta-phase half-life ($T_{1/2,\beta}$) and gamma-phase half-life ($T_{1/2,\gamma}$) will be calculated for each patient using the individual post-hoc PK parameters. Summary statistics (mean, standard deviation, median, minimum and maximum) will be calculated using CL, V_c, V_{p1}, V_{p2}, V_{ss}, $T_{1/2,\alpha}$, $T_{1/2,\beta}$, and $T_{1/2,\gamma}$ values.

Exposure-Response Relationship Analysis

Using the final population PK model, individual post-hoc PK parameters, and the individual patient dosing histories, simulations will be performed to generate plasma dalbavancin concentration-time profiles and calculate plasma dalbavancin exposure measures for each study subject. The following exposure variables will be calculated for each patient: C_{max}, C_{8day}, C_{22day}, C_{42day}, C_{70day}, $AUC_{0\text{-}8days}$, $AUC_{0\text{-}22days}$, $AUC_{0\text{-}42day}$, $AUC_{0\text{-}70days}$, $AUC_{8\text{-}22days}$, $AUC_{22\text{-}42day}$, $AUC_{42\text{-}70day}$, and AUC to infinity (AUC0–∞). The associations between each of the simulated dalbavancin exposures, as appropriate, and each outcome of interest will be explored using standard exposure-response methodologies. Only simulated exposures that occurred prior to the outcome of interest will be considered. The outcomes evaluated will include (1) DOOR outcomes at day 42, mortality at day 42, infectious complications at day 42, adverse drug effects (grade 3 or higher) at day 42, late recurrence at 6 months (within the subset having osteomyelitis), and occurrence of AST/ALT elevation >3x upper limit of normal during treatment. Multivariable models will be used to estimate the effect of individual exposures measures on outcomes while accounting for relevant covariates.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Each site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, each participating site(s) and its subcontractors are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site principal investigator will provide direct access to all study-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site principal investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the participating site(s) for clarification and resolution.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue permanent ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source data collection forms and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source data collection forms should be consistent or the discrepancies should be explained.

The sponsor and/or its designee will provide guidance to the site principal investigators and other study personnel on making corrections to the data collection forms and eCRF.

13.2 Data Coordinating Center/Biostatistician Responsibilities

Data collection is the responsibility of the study personnel at the participating clinical study site under the supervision of the site principal investigator. During the study, the site principal investigator must maintain complete and accurate documentation for the study.

The data coordinating center for this study, the Emmes Company, will be responsible for data management, quality review, analysis, and reporting of the study data.

13.3 Data Capture Methods

Clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory values) will be collected on data collection forms by study personnel then entered into eCRFs via a 21 CFR Part 11-compliant internet data entry system provided by the study data coordinating center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

13.4 Types of Data

Data for this trial will include clinical, safety, and outcome measures (e.g., clinical laboratory values).

13.5 Study Records Retention

Study records and reports including, but not limited to, eCRFs, source documents, ICFs, laboratory test results, and study drug disposition records will be retained for 2 years after a marketing application is approved for the study product for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for the study product, until 2 years after the investigation is discontinued and the FDA has been notified. These documents will be retained for a longer period, however, if required by local regulations. ICFs for future use will be maintained as long as the sample/specimen exists.

No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the site principal investigator when these documents no longer need to be retained.

14 CLINICAL MONITORING

Site monitoring is conducted to ensure that the human subjects' protections, study and laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, ICH/GCP guidelines and applicable regulations, and that this trial is conducted in accordance with the protocol, protocol-specific MOP and applicable sponsor standard operating procedures. DMID, the sponsoring agency, or its designee will conduct site-monitoring visits as detailed in the clinical monitoring plan.

Site visits will be made at standard intervals as defined by DMID and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, eCRFs, informed consent forms, medical and laboratory reports, and protocol and GCP compliance. Site monitors will have access to each participating site, study personnel, and all study documentation according to the DMID-approved site monitoring plan. Study monitors will meet with site principal investigators to discuss any problems and actions to be taken, and will document site visit findings and discussions.

15 PUBLICATION POLICY

Following completion of the study, the lead Principal Investigator is expected to publish the results of this research in a scientific journal. All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- NIH Public Access Policy, http://publicaccess.nih.gov/
- NIH Office of Extramural Research (OER) Grants and Funding, http://grants.nih.gov/grants/oer.htm

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first subject. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting a copy of this protocol (and its amendments) and a copy of the Statistical Analysis Plan will be posted on ClincialTrials.gov.

For this trial the responsible party is NIH/NIAID/DMID which will register the trial and post results.

The responsible party does not plan to request certification of delayed posting.

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases
- 42CFR11
- NIH NOT-OD-16-149

16 LITERATURE REFERENCES

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17 APPENDICES

Appendix A. Schedule of Events

	Induction Period	Screening/ Enrollment	Open Label Treatment Period				Post-treatment Follow-up Period		
	Visit 0 (Pre-Screening, Day -10 to Day 1)	Visit 1 (Day –1 to Day 1)	Visit 2 (Baseline, Day 1)	Visit 3 (Day 8 ± 1 day)	Visit 4 (Day 22 ± 2 days)	Visit 5 (Day 42 ± 3 days)	Visit 6 (TOC, Day 70 ± 7 days)[a]	ET[b]	Visit 7 (Day 180 ± 14 days, Osteomyelitis group)[a]
Informed Consent		X							
Dalbavancin[c]			X	X					
Standard of care antibiotic therapy[c]	X	X	X (Duration 28-56 days)						
Medical history[d]		X	X			X	X	X	
Medication history[e]		X							
Randomization			X						
AEs/AESIs/SAEs			X	X	X	X	X	X	
Hematology and serum chemistry blood sampling[f]		X		X[g]	X	X			
Coagulation lab tests[f]		X							

	Induction Period	Screening/ Enrollment	Open Label Treatment Period				Post-treatment Follow-up Period		
	Visit 0 (Pre-Screening, Day -10 to Day 1)	Visit 1 (Day –1 to Day 1)	Visit 2 (Baseline, Day 1)	Visit 3 (Day 8 ± 1 day)	Visit 4 (Day 22 ± 2 days)	Visit 5 (Day 42 ± 3 days)	Visit 6 (TOC, Day 70 ± 7 days)[a]	ET[b]	Visit 7 (Day 180 ± 14 days, Osteomyelitis group)[a]
Pregnancy test[h]		X							
PK sampling[i]			X	X	X	X	X	X	
Vital signs[j]		X	X	X[k]	X	X	X	X	X
Physical examination[l]		X	X	X	X	X	X	X	X
Echocardiogram[m]		X							
Investigator assessment of efficacy						X	X	X	X
Concomitant medications[n]		X	X	X	X	X	X	X	X
Concomitant nondrug interventions		X	X	X	X	X	X	X	X
QoL assessment[o]			X	X	X	X	X	X	X

AEs = adverse events; AESIs = adverse events of special interest; eCRF = electronic case report form; ET = Early Termination; PK = pharmacokinetic; SAE = serious adverse events

[a]Telephone visit permissible if in-person visit is not possible; in person visit still preferred.

[b]Patients who prematurely discontinue therapy should have an ET Visit within 72 hours.

[c]All subjects will be receiving standard of care prior to randomization; after randomization, subjects will receive either dalbavancin or standard of care based on their assigned treatment group.

[d]Includes targeted/pertinent medical and surgical history only

[e]A complete medication history will be completed through 30 days prior to ICF signing; an extended 60 day review will be conducted for dalbavancin and oritavancin given the long half-lives of both drugs.

[f]Visit 1 hematology, coagulation lab tests (PT, PTT, and/or INR) and serum chemistry will be done in order to qualify the patient for the study, if not already collected per standard of care within 48 hours prior to randomization.

[g]A serum creatinine assessment will be required within the 72 hours prior to the 2nd (Day 8) dalbavancin dose. Whether a serum creatinine must be repeated on Day 8 will be at the discretion of the site investigator based upon stability of the serum creatinine in the preceding 72 hours and whether the serum creatinine is near the threshold where dose adjustment would be necessary (e.g., near 30 mL/min).

[h]Women of childbearing potential only, if not already performed (see Appendix B, Definitions); ensure test is negative within 48 hours before randomization. If the serum test results cannot be obtained before randomization, a urine pregnancy test may be used for enrollment.

[i]Dalbavancin PK samples will be drawn only for subjects receiving dalbvacancin. PK samples will be drawn at Day 1 prior to dose, at end of infusion ± 10 minutes, 6 ± 2 hours post end of dose, 12 ± 4 hours post end of dose, 24 ± 6 hours post end of dose), Day 8 (prior to 2nd dose), Day 22 ± 2 days (at time of clinic visit), day 42 ± 3 days, day 70 ± 7 days, and with any ET visit. Each sample must be accompanied by draw time and date.

[j]Vital signs include blood pressure, respiration rate, pulse rate, and temperature.

[k]Day 8 vital signs not required for subjects receiving SOC antibiotics if discharge occurs prior to day 8.

[l]A physical examination (including general appearance, examination of head, eyes, ears, nose, throat, neck, skin, heart, lungs, abdomen, neurologic system, musculoskeletal system**,** extremities, height, and body weight) will be done at Screening (Visit 1). If height or weight is not obtainable (eg, patient is immobilized), use the last known or stated height and weight. At subsequent visits, targeted physical exams will focus on changes from prior exams and on the evaluation of newly reported symptoms.

[m]Transthoracic echocardiogram or, if clinically indicated, transesophageal echocardiogram to be performed (local laboratory), unless one has been performed as standard of care for this episode of bacteremia/endocarditis

[n]All concomitant medications from Screening (Visit 1) through Day 42 (± 3 days) (Visit 5) must be recorded in the patient's medical record and on the eCRFs. Between the Day 42 Visit and Day 70 Visit, all concomitant medications for an AE or any antibacterial therapy should be recorded in the patient's medical record and on the eCRF.

[o]QoL assessments include the ARLG Bloodstream Infection QoL Measure (Appendix C), the EQ-5D-5L (https://euroqol.org/eq-5d-instruments/sample-demo/), and the PROMIS Global Health Short Form (http://www.healthmeasures.net/administrator/components/com_instruments/uploads/Global%20Health%20Scale%20v1.2%2008.22.2016.pdf).

Appendix B. Definitions

Childbearing Potential: a woman is considered of childbearing potential unless post-menopausal [≥1 year of spontaneous amenorrhea] or permanently surgically sterilized [bilateral oophorectomy, salpingectomy, hysterectomy, tubal ligation].

Effective Contraception: Must include at least one of the following: non-male sexual relationships only, abstinence from sexual intercourse with a male partner, monogamous relationship with a vasectomized partner who has been vasectomized ≥180 days before the subject received the first dose of study drug, barrier methods such as condoms or diaphragms, effective intrauterine devices (IUDs), NuvaRing®, or licensed hormonal methods such as implants, injectables, or oral contraceptives.

Uncomplicated *Staphylococcus aureus* Bacteremia: defined as all of the following: exclusion of endocarditis by echocardiography; catheter-associated bacteremia and removal of catheter; no implanted prostheses; follow-up blood cultures drawn within 48 hours after initial set that do not grow screening pathogen and all follow-up blood cultures thereafter do not grow the screening pathogen; defervescence within 72 hours of initiating effective therapy; and no evidence of metastatic sites of infection.

Complicated *S. aureus* Bacteremia:

The following are examples of complicated *S. aureus* bacteremia. This is not an exhaustive list. If a patient's infection does not meet the definition of uncomplicated bacteremia above, then that patient has complicated bacteremia.

Positive follow-up blood cultures: blood cultures positive for *S. aureus* drawn at least 24 hours after the initial qualifying blood culture

Persistent fever: oral temperature ≥38.0C for >72 hours after the initial positive blood culture for *S. aureus*

Endocarditis:

These criteria have been adjusted to be specific to *S. aureus* bacteremia, i.e. microbiological criteria related to organisms other than *S. aureus* have been removed. In addition, references to prosthetic valve infections have been removed, as these patients will be excluded from the study.

According to modified Duke Criteria, diagnosis of IE can be definite, possible, or rejected. A diagnosis of IE is **definite** if either the following pathological or clinical criteria are met:

Pathologic criteria:

- pathologic lesions: vegetation or intracardiac abscess demonstrating active endocarditis on histology, or
- microorganism: demonstrated by culture or histology of a vegetation or intracardiac abscess

One of these combinations of clinical criteria (see definitions below):

- two major clinical criteria
- one major and three minor criteria
- five minor criteria

Diagnosis of IE is **possible** if one of the following combinations of clinical criteria (see definitions below) are met:

- one major and one minor criteria
- three minor criteria are fulfilled

Diagnosis of IE is **rejected** if one of the following criteria are met:

- a firm alternate diagnosis is made
- resolution of clinical manifestations after ≤ 4 days of antibacterial treatment
- no pathological evidence of IE is found at surgery or autopsy after antibacterial treatment therapy for ≤ 4 days
- clinical criteria for possible or definite IE are not met

Major criteria for the diagnosis of infective endocarditis:

1. Positive blood culture with *S. aureus* from two separate blood cultures
2. Evidence of endocardial involvement with positive echocardiogram defined as

- oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets in the absence of an alternative anatomic explanation
- abscess
- new valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor criteria for the diagnosis of infective endocarditis:

1. Predisposing factor: intravenous drug use or presence of a predisposing heart condition (a valve lesion associated with significant regurgitation or turbulence of blood flow)
2. Fever ≥38°C (100.4 °F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages or Janeway lesions
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, Rheumatoid factor
5. A single positive blood culture with *S. aureus*

Visceral Abscess (e.g. liver, spleen, kidney, etc.) – either of the following:

- Abscess visualized on radiographic exam, or
- Isolation of *S. aureus* from culture of abscess contents

Pleuropulmonary Infection – one of the following:

- Pulmonary infiltrate consistent with pneumonia in patients with *S. aureus* bacteremia
- *S. aureus* in pleural fluid, needle aspirate biopsy, or growth from bronchoalveolar lavage (BAL)/protected specimen brush (PSB)
- Clinical evidence of pneumonia (e.g. increased O_2, increased respiratory rate, cough, mechanical ventilation, purulent sputum, etc.)

Osteomyelitis - Either of the following:

- Radiographic evidence of bone lesion consistent with osteomyelitis/discitis; or
- Culture of bone yields *S. aureus*.

Pyomyositis – Either of the following:

- Radiographic evidence consistent with pyomyositis; or
- Culture of abscess contents yields *S. aureus*.

Septic Arthritis – Either of the following:

- *S. aureus* in culture of synovial fluid; or
- Positive Gram stain of synovial fluid for Gram positive cocci AND synovial fluid cell count ≥20,000 WBC/mL without alternate explanation

Septic Thrombophlebitis – Either of the following:

- Palpable venous cord
- Evidence of thrombosis on radiologic exam

Relapsing Bacteremia: Relapsing bacteremia is defined as a *S. aureus* that:

- Represents the same bacterial strain as the Baseline Infecting Pathogen (based on bacterial speciation, antibiotic susceptibility testing, and/or genotyping tests, as appropriate);
- Is documented by a blood culture yielding *S. aureus* obtained after randomization

Source Control Procedure: a procedure intended to treat *S. aureus* infection. Examples include, but are not limited to, surgical debridement or amputations, drainage of infected spaces, and removal of prosthetic material

Vascular Access Procedures: insertion or removal of vascular catheters

Microbiologic Success: no post-randomization growth of the baseline pathogen from blood cultures or another sterile body site

Blood Culture Contaminant: the following organisms may be considered a contaminant if grown from only one blood culture (either alone or in addition to *S. aureus* isolated from the same blood culture): *Cutibacterium* species, *Micrococcus* species, viridans-group streptococcus, coagulase-negative staphylococci, *Corynebacterium* species, *Bacillus* species other than *B. anthracis*, or enterococcus species.

Appendix C. ARLG Bloodstream Infection Quality of Life Measure

Please respond to each item by marking one box per row.							
Global			**Excellent**	**Very Good**	**Good**	**Fair**	**Poor**
Global01	1	In general, would you say your health is:	☐	☐	☐	☐	☐
Global02	2	In general, would you say your quality of life is:	☐	☐	☐	☐	☐
Thinking of your bloodstream infection, please answer the following questions to best capture your experiences.							
Fatigue			**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	3	During the past 7 days, I feel fatigued	☐	☐	☐	☐	☐
AN3	4	During the past 7 days, I have trouble starting things because I am tired	☐	☐	☐	☐	☐
FATEXP41	5	In the past 7 days, how run-down did you feel on average?	☐	☐	☐	☐	☐
FATEXP40	6	In the past 7 days, how fatigued were you on average?	☐	☐	☐	☐	☐
Gastrointestinal Nausea and Vomiting			**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
GISX49	7	In the past 7 days, how often did you have nausea—that is, a feeling	☐	☐	☐	☐	☐

		like you could vomit? (If never, skip to 9)					
GISX52	8	In the past 7 days, how often did you know that you would have nausea before it happened?	☐	☐	☐	☐	☐
GISX55	9	In the past 7 days, how often did you have a poor appetite?	☐	☐	☐	☐	☐
			Never	**One day**	**2-6 days**	**Once a day**	**More than once a day**
GISX59	10	In the past 7 days, how often did you throw up or vomit?	☐	☐	☐	☐	☐
Pain Intensity			**Had no pain**	**Mild**	**Moderate**	**Severe**	**Very severe**
PAINQU6	11	In the past 7 days, how intense was your pain at its worst?	☐	☐	☐	☐	☐
PAINQU8	12	In the past 7 days, how intense was your average pain?	☐	☐	☐	☐	☐
			No pain	**Mild**	**Moderate**	**Severe**	**Very severe**
PAINQU21	13	What is your level of pain right now?	☐	☐	☐	☐	☐
Sleep Disturbance			**Very poor**	**Poor**	**Fair**	**Good**	**Very Good**
Sleep109	14	In the past 7 days, my sleep quality was	☐	☐	☐	☐	☐

			Not at all	A little bit	Somewhat	Quite a bit	Very much
Sleep116	15	In the past 7 days, my sleep was refreshing	☐	☐	☐	☐	☐
Sleep20	16	In the past 7 days, I had a problem with my sleep	☐	☐	☐	☐	☐
Sleep44	17	In the past 7 days, I had difficulty falling asleep	☐	☐	☐	☐	☐
Emotional Distress - Depression			**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	18	In the past 7 days, I felt worthless	☐	☐	☐	☐	☐
EDDEP06	19	In the past 7 days, I felt helpless	☐	☐	☐	☐	☐
EDDEP29	20	In the past 7 days, I felt depressed	☐	☐	☐	☐	☐
EDDEP41	21	In the past 7 days, I felt hopeless	☐	☐	☐	☐	☐
Emotional Distress - Anxiety			**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	22	In the past 7 days, I felt fearful	☐	☐	☐	☐	☐
EDANX40	23	In the past 7 days, I found it hard to focus on anything other than my anxiety	☐	☐	☐	☐	☐
EDANX41	24	In the past 7 days, my worries overwhelmed me	☐	☐	☐	☐	☐
EDANX53	25	In the past 7 days, I felt uneasy	☐	☐	☐	☐	☐

Cognitive Function - Abilities			**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PC43_2r	26	In the past 7 days, my mind has been as sharp as usual	☐	☐	☐	☐	☐
PC44_2r	27	In the past 7 days, my memory has been as good as usual	☐	☐	☐	☐	☐
PC45_2r	28	In the past 7 days, my thinking has been as fast as usual	☐	☐	☐	☐	☐
PC47_2r	29	In the past 7 days, I have been able to keep track of what I am doing, even if I am interrupted	☐	☐	☐	☐	☐
Physical Function			**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	30	Are you able to do chores such as vacuuming or yard work?	☐	☐	☐	☐	☐
PFA21	31	Are you able to go up and down stairs at a normal pace?	☐	☐	☐	☐	☐
PFA23	32	Are you able to go for a walk of at least 15 minutes?	☐	☐	☐	☐	☐
PFA53	33	Are you able to run errands and shop?	☐	☐	☐	☐	☐
			Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**

PFC12	34	Does your health now limit you in doing two hours of physical labor?	☐	☐	☐	☐	☐
PFB1	35	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐	☐	☐	☐	☐
Ability to Participate in Social Roles and Activities			**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
SRPPER11_CaPS	36	I have trouble doing all of my regular leisure activities with others	☐	☐	☐	☐	☐
SRPPER18_CaPS	37	I have trouble doing all of the family activities that I want to do	☐	☐	☐	☐	☐
SRPPER23_CaPS	38	I have trouble doing all of my usual work (include work at home)	☐	☐	☐	☐	☐
SRPPER46_CaPS	39	I have trouble doing all of the activities with friends that I want to do	☐	☐	☐	☐	☐
			Excellent	**Very Good**	**Good**	**Fair**	**Poor**
	40	Because of your bloodstream infection, would you say your health is..	☐	☐	☐	☐	☐

	41	Because of your bloodstream infection, would you say your quality of life is..	☐	☐	☐	☐	☐