CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 20-0002
Study 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

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Version 2.0

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RESTRICTED

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 20-0002**
Development Phase:	Phase 2b
Products:	Dalbavancin Standard of Care Antibiotics: Cefazolin, nafcillin, oxacillin, vancomycin, and daptomycin
Form/Route:	IV
Indication Studied:	Complicated *S. aureus* Bacteremia
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	15MAR2021
Clinical Trial Completion Date:	TBD
Date of the Analysis Plan:	03JAN2024
Version Number:	Version 2.0

This study was performed in compliance with Good Clinical Practice.

TABLE OF CONTENTS

Table of Contents (continued)

Table of Contents (continued)

Table of Contents (continued)

LIST OF ABBREVIATIONS

ABSSSI	Acute Bacterial Skin and Skin Structure Infections
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ARLG	Antibacterial Resistance Leadership Group
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CE	Clinically Evaluable
CI	Confidence Interval
CRF	Case Report Form
CrCl	Creatinine Clearance
DCC	Data Coordinating Center
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
DOOR	Desirability of Outcome Ranking
DOTS	Dalbavancin as an Option for Treatment of *S. aureus* Bacteremia
eCRF	Electronic Clinical Report Form
EDC	Electronic Data Capture
ET	Early Termination
F	Fahrenheit
FDA	Food and Drug Administration
GEE	Generalized Estimating Equations
GLMM	Generalized Linear Mixed Model
HLGT	High Level Group Term
ICH	International Council for Harmonisation
IE	Infective Endocarditis
IPW	Inverse Probability Weighting
IRB	Institutional Review Board
ITT	Intent-to-Treat
L	Liter
MAR	Missing at Random
MCAR	Missing Completely at Random

List of Abbreviations (continued)

MedDRA	Medical Dictionary for Regulatory Activities
mEq	Milliequivalent
mg	Milligram
mITT	Modified Intent-to-Treat
mL	Milliliter
MNAR	Missing Not at Random
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MVUE	Minimum Variance Unbiased Estimator
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PCS	Potentially Clinically Significant
PD	Pharmacodynamics
PI	Principal Investigator
PID	Patient Identification
PIPS	Predicted Interval Plots
PK	Pharmacokinetics
PT	Preferred Term
PTime	Prothrombin Time
PTT	Partial Thromboplastin Time
PWID	Person Who Injects Drugs
SAE	Serious Adverse Event
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedures
TEE	Transesophageal Echocardiography
TOC	Test of Cure
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "Dalbavancin as an Option for Treatment of *Staphylococcus aureus* (*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" (DMID Protocol 20-0002) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, listings, and figures planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E6 (Good Clinical Practice: Integrated Addendum to ICH E6(R2)), Topic E8 (General Considerations for Clinical Trials), Topic E9 (Statistical Principles for Clinical Trials), Topic E9 (R1: Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guidelines on Statistical Principles for Clinical Trials) and Topic E10 (Choice of Control Group and Related Issues in Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for efficacy and safety outcomes, and (4) a list of proposed tables and figures. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments.

2. INTRODUCTION

This is a Phase 2b, multicenter, randomized, open-label, assessor-blinded superiority clinical trial of dalbavancin vs. standard of care antibiotic therapy for treating complicated *S. aureus* bacteremia. The study is designed and powered for the primary analysis of a comparison of the efficacy of dalbavancin to standard of care therapy for the completion of therapy in patients with complicated bacteremia or right-sided native valve Infective Endocarditis (IE) caused by *S. aureus* who have cleared their baseline bacteremia using a superiority approach.

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 intravenous (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. The duration of standard of care antibiotics may be extended to a maximum of 8 weeks at the discretion of the treating clinician.

2.1. Purpose of the Analyses

Analysis of Desirability of Outcome Ranking (DOOR) at Day 70 will be used to assess the efficacy of dalbavancin versus standard of care therapy. Superiority of dalbavancin versus standard of care on Day 70 based on DOOR will be the primary analysis. With DOOR being a composite endpoint, the advantage of dalbavancin on the DOOR analysis does not necessarily imply an advantage on all DOOR components. Thus, examination of the effects on the overall clinical outcome and each component of DOOR is standardly conducted via a secondary or sensitivity analysis. Hence, the secondary outcome measures which include a comparison of clinical outcomes, safety outcomes, and comparison of each individual DOOR component will be conducted. Note that DOOR categories will be calculated using cumulative data from Day 1 through Day 70, except that clinical success or failure is specific to the date of assessment. For example, suppose a subject had experienced an SAE and clinical failure at Day 42 but at Day 70 they were considered to be cured. In this case, the SAE would still contribute to the DOOR at Day 70; however, the change from clinical failure at Day 42 to clinical success at Day 70 would result in a lower (better) DOOR at Day 70, reflective of the improvement in clinical outcome.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary

To compare 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.

3.1.2. Secondary

1. 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 (see Section 6.3 for definitions of study populations).
2. To compare the safety of dalbavancin with that of the standard of care treatment in the mITT population.
3. To compare each individual component of DOOR outcome by treatment arm, in the ITT population.

3.1.3. Exploratory

1. To compare the clinical outcomes of dalbavancin with the standard of care antibiotic therapy at Day 70 in the Clinically Evaluable (CE) population (see Section 6.3 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/skin structure pulmonary); e) subjects with immune-suppression (not severe enough to trigger exclusion)[1]; 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.

1 Defined as: On chemotherapy or immunotherapy for active hematologic malignancy expected to cause ANC < 500 cells/mm3 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/mm3 based on last known measurement or patient-reported value

6. To characterize the population pharmacokinetic (PK) 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 Test of Cure (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.

3.2. Endpoints

3.2.1. 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 at least 4 weeks after treatment completion for most patients, allowing time for detection of relapse.

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

For the primary analysis of DOOR, QoL will be used as a tie-breaker and will be calculated as change from baseline QoL to Day 70 QoL score, as assessed by questions from the PROMIS physical function item bank (PROMIS Item Bank v2.0, short form 6b) on the Antibacterial Resistance Leadership Group (ARLG) Bloodstream Infection QoL Measure (Appendix C of the protocol).

3.2.2. 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.

Safety, defined as proportion of patients who have either 1) an SAE; or 2) an AE leading to study drug discontinuation

Each component of DOOR will also be examined separately:

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

3.2.3. 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. 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.
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.
5. QoL at Baseline, Day 42, and Day 70, which will be assessed by the score obtained from questions from the PROMIS physical function item bank (PROMIS Item Bank v2.0, short form 6b), included in the ARLG Bloodstream Infection QoL Measure (Appendix C of the protocol), 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.

3.3. Study Definitions and Derived Variables

DOOR:

There are 5 possibilities for the DOOR:

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

Note that if an infectious complication is also an SAE, or an AE leading to study drug discontinuation the event will count twice towards the DOOR. For example, if a subject is alive at Day 70 point and the only observed event between Day 1 and Day 70 is a serious infectious complication, the subject will have Rank 3 at Day 70. Additionally, DOOR is calculated using cumulative data from Day 1 through Day 70, except that clinical success or failure is specific to the date of assessment.

Additional details for deriving DOOR, including handling of missing data, are provided in Section 6.5.

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.

Determination of clinical success/failure and infectious complications at Day 42 and Day 70 will be determined by the adjudication committee after review of all relevant data up to Day 42 and Day 70, respectively.

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.

Microbiologic Success: No post-randomization growth (e.g., no positive cultures) of the baseline pathogen from blood cultures or another sterile body site. Subjects who discontinue from the study before Day 42 and have no post-randomization growth will have missing microbiologic success.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 2b, multicenter, randomized, open-label, assessor-blinded, superiority study to 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. The duration of standard of care antibiotics may be extended to a maximum of 8 weeks at the discretion of the treating clinician.

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

The primary outcome measure is the superiority of dalbavancin versus standard of care therapy on Day 70 based on DOOR using the ITT population. Secondary endpoints include comparison of clinical efficacy and clinical safety with clinical efficacy measured by clinical failure, infectious complications, and all-cause mortality while clinical safety is measured by the proportion of SAEs and AEs leading to study drug discontinuation.

4.2. Discussion of Study Design, Including the Choice of Control Groups

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) [9].

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 [10] for most patients, and up to 8 weeks for patients with osteomyelitis/discitis.

The proposed clinical study design offers several 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 [13]. 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 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 [14 and 15]. 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.

4.3. Selection of Study Population

The study will enroll approximately 200 eligible subjects to the study in the United States and Canada. Eligible subjects are adults 18 years of age or older 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 tested negative after at least 72 hours of initial antibiotic therapy (maximum 10 days). Subjects with uncomplicated bacteremia due to *S. aureus* will be excluded.

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.

4.3.1. Inclusion Criteria

For a list of inclusion criteria, see the most recent version of the Protocol.

4.3.2. Exclusion Criteria

For a list of exclusion criteria, see the most recent version of the Protocol.

4.3.3. Reasons for Withdrawal

Subject Withdrawal:

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

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
- 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

Discontinuation of Treatment:

An investigator may also discontinue a subject from receiving the study product for any reason. Follow-up safety evaluations for discontinued subjects will be conducted if the subject agrees.

The reasons to discontinue study product might include, but are not limited to, the following:

- Subject meets individual halting criteria (see Protocol)
- 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
- 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 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 (Table 1). A clear description of reason for early withdrawal or discontinuation from investigational product 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. 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.

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.

4.4. Treatments

4.4.1. Treatments Administered

Subjects will be randomized to either receive dalbavancin or standard of care antibiotics. Dalbavancin 1500 mg will be administered IV over 30 (± 10) minutes on Day 1 and Day 8, renally dose-adjusted to 1125 mg for subjects with Creatinine Clearance (CrCl) <30 or not on dialysis.

Standard of care antibiotics will be administered based on the methicillin susceptibility pattern of the pathogen isolated at baseline. Subjects with methicillin-sensitive S. aureus (MSSA) will receive nafcillin (2 g IV q4h × 4-6 weeks) OR oxacillin (2 g IV Q4h x 4-6 weeks) OR cefazolin (2 g IV q8h × 4-6 weeks) while subjects with methicillin-resistant S. aureus (MRSA) will receive vancomycin (dose per local standard of care × 4-6 weeks) OR daptomycin (6-10 mg/kg IV daily × 4-6 weeks).

4.4.2. Identity of Investigational Product(s)

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

4.4.3. Method of Assigning Subjects to Treatment Groups (Randomization)

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 Statistical and Data Coordinating Center (SDCC) (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.

4.4.4. Selection of Doses in the Study

The dalbavancin dosing regimen consists of 1500 mg on Day 1 and 1500 mg on Day 8 for subjects with normal renal function (i.e., CrCl >= 30 mL/min) or who are receiving regular hemodialysis or peritoneal dialysis, administered over 30 minutes by IV infusion. Patients with CrCl <30 mL/min who are not receiving regular hemodialysis or peritoneal 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 /pharmacodynamics (PD) target of the area under the unbound drug concentration-time curve [fAUC]/MIC ([11]), this regimen is expected to provide sufficient therapeutic concentrations of free drug against *S. aureus* through Day 42.

4.4.5. Blinding

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.

4.4.6. Prior and Concomitant Therapy

Medication history during the 30 days prior to ICF signing will be recorded at Screening (Visit 1) in the eCRF. Thereafter, any changes in concomitant medications or new medications added will be recorded in the eCRF.

Any systemic medication taken by the subject, other than study drugs, is considered a concomitant medication. Topical medications including eye drops, ear drops, or dermatologic treatments do not need to be recorded in the eCRFs. All 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. 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 *Clostridioides difficile (C. 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.

4.4.7. Treatment Compliance

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.

4.5. Efficacy and Safety Variables

The primary efficacy variable for this study is DOOR at Day 70. Secondary analyses will analyze DOOR components measured by clinical failure, infectious complications, and AE leading to study drug discontinuation. Quality of life score will be used as a tie-breaker for DOOR analysis.

Safety will be assessed by the frequency of SAEs, AESIs, and the frequency of AEs leading to study drug discontinuation in each treatment group.

5. SAMPLE SIZE CONSIDERATIONS

The study is powered for a superiority comparison based on the primary objective, a comparison of DOOR. The probability of a subject from the dalbavancin arm having a superior DOOR 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 with dalbavancin does not cross 50%. If the confidence interval crosses 50% however, the null hypothesis cannot be rejected.

Sample size was calculated based on 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 subjects 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 described in Lachin, et al, [12] 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).

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment group in the following order:

- Dalbavancin
- Standard of Care

All summary tables will be annotated with the total population size relevant to that table/treatment, including any missing observations.

6.2. Timing of Analyses

There will be one planned interim analysis for futility after approximately 50% of subjects have completed the trial. The interim analysis for futility will be performed by the SDCC and will consist of a quantitative evaluation of potential effect sizes and associated precision using a predicted intervals and predicted interval plots (PIPS) approach [7 and 8]. The results of the interim analysis will be presented in the closed session of the Data and Safety Monitoring Board (DSMB).

The DSMB will evaluate safety annually; 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.

The final analysis will be performed after database lock.

6.3. Analysis Populations

The primary analysis will be done using the ITT analysis population. Other analyses might use mITT and/or CE analysis populations. Analyses using ITT and mITT will include imputations for missing values using multiple imputation or adjusting for missing data using IPW for DOOR, clinical efficacy, and microbiologic success.

Reasons for exclusion from the screened analysis population are summarized in Table 8 while reasons for exclusions from the rest of the analysis populations (ITT, Safety, mITT, CE) are summarized in Table 4 by treatment group. Individual subject listing of exclusion reasons is also provided in Listing 5. Excluded subjects might satisfy multiple criteria justifying their exclusion but will have only one reason indicated in Table 4 and Listing 5. The exclusion reason indicated will be determined by first exclusion reason met based on the following rules in the order they are listed for each analysis population.

Screened Population Exclusions:

- Subject did not complete the Screening Visit (Visit 1)

ITT Population Exclusions:

- Subject not randomized to receive study product

Safety Population Exclusions:

- Subject not treated with at least one dose of study product

Modified ITT Population Exclusions:

- Subject was excluded from ITT population
- Subject not treated with at least one dose of study product

Clinically Evaluable at Day 42 Population Exclusions:

- Subject was excluded from mITT population
- Subject has missing data or major protocol violation preventing the adjudication committee from evaluating their outcomes at Day 42.

Clinically Evaluable at Day 70 Population Exclusions:

- Subject was excluded from mITT population
- Subject has missing data or major protocol violation preventing the adjudication committee from evaluating their outcomes at Day 70.

6.3.1. Screened Analysis Population

The screened population will consist of all patients who undergo the Screening Visit (Visit 1), signed informed consent, and receive a Patient Identification (PID) number. This population will include both enrolled and not enrolled subjects.

6.3.2. Intent-to-Treat Analysis Population

The intent-to-treat (ITT) population will consist of all randomized patients regardless of whether or not they received study treatment. This analysis population will be used for primary, secondary, and some exploratory analyses. Patients will be analyzed based on the treatment they were randomized to.

6.3.3. Safety Population

The safety population will consist of all randomized patients who received at least 1 dose of study drug. This population will be used for all safety analyses, and patients will be analyzed based on the treatment received.

6.3.4. 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. This analysis population will be used for secondary and some exploratory analyses. Patients will be analyzed based on the treatment received.

6.3.5. Clinically Evaluable Analysis Population

The CE populations will consist of all patients in the mITT population who met criteria for clinical evaluability. Patients will be considered clinically evaluable at Day 70 if they have a primary outcome assessment of DOOR at Day 70 and do not have missing data or major protocol violations that prevent the

adjudication committee from evaluating their outcomes at Day 70. Similarly, clinically evaluable at Day 42 if they have a primary outcome assessment of DOOR at Day 42 and do not have missing data or major protocol violations that prevent the adjudication committee from evaluating their outcomes at Day 42. These analysis populations will be used for exploratory analyses and patients will be analyzed based on the treatment received.

6.4. Covariates and Subgroups

Subgroup analyses comparing clinical and microbiologic outcomes will be conducted and will include 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/skin structure pulmonary); e) subjects with immune-suppression[2] (Yes vs. No); f) duration of initial bacteremia (<2, 2-4, >4 days). Note that, if the number of subjects in a subgroup category is less than 5 for at least one of the treatment groups, that subgroup category will be combined with the next subgroup category with the least number of subjects to form a combined subgroup category with that has at least 5 subjects for at least one of the study groups. However, if a subgroup only has two categories (Yes and No for example), the subgroup category with less than 10 subjects will be excluded from the analyses.

6.5. Missing Data

While all efforts will be made to minimize missing data, some missing data are expected. Whenever possible, subjects terminating from the study early will be given an early termination visit during which the available components of DOOR and related measures can be recorded. The analyses of DOOR, clinical efficacy, and microbiological success for ITT and mITT analyses populations will use Inverse Probability Weighing (IPW) and multiple imputation with linear models to impute values using available information (treatment, randomization strata variables, and available visit information), assuming a missing at random (MAR) model.

The effect that any missing data might have on results will be assessed via sensitivity analysis. If the pattern of missing data are different to that envisaged at the design stage, further sensitivity analyses will be provided that are tailored to the missing data pattern observed.

6.5.1. DOOR Categories

Subjects will be grouped into the five categories based their clinical outcomes. The clinical components of DOOR which include clinical failure, infectious complication, SAE or AE leading to study drug discontinuation will be determined by an independent adjudication committee. DOOR at Day 70 will be defined as follows:

1. If a subject died at any point prior or on to Day 70, then the DOOR at Day 70 will be **Rank 5**.
2. If a subject is alive but has at least one of clinical failure at Day 70, infectious complication, any SAE (except for death), or an AE leading to study drug discontinuation prior or on Day 70, then the DOOR at Day 70 will be **2, 3 or 4**, depending on how many events the subject experienced.

2 Defined as: On chemotherapy or immunotherapy for active hematologic malignancy expected to cause ANC < 500 cells/mm3 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/mm3 based on last known measurement or patient-reported value

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

3. Even if the adjudication committee does not have sufficient evidence to determine clinical failure, if a subject is alive but with any event of infectious complication, any SAE (except for death), or an AE leading to study drug discontinuation by Day 70, then DOOR at Day 70 will be **Rank 3 or 4**, depending on how many events the subject experienced by Day 70.
    - Rank 3: Alive but with one of the following: (2) an infectious complication; or (3) any SAE, or an AE leading to study drug discontinuation
    - Rank 4: Alive but with both of the following: (2) an infectious complication; or (3) any SAE, or an AE leading to study drug discontinuation
4. If a subject is alive (a) with no event of infectious complication, any SAE (except for death), or an AE leading to study drug discontinuation, (b) but the adjudication committee does not have sufficient evidence to determine clinical failure, then the DOOR will be **Rank 2**.
5. If a subject is withdrawn from the study before any assessment (no assessments on any components of DOOR after randomization), then the DOOR will be **missing**.

A similar algorithm will be used to determine DOOR at Day 42.

6.5.2. Quality of Life Score (QoL)

Three types of instruments will be used to assess qualify of life: questions from the PROMIS physical function item bank (PROMIS Item Bank v2.0, short form 6b) on the ARLG Bloodstream Infection QoL Measure, the full PROMIS Global Health short form, and the EQ-5D-5L. For the QoL assessments that utilize PROMIS questions the HealthMeasures Scoring Service (https://assessmentcenter.net/ac_scoringservice) will be used to obtain the final QoL score for each subject for a given item of the quality-of-life instrument and for each assessed timepoint. HeathMeasures is a free publicly available software which requires the user to submit subject responses. No data are stored or saved by this service, and no identifying information is submitted. Even so, as an extra precaution each subject will be assigned a dummy identifier with their corresponding responses. The patient ID assigned by eClinical will not be shared.

A change in QoL from baseline at Day 70 (or Day 42) is calculated by taking the QoL score at Day 70 (or Day 42) minus QoL score at baseline.

- **PROMIS Global Health short form**
    - A value of 5 represents an excellent QoL outcome while a value of 1 represents a poor QoL outcome using the PROMIS Global Health short form.
    - Higher QoL scores represent a better QoL outcome.
    - Higher change in QoL scores from baseline represents a better QoL outcome.

- **ARLG Bloodstream Infection QoL Measure**
  - A value of 5 represents an excellent QoL outcome while a value of 1 represents a poor QoL outcome using the ARLG Bloodstream Infection QoL Measure.
  - Higher QoL scores represent a better QoL outcome.
  - Higher change in QoL scores from baseline represents a better QoL outcome.
- **EQ-5D-5L**
  - A value of 1 represents an excellent QoL outcome while a value of 5 represents a poor QoL outcome using the EQ-5D-5L instrument.
  - Lower QoL scores represent a better QoL outcome
  - Lower change in QoL scores from baseline represents better outcomes.

A subject could have missing data for QoL if a subject missed a visit and/or responses to all the items of the QoL form are missing.

The change in the ARLG Bloodstream Infection QoL from baseline to Day 70 (or Day 42) will be utilized as a tie breaker for DOOR calculations as described in Section 6.5.3 below. Please note that for tie breaking, the standardized score is obtained from the questions arising from the PROMIS physical function item bank (PROMIS Item Bank v2.0, short form 6b) item bank on the ARLG Bloodstream Infection QoL.

6.5.3. Desirability of Outcome Ranking at Day 70 or Day 42

The QoL-adjusted DOOR considers QoL as a tie breaker when calculating the DOOR probability. This is accomplished by using the standardized score from the questions from the PROMIS physical function item bank (PROMIS Item Bank v2.0, short form 6b) item bank on the ARLG Bloodstream Infection QoL (higher QoL is better) as a tie-breaker for subjects with the same DOOR. However, if both subjects have a DOOR of 5, the change in QoL will not be used as a tie-breaker. If change in QoL cannot be calculated due to missing data, we proceed as follows:

- If two subjects have the same DOOR at Day 70 but the QoL is missing for one of the subjects at that timepoint then the subject with missing QoL will be ranked below the subject with non-missing QoL.
- If two subjects have the same DOOR at Day 70 but the QoL is missing for both of the subjects at that timepoint then they will have the same rank and will be indistinguishable for the primary endpoint analysis.

The tie-breaking algorithm to obtain the QoL-Adjusted DOOR from DOOR and change in QoL is implemented as follows. First, subjects are ranked based on their DOOR and then by their change in QoL. Next, the QoL-Adjusted DOOR is calculated from the rank based on the subjects DOOR and the change in QoL. If no two subjects have the same DOOR and change in QoL, then the QoL-Adjusted DOOR is the same as the rank. For subjects with tied DOOR and tied change in QoL the QoL-Adjusted DOOR is calculated as the mean of their ranks. The QoL-Adjusted DOOR, obtained after the tie-breaking algorithm, will be denoted as R_i. This algorithm is exemplified below.

Subject	DOOR	Change in QOL
A	1	10
B	1	-10
C	2	5
D	1	-5
E	2	-5
F	2	5
G	5	NA
H	5	NA

DOOR	Subject	Change in QOL	QoL-Adjusted DOOR
1	A	10	1
1	D	-5	2
1	B	-10	3
2	C	5	4.5
2	F	5	4.5
2	E	-5	6
5	G	NA	7.5
5	H	NA	7.5

Since subjects A, D, and B have a DOOR of 1, the change in QOL is used as a tie-breaker among these subjects and the QoL-Adjusted DOOR is 1, 2, and 3 for subjects A, D, and B, respectively. Similarly, since subjects C, F, and E all have a DOOR of 2, the change in QOL is used as a tie-breaker among these 3 subjects. Notice that since subjects C and F have the same change in QOL their QoL-Adjusted DOOR is equal to the mean of their rank.

DOOR at Day 70 without tie-breaking is defined by ranking all subjects (pooling together both treatment group) according to their DOOR at Day 70 (lower is more desirable) ignoring their change in QoL score.

The QoL-Adjusted DOOR at Day 42 is calculated similarly using the change in QoL at Day 42.

6.6. Interim Analyses and Data Monitoring

A single interim analysis will be performed after approximately 50% of subjects have completed the trial. The interim analysis for futility will consist of a quantitative evaluation of potential effect sizes and associated precision using a predicted intervals and 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 observed at interim analysis continue to end of study, 2) the null hypothesis is true (i.e., the DOOR distributions are identical between treatment groups), and 3) the worst-case scenario as an alternative outcome. By relying on prediction intervals, no statistical hypothesis testing is required, and no power is lost at interim analysis. Details of interim analysis, including best and worst case scenarios for alternative outcomes are provided in Section 8.5.

6.7. Multicenter Studies

This is a multicenter study, but randomization is not stratified by site. Data will be pooled across all clinical sites and analyses will not adjust for potential site effects.

6.8. Multiple Comparisons/Multiplicity

Only one hypothesis test will be performed for the primary analysis. Secondary and exploratory analyses will not be corrected for multiplicity.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

Reasons for screening failures will be summarized in Table 8. The completion status and reasons for early termination or treatment discontinuation by Day 42 will be summarized (Table 3 and Listing 2) for each treatment group and pooled across treatment groups for the ITT population. A subject could be discontinued early due to an adverse event (AE) (serious or non-serious), loss to follow-up, non-compliance with study, voluntary withdrawal, withdrawal at the investigator request, termination of the site by the sponsor, termination of the study by the sponsor, death, lack of eligibility at enrollment, inadequate clinical response, or becoming ineligible after enrollment. Number and percentage of subjects completing each visit will be presented in Table 3 by treatment group for all randomized subjects.

Subject disposition and eligibility for analysis will be summarized in a CONSORT flow diagram (Figure 1).

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and treatment group for all subjects (Table 2 and Listing 3). Non-subject specific protocol deviations will be in Listing 4. All subject-specific protocol deviations and non-subject specific protocol deviations will be presented. Major protocol deviations preventing the adjudication committee from evaluating the outcome will be determined by the adjudication committee.

8. EFFICACY EVALUATION

All efficacy variables will be listed by subject. Data will be summarized by treatment group. Continuous efficacy variables will be summarized with the number of observations, mean, median, standard deviation, minimum, and maximum. Categorical efficacy variables will be summarized by number and percent in each category.

All statistical tests are two-sided and performed at the α=0.05 significance level; all confidence intervals are two-sided with 95% confidence level.

8.1. Primary Efficacy Analysis

The primary efficacy endpoint is DOOR assessed at Day 70 post study entry (TOC) performed on the ITT analysis population.

8.1.1. Analysis of DOOR at Day 70 Using ITT Analysis Population

DOOR at Day 70 is defined in Section 6.5.3 with and without tie-breaking. The primary analysis in this section is based on the QoL-Adjusted DOOR, which is calculated after using QoL as a tie-breaker.

The null and alternative hypotheses corresponding to the primary analysis of this study are:

H_0: $Pr[DOOR_D > DOOR_C] + \frac{1}{2} Pr[DOOR_D = DOOR_C] \leq 50\%$ (i.e., no difference in DOOR at Day 70).

H_1: $Pr[DOOR_D > DOOR_C] + \frac{1}{2} Pr[DOOR_D = DOOR_C] > 50\%$ (i.e., difference in DOOR at Day 70).

where $DOOR_D$ and $DOOR_C$ are the QoL-Adjusted DOOR for dalbavancin and control, or standard of care, groups, respectively, and $Pr[DOOR_D > DOOR_C]$ is the probability of a DOOR from dalbavancin being more desirable than a DOOR from standard care and $Pr[DOOR_D = DOOR_C]$ is the probability of two DOOR being the same.

$Pr[DOOR_D > DOOR_C] + \frac{1}{2} Pr[DOOR_D = DOOR_C]$ will be referred to as the DOOR probability throughout this SAP.

The superiority of Dalbavancin vs Standard of Care is concluded if the lower bound of the 95% CI for the DOOR probability is larger than 50%.

Due to the presence of missing data, IPW and multiple imputation (MI) will be used to handle missing data. For the primary analysis of DOOR, IPW method will be used. MI described in Section 8.1.1.2 will be used for sensitivity analysis.

8.1.1.1. ITT Analysis of DOOR using IPW

ITT analysis requires that all randomized subjects be included in the analysis. However, missing data are prone to happen in clinical trials due to missing scheduled visits or loss to follow up for example. In this case, analysis that is only based on complete data may be biased if the excluded subjects are systematically different from those included. IPW is one approach commonly used to reduce this bias under a missing at random (MAR) assumption. This is achieved by weighting complete cases with the inverse of their probability of being a complete case. While subjects missing the DOOR are excluded from the analysis per se, they may still inform the fitting of the logistic regression model used to provide predictions of the probability of completeness which are used to calculate the weights.

Specifically, let Y_i represent the outcome of interest (QoL-Adjusted DOOR; see Section 6.5.3), X_i represent the covariates of interest, Z_i represent any other variables measured in the data but not used in the analysis model. For the IPW approach, we first define the missingness model to estimate the weights (w_i) using a logistic regression model with outcome L and covariates taken from set (X, Z) where L_i is defined as 1 if DOOR data are complete (not missing) and 0 otherwise. Through this model, we obtain the fitted probabilities of each subject being complete, denoted as π_i. Note that as described in Section 6.5.3, the QoL-Adjusted DOOR is calculated by accounting for tied DOORs using QoL as a tie-breaker for primary analysis.

The DOOR probability can then be calculated using the QoL-Adjusted DOOR at Day 70 as the outcome following the algorithm below:

1. Name QoL-Adjusted DOOR from the group that received standard of care antibiotics "sample 1" and the QoL-Adjusted DOOR from the group that received dalbavancin "sample 2". Rename weights from sample 1 as w_{1i} and weights from sample 2 as w_{2i}.
2. For each observation in sample 2. If an observation in sample 2 has a smaller QoL-Adjusted DOOR than an observation in sample 1, then that observation in sample 2 gets an indicator of value of 1. Else if the observation in sample 2 is equal to the observation in sample 1, the observation in sample 2 gets an indicator value of ½.
3. Let π_{1i} be the fitted probability of being complete for each observation in sample 1 and π_{2i} be the fitted probability for being complete for each observation in sample 2 obtained from the logistic regression model with an indicator for having non-missing QoL-Adjusted DOOR as the outcome.
4. For each pair in step 2, create the weight w_j as the inverse of the probability of both values in the pair being non-missing, i.e., $w_j = 1/(\pi_{1i} \times \pi_{2i})$ with j being the index for observations in sample 2
5. For each pair in step 2, create the weighted indicator value as $w\_ind_j = w_j \times indicator_j$
6. Repeat step 2 through 5 for all observations in sample 2.
7. The DOOR probability can then be obtained by *DOOR_prob_IPW* = weighted average of all the indicator values in step 5, i.e., $DOOR\_prob\_IPW = \frac{\sum_j w\_ind_j}{\sum w_j}$,

The DOOR probability (i.e. Pr(Desirable DOOR in dalbavancin) + 0.5 Pr(Equal DOOR)) using IPW is given by the value in *DOOR_prob_IPW*.

To estimate the 95% confidence intervals for the DOOR probability, the approach discussed in Halperin et al. after incorporating IPW weights [2]. The superiority of Dalbavancin vs Standard of Care is concluded if the lower bound of the 95% CI for the DOOR probability is larger than 50%.

Pseudocode for Missingness model to estimate fitted probabilities and IPW weights:

Define complete as 1 for complete and 0 for missing and trt=1 for Standard of care and 2 for Dalbavancin.

```
proc logistic data = dat;
  model complete (event='1') = [trt baseline_pathogen age infection_site
bacteremia_duration ];
  output out = out1 p = probs xbeta = logit;
run;
proc transpose data=out1 out=out2;by patid;id trt; var probs;run;
data out2;
      set out2;
      wts=1/(probs_dalba * probs_soc);
run;
```

8.1.1.2. ITT Analysis of DOOR using Multiple Imputation

As a sensitivity analysis, multiple imputation with a linear model to impute missing DOOR at Day 70 will be used. Details of multiple imputation methods are described in Section 8.6.1.

For each of the 20 complete multiple imputation datasets, a DOOR probability, estimated by the Wilcoxon Mann-Whitney U Statistic corrected for ties, will be computed using randomization to dalbavancin versus randomization to standard of care therapy to define the binary grouping and DOOR at Day 70 as the outcome. The U statistics are asymptotically normally distributed, and so they can be combined into a single test statistic using Rubin's Rules [1].

Defining the following:

n_1: number of subjects in ITT population randomized to standard of care

n_2: number of subjects in ITT population randomized to dalbavancin

m: number of imputed datasets ($m = 20$)

Q_i: U statistic computed from the i^{th} multiply imputed dataset

$\bar{Q} = \frac{1}{m}\sum_{i=1}^{m} Q_i$

Q_0: the expected value of a U statistic under the null hypothesis ($Q_0 = \frac{n_1 n_2}{2}$)

U_i: The variance from the i^{th} multiply imputed dataset (this is not the U statistic). Correcting for ties, the formula for the variance of the Mann-Whitney U statistic, as described in Halperin et al. [2], is:

$$U_i = Var(Q_i) = \frac{1}{n_1 n_2}[n_1 + n_2 + 1 - (n_1 + n_2 - 2)\theta]\zeta(1-\zeta)$$

Where

$$\zeta = \frac{1}{n_1 n_2} Q_i$$

$$\theta = \frac{[(n_1 + n_2 - 2)\zeta - (n_2 - 1)A - (n_1 - 1)B]}{(m + n - 2)\zeta(1-\zeta)}$$

To obtain an estimator $\hat{\theta}$ of θ, use the following formulas for A and B, respectively:

$$A = A_1 - \frac{1}{n_2 - 1}\sum_{i=1}^{D-1} p_{1i}\left[q_{2i}\sum_{j=i+1}^{D} p_{2j} - \left(\sum_{j=i+1}^{D} p_{2j}\right)^2\right] - \frac{1}{4(n_2 - 1)}\sum_{i=1}^{D} p_{1i}p_{2i}q_{2i}$$

Where

$$A_1 = \sum_{i=1}^{D-1} p_{1i}\left[\sum_{j=i+1}^{D} p_{2j} + \frac{p_{2i}}{2}\right]^2 + \frac{p_{1D}p_{2D}^2}{4}$$

And

$$B = B_1 - \frac{1}{n_1 - 1}\sum_{j=2}^{D} p_{2j}\left[q_{1j}\sum_{i=1}^{j-1} p_{1i} - \left(\sum_{i=1}^{j-1} p_{1i}\right)^2\right] - \frac{1}{4(n_1 - 1)}\sum_{j=1}^{D} p_{2i}p_{1i}q_{1i}$$

Where

$$B_1 = \sum_{j=2}^{D} p_{2j}\left[\sum_{i=1}^{j-1} p_{1i} + \frac{p_{1j}}{2}\right]^2 + \frac{p_{11}^2 p_{21}}{4}$$

In the equations for A and B above, D is the number of distinct values of DOOR in the dataset; p_{1i}, for i = 1, 2, …, D, represents the proportion of subjects randomized to standard of care with the i[th] value of DOOR; p_{2j}, for j = 1, 2, … D, represents the proportion of subjects randomized to dalbavancin with the j[th] value of DOOR; and q = 1 – p in general.

Additionally, the equation for an unbiased estimate of $\zeta(1-\zeta)$ is given by:

$$\frac{(n_1 n_2 - n_1 - n_2 + 2)\zeta - n_1 n_2 \zeta^2}{(n_1 - 1)(n_2 - 1)} + \frac{A}{n_1 - 1} + \frac{B}{n_2 - 1}$$

After substituting the values of A, B and $\zeta(1-\zeta)$ in the equation θ to obtain an estimate $\hat{\theta}$ of θ, define θ as follows: If $\hat{\theta} < 0$ then $\theta = 0$, if $\hat{\theta} > 1$ then $\theta = 1$, otherwise $\hat{\theta} = \theta$.

$\bar{U} = \frac{1}{m}\sum_{i=1}^{m} U_i$ (The within imputation variance. This is not the mean of the U statistics.)

$B = \frac{1}{m-1}\sum_{i=1}^{m}(Q_i - \bar{Q})^2$

$T = \bar{U} + \frac{m+1}{m}B$

$W = \frac{(\bar{Q}-Q_0)^2}{T}$

$r = \frac{m+1}{m}\frac{B}{\bar{U}}$

$$\nu = (m-1)\left(1 + \frac{1}{r}\right)^2$$

As a sensitivity analysis, a 95% CI for U will be computed using the overall test statistic W through the inversion of the F-test. Dividing the bounds of this CI by $n_1 n_2$ will yield the bounds for the 95% CI of the DOOR probability. Thus, the CI for DOOR probability is given by:

$$95\%\ \text{CI: } \left(\frac{\bar{Q} - \sqrt{T \times F_{0.95,1,\nu}}}{n_1 n_2}, \frac{\bar{Q} + \sqrt{T \times F_{0.95,1,\nu}}}{n_1 n_2}\right)$$

A point estimate of the DOOR probability will be obtained by dividing $\bar{Q}$ by $n_1 n_2$. Results will be shown in Table 20 for ITT population with and without QoL as a tie-breaker. This analysis will be repeated in the mITT population and results will be reported in Table 21 with and without QoL as a tie-breaker. A listing of DOOR and its components is provided in Listing 10. A listing of investigator assessments of clinical success and infectious complications are provided in Listing 11 and Listing 12, respectively.

8.2. Secondary Efficacy Analyses

8.2.1. Analysis of Clinical Efficacy at Day 70 using IPW for the ITT and mITT Analysis Populations

Let Y_i represent the outcome of interest (clinical efficacy), X represent the covariates of interest, Z represent any other variables measured in the data but not used in the analysis model. For the IPW approach, we first define the missingness model to estimate the weights (w_i) using a logistic regression model with outcome R and covariates taken from set (X, Z) where R_i is defined as 1 if is complete (not missing clinical success) and 0 otherwise. Through this model, we obtain the fitted probabilities of being complete, denoted as π_i. Weights w_i are then obtained by the inverse of the fitted probabilities of being complete ($w_i = 1/\pi_i$).

To estimate the proportions of clinical efficacy, we will fit a linear regression model with treatment as a covariate adjusting for IPW weights ($Y_i = \beta_0 + \beta_1 trt + \epsilon_i$, where $\epsilon_i \sim N(0, w_i\sigma^2)$

The difference in proportions of clinical efficacy for dalbavancin compared to standard of care ($p_d - p_s$) will then be obtained by β_1. The rate of clinical efficacy for dalbavancin will be estimated as $p_d = \beta_0 + \beta_1$ and the rate of clinical efficacy for standard of care will be obtained by $p_s = \beta_0$. The two-sided 95% CI for the proportions of clinical efficacy and difference in proportions in clinical efficacy will use estimates from the linear regression with IPW.

Proportions of clinical efficacy for each treatment group along with their 95% CI, a point estimate of the difference in proportions of clinical efficacy at Day 70 along with 95% CI obtained from linear regression with multiple imputation model as described above will be provided in Table 35 for Day 70 using the ITT analysis population. These analyses will be repeated for the mITT analysis population and results will also be provided in Table 36.

The null hypothesis will be rejected and non-inferiority of dalbavancin versus standard of care with respect to clinical efficacy at Day 70 using a non-inferiority margin of 20% will be concluded if the lower bound of the 95% CI for the difference in proportions of clinical efficacy for dalbavancin relative to standard of care is greater than -20%.

Subgroup analyses of clinical efficacy at Day 70 will be performed for the ITT and mITT populations using IPW for different 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; f) divided by duration of initial bacteremia, in the ITT, mITT, and CE populations and results will be reported in Table 38 for ITT and Table 39 for mITT analysis population. Proportions and difference in proportions of clinical efficacy along with their 95% CI estimated from linear regression model following multiple imputation will be reported.

Pseudocode:

Missingness model to estimate fitted probabilities and IPW weights:

Define complete as 1 for complete and 0 for missing and trt=1 for standard of care and 2 for Dalbavancin.

```
proc logistic data = dat;
  model complete (event='1') = [age sex trt and other covariates that affect
completeness of the data];
  output out = out1 p = probs xbeta = logit;
run;
data out1;
      set out1;
      wts=1/probs;
run;
```

Final model:

```
proc glm data=out1;
      class trt(ref='1');
      model clinsuccess= trt solution;
      weight wts;
      lsmeans TRTPN/ pdiff=all tdiff cl stderr;
run;
```

8.2.2. Sensitivity Analysis of Clinical Efficacy at Day 70 using Multiple Imputation for the ITT and mITT Analysis Populations

Clinical efficacy at Day 70 is defined as absence of clinical failure, infectious complications, and all-cause mortality. A subject will be defined as not having clinical efficacy of at least one of these three components occurred. This endpoint will be analyzed using a non-inferiority approach. The corresponding hypotheses are:

Null hypothesis: $\pi_{\text{dalbavancin}} - \pi_{\text{standard of care}} \leq$ -20%,

Alternative hypothesis(non-inferiority): $\pi_{\text{dalbavancin}} - \pi_{\text{standard of care}} >$ -20%,

where π represents the probability of clinical efficacy at study Day 70. 20% is the non-inferiority margin used for this study and is also used for all secondary non-inferiority analyses of clinical efficacy.

The non-inferiority of dalbavancin versus standard of care with respect to clinical efficacy using a non-inferiority margin of 20%, will be determined for the ITT analysis population using a two-sided 95% CI of the difference in proportions of clinical efficacy as constructed using multiple imputation of clinical efficacy with linear regression. A lower bound of the CI greater than -20% will result in the conclusion of non-inferiority of dalbavancin. The imputation model will utilize available information collected at baseline and any completed study visits.

The secondary analysis will use multiple imputation with a linear regression model without rounding to impute missing values of clinical efficacy at Day 70 using the ITT population [3 and 4].

Although the linear regression without rounding can sometimes yield implausible imputed values of treatment success, Horton et.al [4] showed that this method yields an unbiased estimate of the binomial proportion.

- Let $Y_1, Y_2, \ldots, Y_N$ be independent and identically distributed (iid) Bernouilli random variables
- Let $p = E(Y_i)$ be the probability of success

- Assume that only n out of the N Bernoulli data points are observed; the rest are missing. For simplicity, assume Let $Y_1, Y_2, \ldots, Y_n$ are observed and Let $Y_{n+1}, \ldots, Y_N$ are missing. Further assume that data are Missing Completely at Random (MCAR).

For estimating p, the minimum variance unbiased estimate (MVUE) of p denoted by $\hat{p}$ which is simply the mean of observed data, i.e.,

$$\hat{p} = \frac{1}{n}\sum_{i=1}^{n} Y_i$$

Rubin and Schenker [5] proposed using a full normal imputation method to impute missing values $Y_{n+1}, \ldots, Y_N$ which assumes that the Y_i are iid from normal distribution with mean p and variance σ^2. This method follows the following algorithm to generate the missing values.

This full normal imputation method without rounding incorrectly assumes a normal distribution and can sometimes yield implausible imputed values (above 1 or below 0). However, it produces an unbiased estimate of the probability of success p.

Allison [3] showed that this approach can be extended to allow covariates in the model. Hence, using simulation studies, Allison showed that multiple imputation using linear regression performed well in estimating regression coefficients in different missing data scenarios (MCAR, MAR) even when compared to logistic regression. The added benefit of using the linear regression model is that it directly provides proportion differences along with their 95% CI after applying PROC MIANALYZE to the model fits from the M multiply imputed datasets. This approach will follow the three steps described below:

Step 1: A multiple regression model: $Y_i = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \cdots + \beta_c X_c + \epsilon_i \;\; , \epsilon_i \;\sim N(0, \sigma^2)$ where Y_i represents the indicator for clinical efficacy and X_c are the covariates described in Section 8.6.2 to be used in the multiple imputation model to generate *M* multiply imputed datasets.

Step 2: A linear regression model $Y_i = \beta_0 + \beta_1 trt + \epsilon_i$ will be fit on each of the *M* multiply imputed datasets with *trt* defined as 0 for standard of care and 1 for dalbavancin.

Step 3: The final clinical efficacy estimates will be obtained by combining *M* estimates of clinical efficacy estimates using PROC MIANALYZE as described in in Section 8.6.2. The rate of clinical efficacy for dalbavancin will be estimated as $p_d = \beta_0 + \beta_1$ and the rate of clinical efficacy for standard of care will be obtained by $p_s = \beta_0$. The difference in proportions of clinical efficacy for dalbavancin compared to standard of care $(p_d - p_s)$ will then be obtained by β_1. The two-sided 95% CI for the proportions of clinical efficacy and difference in proportions in clinical efficacy will use estimates from the linear regression with multiple imputation.

Proportions of clinical efficacy for each treatment group along with their 95% CI, a point estimate of the difference in proportions of clinical efficacy at Day 70 along with 95% CI obtained from linear regression with multiple imputation model as described above will be provided in Table 35 for Day 70 using the ITT analysis population. These analyses will be repeated for the mITT analysis population and results will also be provided in Table 35.

The null hypothesis will be rejected and non-inferiority of dalbavancin versus standard of care with respect to clinical efficacy at Day 70 using a non-inferiority margin of 20% will be concluded if the lower bound of the 95% CI for the difference in proportions of clinical efficacy for dalbavancin relative to standard of care is greater than -20%.

An individual listing of observed values of clinical efficacy components is provided in Listing 10.

8.2.3. Analysis of DOOR Components Using ITT Analysis Population

Results for the analysis of DOOR components at Day 70 will be presented. Proportions of subjects with clinical failure, infectious complications, SAEs & AEs leading to study drug discontinuation, and all-cause mortality at Day 70 will be reported in Table 42 by treatment group. Note that this analysis will consider subjects in the ITT population who have non-missing values for the corresponding DOOR component. The DOOR component will be summarized by the DOOR probability and 95% confidence interval (computed as the probability that a randomly selected patient will have a better DOOR if assigned to the intervention arm using the Wilcoxon-Mann-Whitney statistic corrected for ties). A summary of DOOR by component will be presented at Day 70 for the ITT population in Table 47. The DOOR probability will also be presented graphically using forest plots in Figure 2. These analyses will be repeated for Day 42, and analogous results will be reported in Table 45, Table 48, and Figure 5, respectively.

8.2.4. Analysis of Clinical Failure at Day 70 Using ITT Population

Clinical failure at Day 70 will be analyzed using weighted generalized estimating equations (GEE) assuming an unstructured correlation structure, including clinical failure at Day 42. The difference in proportions of clinical failure between the two groups at Day 70 will be calculated with the corresponding 95% confidence interval (Table 49). The GEE model will use subject random effects with an unstructured correlation structure to generate the average difference in proportions of clinical failure for dalbavancin compared to standard of care at Day 70 and IPW weights will be obtained using a similar approach as that described in Section 8.2.1 using the following pseudocode:

```
Weighted GEE:
proc gee data=temp descending;
class id trt clinfailure time/param=ref
missmodel trt time trt*time / type=obslevel; /* missingness model */
model clinfailure= trt time trt*time; /* marginal model */
repeated subject=id/ corr=un;
    estimate 'trt 1 at time=2' intercept 1 trt 1 time 2 trt*time 2;
    estimate 'trt 0 at time=2' intercept 1 time 2;
    estimate 'trt 1 vs 0 at time=2' trt 1 trt*time 2;
run;
```

where temp is a dataset with one row per timepoint per subject (one row for time=1 and another row for time=2 per subject). Clinfailure is a binary variable with a value of 1 indicating clinical failure and a value of 0 indicating clinical success, trt is a binary variable with a value of 1 indicating dalbavancin and a value of 0 indicating standard of care, id indicates each subject identifier, and time is binary variable with a value of 1 indicating Day 42 and a value of 2 indicating a Day 70 timepoint.

A linear model was used in this scenario since the outcome of interest is difference in proportions instead of odds ratios. The difference in proportions will be given by the sum of coefficient for the treatment and the coefficient for treatment*time interaction and will be interpreted as ‘on average, the proportion clinical failure at Day 70 is increased (or decreased if the sign if negative) by xx amount when taking dalbavancin compared to standard of care’.

As a sensitivity analysis, generalized linear mixed model (GLMM) approach will be used to analyze clinical failure (Table 49) to model individual treatment differences for dalbavancin compared to standard of care using the following pseudocode:

```
proc mixed data=temp;
     class id;
     weight wts;
     model clinfailure=trt time trt*time;
     repeated/ subject=id type=un;
    estimate 'trt 1 at time=2' intercept 1 trt 1 time 1 trt*time 1;
    estimate 'trt 0 at time=2' intercept 1 time 1;
    estimate 'trt 1 vs 0 at time=2' trt 1 trt*time 1;

run;
```

Note that wts will be calculated from a similar missingness logistic regression model as that used for the weighted GEE model above.

Similarly, to GEE, the difference in proportions using GLMM will be given by the sum of coefficient for the treatment and the coefficient for treatment*time interaction. This treatment difference will be interpreted as 'for a specific individual, the proportion clinical failure at Day 70 is increased (or decreased if the sign if negative) by xx amount when taking dalbavancin compared to standard of care'.

8.3. Exploratory Efficacy Analyses

8.3.1. Analysis of Clinical Efficacy at Day 42

Clinical efficacy at Day 42 will be analyzed using a similar approach as that described in Section 8.2.1 using IPW and as described in Section 8.2.2 using multiple imputation for the ITT and mITT analysis populations, and results will be reported in Table 36.

Subgroup analyses of clinical efficacy at Day 42 will be performed for the ITT and mITT populations using IPW for different 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) divided by duration of initial bacteremia and results will be reported in Table 38 for ITT and Table 39 for mITT analysis population. Proportions and difference in proportions of clinical efficacy along with their 95% CI estimated from linear regression model following multiple imputation will be reported.

8.3.2. Additional Analyses of DOOR

8.3.2.1. Analysis of DOOR at Day 42 Using ITT and mITT Analysis Populations

The analysis of DOOR at Day 42 for the ITT and mITT analysis populations will be performed in an analogous manner as those described in Section 8.1.1.1 for the primary analysis using IPW and as described in Section 8.1.1.2 using multiple imputation and results will be reported in Table 22 for the ITT population and Table 23 for the mITT population.

8.3.2.2. Subgroup Analyses of DOOR

Subgroup analysis of DOOR will be performed using subjects in each of the following subgroups 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; f) divided by duration of initial bacteremia, in the ITT, mITT, and CE populations for Day 42 and Day 70. Analyses for the ITT and mITT will use a similar approach as that described in Section 8.1.1.1 using IPW and results will be reported in Table 25 for ITT

population and Table 26 for mITT population. Subgroup analysis of DOOR for the CE population will use the approach described in Section 8.3.3.2 for complete data and results will be reported in Table 27. Forest plots for DOOR probabilities are also presented for the ITT analysis population in Figure 20 for Day 70 and Figure 21 for Day 42.

8.3.3. Analysis of DOOR Components at Day 42 and Day 70 Using mITT Analysis Populations

Results for the analysis of DOOR components at Day 70 will be presented. Proportions of subjects with clinical failure, infectious complications, SAEs, AEs leading to study drug discontinuation, and all-cause mortality at Day 70 will be reported in Table 42 for each treatment group using mITT population. The DOOR component will be summarized by the DOOR probability and 95% confidence interval. The DOOR probability will also be presented graphically using forest plots in Figure 3 for the mITT population. This analysis will be repeated for Day 42, and results with be reported in Table 45 and Figure 6.

8.3.3.1. Analysis of DOOR Categories at Day 42 and Day 70 Using ITT and mITT Analysis Populations

The number and percent of subjects along with 95% CI for the percentages computed using the Wilson method in each DOOR category will be presented in Table 28, Table 29, and Table 30 for the ITT, mITT, and CE analysis populations, respectively. The percentage of subjects in each DOOR category will also be presented graphically in Figure 8, Figure 9, Figure 10 for Day 70 and Figure 11, Figure 12, Figure 13 for Day 42. The percentage of subjects in each DOOR category is also presented per subgroup for Day 70 using the ITT analysis populations starting with Figure 14 through Figure 19.

8.3.3.2. Distribution of DOOR by Treatment Group Using ITT and mITT Analysis Populations

The distribution of DOOR by treatment group will be presented by number and percentage of by Subgroup Categories for the ITT analysis population in Table 55 for Day 42 and Table 56 for Day 70.

8.3.3.3. Cumulative Difference in DOOR Categories Using ITT and mITT Analysis Populations

Cumulative DOOR probability as well as 95% CI will be provided in Table 31 for Day 42 and Day 70 Using the ITT analysis population. The Wilcoxon-Mann-Whitney statistic corrected for ties will be used as an estimate of the cumulative DOOR probability. Analogous results will be presented for the mITT population in Table 32. These results will also be presented graphically in Figure 22.

8.3.3.4. Analysis of Difference in Mean Partial Credit Using ITT and mITT Analysis Populations

The partial credit will be calculated assigning a partial credit score to each of the DOOR categories. For this analysis, DOOR categories 3 (alive with two events) and 4 (alive with three events) will be combined such that DOOR will be analyzed using a 4-category ranking. QoL is not considered for analysis of partial credit score. The difference in mean partial credit score will be summarized in Figure 23.

8.3.3.5. Analysis of Expected DOOR Category Distribution and Expected Numbers Gained Loss Using ITT and mITT Analysis Populations

The expected number for the DOOR category will be calculated by multiplying the proportion of subjects in that DOOR category by 1000 separately for each treatment group. The gained loss for each DOOR category will be calculated by taking the difference in expected number for Dalbavancin minus the expected number for standard of care. The total gained loss will be obtained by summing up all the gained losses for all the

DOOR categories (i.e., add up all the differences in expected numbers for dalbavancin minus standard of care) and results will be reported in Table 34 for Day 42 and 70 for ITT and mITT analysis populations.

8.3.4. Analysis of Microbiological Success at Day 42 and Day 70 using the ITT and mITT Analysis Populations

Microbiological success at Day 42 is defined as the absence of a post-randomization growth (i.e., no positive cultures) of the baseline pathogen from blood cultures drawn post randomization or from another sterile body site until Day 42. Subjects who will still be in the study at Day 42 and have no post randomization cultures will be considered as having microbiological success. Subjects who are lost to follow up by Day 42 and have no post-randomization blood cultures will have missing microbiologic success. Due to the potential of having missing values of microbiologic success in the ITT and mITT, microbiologic success at Day 42 will be analyzed using a similar approach as that described in Section 8.2.1 using IPW and in Section 8.2.2 using multiple imputation for the ITT and mITT analysis populations and results will be reported in Table 50. These analyses will also be repeated for Day 70 and results will be reported in Table 50 for ITT and mITT analysis populations. Subgroup analyses of microbiologic success will be performed for the ITT and mITT populations using IPW for different 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; f) divided by duration of initial bacteremia and results will be reported in Table 52 for ITT and Table 53 for mITT analysis population. Proportion and difference in proportions of microbiologic success along with their 95% CI estimated from linear regression model with IPW will be reported.

An individual listing of observed values of microbiologic success is provided in Listing 10 and a listing of culture results used to define microbiologic success is provided in Listing 13.

8.3.5. Analysis of QoL Score using ITT and mITT Analysis Populations

Summary statistics (number of subjects, mean, standard deviation, minimum, maximum) for QoL scores and change from baseline of QoL scores obtained from the ARLG Bloodstream Infection QoL Measure at Day 42 and Day 70 will be provided for each analysis population in Table 57. Similarly, summary statistics for QoL scores from the EQ-5D-5L instrument and PROMIS Global Health Short Form will be provided in Table 58 and Table 59, respectively. A listing of QoL data from the three instruments is provided in Listing 14.

Additionally, descriptive statistics of QoL measures will also be presented by item.

8.3.6. Bivariate Analysis of DOOR Probability vs Difference in Mean of Change in QoL Score from Baseline

In addition to the DOOR analyses described in Section 8.1.1 and Section 8.4.1, a two-dimensional analysis of the DOOR probability and difference in the mean change in QoL from baseline in the two treatment groups using the ARLG Bloodstream Infection QoL Measure will also be performed at Day 70. Only subjects with non-missing DOOR and change in QoL from baseline will be included in these analyses. The horizontal axis is the DOOR probability (probability of a more desirable DOOR category when assigned to Dalbavancin vs. Standard of care) based on the DOOR categories without using mean change in QoL from baseline as a tie-breaker. The vertical axis is the difference in the means of the observed difference in mean change in QoL from baseline (dalbavancin minus standard of care). A result in the upper right quadrant represents more desirable results for dalbavancin group, while a result in the lower left represents more desirable standard of care. The other two quadrants represent tradeoffs for clinical outcomes and QoL score.

1000 bootstrap samples will be generated by resampling with replacement from the empirical distribution of DOOR and change in QoL from baseline at Day 70. The DOOR probability and mean difference in the mean change in QoL from baseline will be estimated using the bootstrap samples and plotted as a scatter plot. A 95% joint region of DOOR probability and difference in mean change in QoL from baseline will be constructed first using a parametric method. The parametric method will estimate the confidence region using the ellipse method from the CAR R package which uses a bivariate normal distribution. The 90%, 95%, and 99% confidence regions will be reported. These results will be reported in Figure 24 for Day 70 and Figure 25 for Day 42 using the ITT analysis population. Subjects in the ITT analysis population with missing values of DOOR categories and change in QoL from baseline will be excluded from this analysis.

8.3.7. Analysis of Late Recurrence Within ITT Population with Osteomyelitis

The osteomyelitis population includes all randomized subjects diagnosed with osteomyelitis. Subjects in this population will have an extra follow-up visit approximately 6 months after randomization to evaluate long term recurrence risk. 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.

Protocol amendment version 3.0 expanded Visit 7 (Day 180) to include all subjects with osteomyelitis, instead of only those with vertebral osteomyelitis at baseline (version 2.0). When possible, any subjects who were not originally eligible for Visit 7 under protocol version 2.0, but who were eligible under protocol version 3.0 were re-consented and data was collected. Thus, in addition to the planned analysis, which includes all subjects for whom Visit 7 consent and data were obtained, an additional sensitivity analysis will be conducted that excludes subjects enrolled under protocol version 2.0 who were not eligible prior to protocol version 3.0. That is, the planned analyses will be performed in the following groups:

1. All subjects for whom Visit 7 consent and data was obtained (either at the time of enrollment or retroactively following protocol version 3.0), and
2. Subjects who enrolled after protocol version 3.0 or later (i.e., excluding subjects those enrolled initially under protocol version 2.0 that re-consented under protocol version 3.0).

Note that no eligible subjects were enrolled under protocol version 1.0. If no data are available for subjects who were re-consented the sensitivity analysis will be excluded.

Number and percentage of subjects in each of the osteomyelitis populations above will be presented in Table 62 by treatment group. Difference in proportions along with their 95% CI will also be reported.

8.4. Supplemental Efficacy Analyses

All efficacy analyses performed using the CE analysis population will be considered supplemental.

8.4.1. Analysis of DOOR at Day 42 and 70 Using CE Analysis Populations

Additional analyses of DOOR at Day 42 and Day 70 will be performed using only subjects in the CE population with complete data. These analyses will evaluate the null hypotheses described above using the DOOR probability Pr(Desirable DOOR in dalbavancin) + 0.5 Pr(Equal DOOR), estimated by Wilcoxon-Mann-Whitney Statistic corrected for ties, divided by the product of the two group sample sizes and corresponding CIs calculated by the method described in Halperin et al. [2]. The methods described in Section 8.1.1.2 will be implemented for this analysis.

Results from the analysis using CE analysis population with complete data will be reported in Table 24 for both Day 42 and Day 70.

8.4.2. Analysis of Clinical Efficacy at Day 70 Using CE Analysis Population

The CE analysis populations at Day 70 will have no missing values of clinical efficacy, therefore the analysis of clinical efficacy at Day 70 will be performed using a linear regression without multiple imputation with treatment group as a covariate ($Y_i = \beta_0 + \beta_1 trt_i + \epsilon_i$) for subjects in the CE analysis population at Day 70. The rate of clinical efficacy in the dalbavancin arm will then be estimated by $p_d = \beta_0 + \beta_1$ and the rate of clinical efficacy in the standard of care arm will be provided by $p_s = \beta_0$.

The estimate for the difference in proportions of clinical efficacy will be provided by β_1 and its 95% CI will be calculated first by using the 95% CI for β_1 from the linear regression model above. As a sensitivity analysis, the 95% CI for the difference in proportions of clinical efficacy will be recalculated using the Miettinen–Nurminen method from PROC FREQ with RISKDIFF (CL= MN) in SAS.

Proportions of clinical efficacy for each treatment group, a point estimate of the difference in proportions of clinical improvement at Day 70 along with their 95% CIs obtained methods described above will be provided in Table 37 using the CE analysis population at Day 70. If the lower bound of the 95% CI for the difference in proportions of clinical efficacy is greater than -20%, it will be annotated by a footnote b.

Results from the subgroup analysis of clinical efficacy at Day 70 using CE population will be reported in Table 40.

Proportions and difference in proportions of clinical efficacy along with their 95% CI estimated from linear regression model without imputation will be reported for the CE analysis population.

Clinical efficacy will also be analyzed for the CE analysis population at Day 42 using a similar approach as that used for Day 70, and results will be reported in Table 37. Results from the subgroup analysis of clinical efficacy at Day 42 using CE population will also be reported in Table 40.

8.4.3. Analysis of DOOR at Day 42 and Day 70 Using CE Analysis Population

Analyses described in Section 8.3.3 will be performed using the CE analysis population. Proportions of subjects with clinical failure, infectious complications, SAEs, AEs leading to study drug discontinuation, and all-cause mortality at Day 70 will be reported in Table 43 using the CE population. The DOOR component will be summarized by the DOOR probability and 95% confidence interval. The DOOR probability will also be presented graphically using forest plots in Figure 4 for the CE population. This analysis will be repeated for Day 42 and results with be reported in Table 46 and Figure 7.

8.4.3.1. Cumulative Difference in DOOR Using CE Analysis Population

Cumulative DOOR probability as well as 95% CI will be provided in Table 33 for Day 42 and Day 70 Using the CE analysis population. The Wilcoxon-Mann-Whitney statistic corrected for ties will be used as an estimate of the cumulative DOOR probability. These results will also be presented graphically in Figure 22.

8.4.3.2. Analysis of Difference in Mean Partial Credit Using CE Analysis Population

Analysis of mean partial credit scores described in Section 8.3.3.4 will be repeated using the CE analysis population and results will provided in Figure 22.

8.4.3.3. Analysis of Expected DOOR Distribution and Expected Numbers Gained Loss

Analysis of expected DOOR distribution and expected gained loss described in Section 8.3.3.4 will be repeated for the CE analysis population and results will be reported in Table 34.

8.4.4. Analysis of Microbiological Success at Day 42 and Day 70 using the CE Analysis Populations

Analysis of microbiological success described in Section 8.3.4 will be repeated using the CE analysis population at Day 42 and Day 70. Results will be presented in Table 51. Subgroup analysis of microbiological success at Day 42 and Day 70 will also be performed using the CE population and results will be presented in Table 54.

8.5. Interim Analyses

Predictive intervals and predictive interval plots will be generated for DOOR and clinical efficacy under a range of assumptions including: 1) the trends observed at interim analysis continue to end of study, 2) the null hypothesis is true (i.e., the DOOR distributions are identical between treatment groups), and 3) and the worst-case scenario as an alternative outcome. These predicted interval plots provide a prediction of the trial results were the trial to continue as planned under varying assumptions regarding future data (e.g., current trend continues, null hypothesis is true, and worst-case scenario). For example, using then current trend, the remaining subjects will be simulated assuming outcomes continue to occur at the rates observed at the time of interim analysis. For each assumption, 10,000 complete datasets (N=200 subjects) will be simulated and used to calculate the probability of rejecting the null hypothesis for each scenario. By relying on prediction intervals, no statistical hypothesis testing is required, and no power is lost at interim analysis [7 and 8]. Note interim results will only be presented in the DSMB closed session.

Suppose the following distribution of DOOR is observed at the interim analysis, i.e. $\hat{p}_{D1}$ is the proportion of subjects in the Dalbavancin group observed to have a DOOR of 1 (alive with no events).

DOOR	Dalbavancin	Standard of Care
1 – Alive with no events	$\hat{p}_{D1}$	$\hat{p}_{C1}$
2 – Alive with 1 event	$\hat{p}_{D2}$	$\hat{p}_{C2}$
3 – Alive with 2 events	$\hat{p}_{D3}$	$\hat{p}_{C3}$
4 – Alive with 3 events	$\hat{p}_{D4}$	$\hat{p}_{C4}$
5 – Death	$\hat{p}_{D5}$	$\hat{p}_{C5}$

Let p_{Dk} and p_{Ck} denote the proportions of subjects in the Dalbavancin and Standard of Care groups with DOOR = *k,* for *k* = 1, 2, …, 5, used to simulate the predicted data.

- Under scenario 1, the trend observed at the interim continues, we assume that $p_{Dk} = \hat{p}_{Dk}$ and $p_{Ck} = \hat{p}_{Ck}$ for *k* = 1, 2, …, 5.
- Under scenario 2, the null hypothesis is true, we assume $p_{Dk} = p_{Ck} = \bar{p}_k = \frac{n_d}{n_d+n_c}\hat{p}_{Dk} + \frac{n_c}{n_d+n_c}\hat{p}_{Ck}$; where n_d is the number of subjects in the Dalbavancin group and n_c is the number of subjects in the standard of care arm.
- Under scenario 3, the worst-case scenario as an alternative outcome, we assume that $p_{Dk} = \hat{p}_{Ck}$ and $p_{Ck} = \hat{p}_{Dk}$ if the Standard of Care group is better at the interim analysis (as determined by DOOR probability).

Summary of PIPs statistics are presented in Table 60 and Figure 26 for DOOR at Day 70 and in Table 61 and Figure 27 for clinical efficacy at Day 70 using the ITT analysis population. Other tables and figures from the main analyses will also be presented in the interim report and are indicated via implementation notes in this SAP.

8.6. Imputation of Missing Data

8.6.1. Multiple Imputation of Missing DOOR Day 42 and Day 70

Several analyses depend on multiple imputation of DOOR at Day 70 and Day 42 for ITT and mITT analysis populations. First, a table showing the number and percentage of missing data for DOOR on Day 42 and Day 70 will be presented in Table 18 for ITT and Table 19 for mITT analysis population. In order to use the multiple imputation model to adjust for bias caused by missing data, we assume that data are missing at random (MAR).

Multiple imputations of each of these missing endpoints will be performed independently, and each subject will have their missing endpoints imputed independently of other subject's imputations using a subject-specific imputation model.

Before performing multiple imputation, an ordered list of variables to include in the subject-specific imputation model is constructed. Ordering is specified so that exact imputation results from final data are prespecified may be replicated in SAS (using seeds described below). The complete ordered list of variables for the imputation models for DOOR at Day 70 is below.

- Indicator of dalbavancin as study treatment (binary indicator, standard of care is the reference group)
- Baseline pathogen (binary indicator, MRSA is the reference group)
- Age at enrollment
- Site of infection
- Duration of bacteremia
- Observed DOOR category at Day 70

For DOOR at Day 42, the complete list of model variables is identical to the above with Day 70 being replaced by Day 42.

The actual list of model variables for each subject-specific imputation model will follow the ordering above but omit variables with missing values. The below pseudo-code / SAS code outlines the creation of 20 multiple imputation datasets. Note that the seeds used in the actual analysis must follow the specification given in the pseudo-code and subjects must be processed in the order described in the pseudo-code. The pseudo-code is in terms of Day 70 endpoints, but the general logic is also applicable to the Day 42 endpoints (with references to "D70" replaced with references to "D42").

```
DEFINE i=index variable for subjects having DOOR imputed.
      Subjects requiring imputation are sorted in ascending order
      by PATID.
DEFINE N=number of subjects requiring imputation
DEFINE g&i=analysis dataset containing predictors and DOOR for Subjects with complete
       DOOR at D70 as well as subject i (only one subject with missing data are
       included).  Note that subjects with complete DOOR that are missing a value for
       one or more variables in the subject-specific imputation model are excluded.
```

```
DEFINE imp_g&i = g&i, with 20 imputed values for the missing DOOR
      added by PROC MI
DEFINE &&modelVars_&i  = list of observed variables in subject i, to
      be used for imputation of DOOR.
%do i=1 %to &N;
PROC MI data=g&i out=imp_g&i seed=500&i NIMPUTE=20 noprint;
      var &&modelVars_&i DOOR;
      monotone reg(DOOR_D70 = &&modelVars_&i);
run;
%end;
imp_g&i will be subset to contain only rows for the subjects with imputed DOOR and
merged together and with subjects with complete data to create the twenty complete
multiply imputed datasets
```

8.6.2. Multiple Imputation (MI) of Missing Values of Clinical Efficacy and Microbiologic Success on Day 42 and Day 70

Secondary and exploratory analyses of clinical efficacy and microbiologic success for ITT and mITT populations depend on multiple imputation. First, a table showing the number and percentage of missing data for clinical efficacy and microbiologic success on Day 42 and Day 70 will be presented in Table 18 for ITT and Table 19 for mITT analysis population. In order to use the MI model to adjust for bias caused by missing data, we assume that data are missing at random (MAR).

For missing clinical efficacy on Day 42 and Day 70, multiple imputations of missing clinical efficacy on Day 42 and Day 70 will be performed independently, and each subject will have their missing clinical efficacy imputed independently of other subjects' imputations using a subject-specific imputation model. The pseudocode shown below details how missing data for clinical efficacy for Day 70 (Day 42) will be imputed using *m* multiply imputed datasets from linear models. The following covariates will be used non-missing for the MI model: treatment group, baseline pathogen, age, gender. The number of imputed, *m*, datasets will be chosen based on the average percent of missing data. Default value will be *m*=20 since sample size calculation assumed close to 20% drop-out rate.

As a first step to multiple imputation, an ordered list of variables to include in the subject-specific imputation model is constructed. Ordering is specified so that exact imputation results from final data are prespecified may be replicated in SAS (using seeds described below). The complete ordered list of variables for the imputation models for clinical improvement is below:

- Indicator of dalbavancin as study treatment (binary indicator, standard of care is the reference group
- Baseline pathogen (binary indicator, MRSA is the reference group)
- Age at enrollment
- Site of infection
- Duration of bacteremia
- Observed DOOR

The actual list of MI model variables for each subject-specific imputation model will follow the ordering above but omit variables with missing values. The below pseudo-code / SAS code outlines the creation of 20 multiple imputation datasets. Note that the seeds used in the actual analysis must follow the specification

given in the pseudo-code, and subjects must be processed in the order described in the pseudo-code. The pseudo-code is for Day 70, but the general logic is also applicable to Day 42.

****

*Outcome variables: clinefficacy_D70

DEFINE i=index variable for subjects having clinical efficacy imputed.

Subjects requiring imputation are sorted in ascending order by PATID.

DEFINE N=number of subjects requiring imputation

DEFINE g&i=analysis dataset containing predictors and clinical efficacy for subjects with non-missing efficacy at Day 70 as well as subject i (only one subject with missing clinical efficacy is included). Note that subjects with complete clinical efficacy at Day 70 that are missing a value for one or more variables in the subject-specific imputation model are excluded.

DEFINE imp_g&i = g&i, with 20 imputed values for the missing clinical efficacy

added by PROC MI

DEFINE &&modelVars_&i = list of observed variables in subject i to be used for imputation of clinical efficacy

Step 1: Imputation model: This model will generate 20 datasets with each dataset containing original complete data along with imputed values for subjects with missing endpoint.

```
%do i=1 %to &N;
PROC MI data= g&i out= imp_g&i seed= 22131&i NIMPUTE=20 noprint;
     Var &&modelVars_&i clinefficacy_D70;
     monotone reg(clinefficacy_D70 = &&modelVars_&i;
run;
%end;
```

imp_g&i will be subset to contain only rows for the subjects with imputed clinical improvement and merged together and with ATP-5 data to create the twenty complete multiply imputed datasets

Step 2: Analysis model: This model will fit regression models to the 20 complete datasets to obtain parameter estimates for treatment success, clinical cure, microbiological success.

```
proc reg data= imp_g outest= out_clineff_D70 covout noprint;
model clinefficacy_D70= trt /clb alpha=0.05;
by _imputation_;
run;
```

Step 3: Combine estimates from models in step 2 to obtain overall estimates summarized over 20 imputed datasets;

```
proc mianalyze data= out_clineff_D70 alpha = 0.05;
modeleffects intercept trt;
ods output ParameterEstimates=parms_trts;
run;
```

****

The multiple imputation model for microbiologic success will use a similar algorithm and imputation variables as the clinical efficacy model described above.

9. SAFETY EVALUATION

9.1. Demographic and Other Baseline Characteristics

Summaries of race, ethnicity, sex, age, weight, height, body mass index (BMI), baseline pathogen, baseline QoL, will be presented for the ITT population by site (Table 9 and Table 13) and by treatment group (Table 11 and Table 15). Similar tables will be presented for the Safety population by site in Table 10 and Table 14 and by treatment group in Table 12 and Table 16. Age, weight, height, baseline QoL, and BMI will be summarized as continuous variables. The baseline QoL standardized score is obtained from the questions arising from the PROMIS physical function item bank (PROMIS Item Bank v2.0, short form 6b) item bank on the ARLG Bloodstream Infection QoL. Ethnicity will be categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the case report form (CRF) as "No" to each racial option. For subjects that were previously enrolled in this study, only information associated with their second enrollment will be reported and used for analysis.

Summaries of subject's medical history will be presented by MedDRA® V24.1 or higher system organ class (SOC) and treatment group (Table 17).

Individual subject listings will be presented for all demographics and baseline characteristics (Listing 6),pre-existing medical conditions (Listing 7), and investigator assessment of baseline *S. aureus* bacteremia diagnoses (Listing 8).

9.1.1. Prior and Concurrent Medical Conditions

Number and percentage of subjects' pre-existing and concurrent medical conditions will be presented by MedDRA system organ class and treatment group for the ITT population (Table 17).

Individual subject listings will be presented for all pre-existing medical conditions (Listing 7).

9.1.2. Prior or Concomitant Medications and Nondrug Interventions

Prior medication is defined as any medication taken before the date of the first dose of investigational product. Concomitant medication is defined as any medication started on or after the date of the first dose of investigational product. Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary.

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 (ATC1 and ATC2) for the safety population in Table 107. 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. A summary of subjects taking nondrug interventions by SOC is provided in Table 108.

Individual subject listings will be presented for all concomitant medications (Listing 21). A listing of nondrug interventions is provided in Listing 22.

9.2. Measurements of Treatment Compliance

Dates of first treatment will be summarized by site and treatment group in Table 5. Exposure to investigational 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. Number and percentage of subjects in the dalbavancin group receiving 1 or 2 doses of dalbavancin will be reported in Table 6. For subjects in the standard of care group, the duration of antibiotics will be calculated using the start and stop dates for standard of care antibiotics. Duration of antibiotics will be calculated using three different start dates: (1) date of first positive blood culture, (2) date of first negative blood culture, and (3) date of randomization. The stop date will be the latest end date recorded for each antibiotic. Descriptive statistics for each duration of standard of care antibiotics (n, mean, standard deviation, minimum, median, and maximum) will be presented in Table 7. A listing of individual subjects' treatment duration is provided in Listing 9. A listing of all subjects who took at least one dose of study product is provided in Listing 1.

9.3. Adverse Events

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

When calculating the incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once and any repetitions of adverse events within a subject will be ignored; the denominator will be the number of subjects in the safety population. All adverse events reported will be included in the summaries and analyses. Safety analyses will be based on the safety population. Safety analyses encompass the component events to the DOOR calculation.

9.3.1. Treatment-Emergent 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 investigational product or was present before the first dose of investigational product and increased in severity during the treatment period.

A summary of all treatment-emergent AEs in each treatment group will be tabulated by MedDRA SOC, preferred term (PT), and relationship to the investigational product in Table 65 and by MedDRA system organ class, high level group term (HLGT), and relationship to the investigational product in Table 67. A listing of all treatment-emergent AEs will be presented in Listing 15.

A summary of all treatment-emergent AEs will be tabulated by MedDRA SOC, PT, maximum severity, and causal relationship to the investigational product in Table 66. If more than one AE is coded to the same PT for the same subject, the subject will be counted only once for that PT using the most severe and most related occurrence for the summarization by severity and by causal relationship to the investigational product. Similarly, a summary of all treatment-emergent AEs will be tabulated by MedDRA, SOC, HLGT, maximum severity, and causal relationship to the investigational product in Table 68. If more than one AE is coded to the same HLGT for the same subject, the subject will be counted only once for that HLGT using the most severe and most related occurrence for the summarization by severity and by causal relationship to the investigational product.

The distribution of treatment-emergent AEs by severity and causal relationship to the investigational product will be summarized by treatment group in Table 69.

The distribution of AESIs by severity and causal relationship to the investigational product will be summarized by treatment group in Table 70.

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 investigational product will be summarized by PT and treatment group and will be sorted by decreasing frequency for the investigational product Table 71. In addition, the incidence of fatal on-therapy SAEs (i.e., events that caused death) will be summarized separately by treatment group and PT in Table 72 and by treatment group and HLGT in Table 73. An SAE will be defined as an on-therapy SAE if it occurred during or after the first infusion of investigational product.

Bar charts of all adverse events will be presented by MedDRA SOC, severity and treatment group in Figure 28 and by MedDRA HLGT, severity, and treatment group in Figure 29. Forest plots of differences in risks of experiencing adverse events will be presented by SOC in Figure 30 and by HLGT in Figure 31. The 95% confidence intervals for difference in proportions will be computed using the Miettinen-Nurminen method.

9.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Detailed narratives will be given for any deaths, SAEs, AESIs, and AEs leading to study product discontinuation that occurred during the study. Listings will include Subject IDs, AE description, AE onset date/end date, relationship to treatment, alternate etiology if not related, outcome, and duration of event (days).

Listings for SAEs, AESIs, subjects with AEs leading to discontinuation, and subjects who die (if any) will be presented in Table 74, Table 75, Table 76, and Table 77, respectively. A listing of all treatment-emergent AEs is presented in Table 78.

The number and percentage of subjects reporting SAEs, AEs Leading Discontinuation, Grade 3 or Higher AEs, AESIs, and ALT/AST Elevations will be reported by treatment group in Table 63 for the safety population by study arm and in Table 64 for standard of care antibiotics.

9.5. Pregnancies

For any subject in the Safety population who became pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. Listing 25, Listing 26, Listing 27, Listing 28, and Listing 29 will present any study pregnancies and their outcomes.

9.6. Clinical Laboratory Evaluations

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 starting with Table 82 and ending with Table 95 for serum chemistry parameters and starting with Table 97 and ending with Table 104 for hematology parameters. Forest plots of difference in risks of experiencing abnormal clinical laboratory events by clinical laboratory parameters will be presented in Figure 32 for hematology parameters and in Figure 33 for serum chemistry parameters. The 95% confidence intervals for difference in proportions will be computed using the Miettinen-Nurminen method.

The number and percentage of subjects with potentially clinically significant (PCS) post-baseline clinical laboratory values will be tabulated by treatment group in Table 81 for serum chemistry parameters and

Table 96 for hematology parameters. The criteria for PCS laboratory values will be detailed in the table footnotes. 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 PCS chemistry and hematology laboratory results is provided in Table 79 and Table 80, respectively. A listing of all AEs that occur in subjects who have PCS laboratory values or vital signs will also be provided in Listing 16. Individual laboratory results are provided in Listing 17 for chemistry laboratory parameters and in Listing 18 for hematology laboratory parameters.

9.7. Vital Signs and Physical Evaluations

Vital signs including pulse rate, systolic blood pressure (BP), diastolic BP, respiratory rate, and temperature will be collected at each visit from Visit 1 through Visit 7 and at the early termination visit. Descriptive statistics for vital sign values and changes from baseline will be presented at each timepoint by treatment group in Table 105 for vital signs values and Table 106 for changes from baseline. Individual vital signs measurements will be provided in Listing 19.

Targeted physical examinations will be performed, if indicated, based on a subject's medical history. A listing of physical exam findings will be presented in Listing 20. Echocardiogram will be performed 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, and results of this echocardiogram will be provided in Listing 23. A listing of all subject hospitalizations will be presented in Listing 24.

9.8. Concomitant Medications and Nondrug Interventions

Concomitant medications will be collected for the 30 days prior to ICF signing through Day 70 Visit. Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. A by-subject listing of concomitant medication use will be presented (Listing 21). A listing of non-drug interventions will be presented in Listing 22. The use of concomitant medications during the study will be summarized by ATC1, ATC2 code, and study treatment for the Safety population (Table 107). A summary of subjects taking nondrug interventions by SOC is provided in Table 108.

10. PHARMACOKINETICS

Analysis of PK endpoints will be provided in separate analysis plan document.

11. OTHER ANALYSES

No other analyses are planned.

12. REPORTING CONVENTIONS

For the primary and secondary analyses percentages and probabilities will be reported to one decimal place. P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as "> 0.999". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as two decimal places; values <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values < 1% will be presented as "<1" and values > 99% but below 100% will be presented as ">99". Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients) will be reported to 3 significant figures.

13. TECHNICAL DETAILS

SAS version 9.4 or above or R version 3.2 or above will be used to perform analyses and to generate all tables, figures and listings.

14. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

No changes in the conduct of the study or planned analysis.

15. REFERENCES

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16. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

Table 1: Schedule of Study Procedures

	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							
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

Table 1: Schedule of Study Procedures (continued)

	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]

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

[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 in the protocol); 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 in the protocol), 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).

10.2 Protocol Deviations

Table 2: Distribution of Protocol Deviations by Category, Type, and Treatment Group – ITT Population

Category	Deviation Type	Dalbavancin (N=X)		Standard of Care (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type	X	x	x	x	x	x
	Did not meet inclusion criterion	X	x	x	x	x	x
	Met exclusion criterion	X	x	x	x	x	x
	ICF not signed prior to study procedures	X	x	x	x	x	x
	Other	X	x	x	x	x	x
Treatment administration schedule	Any type	X	x	x	x	x	x
	Out of window visit	X	x	x	x	x	x
	Missed visit/visit not conducted	X	x	x	x	x	x
	Missed treatment administration	X	x	x	x	x	x
	Delayed treatment administration	X	x	x	x	x	x
	Other	X	x	x	x	x	x
Follow-up visit schedule	Any type	X	x	x	x	x	x
	Out of window visit	X	x	x	x	x	x
	Missed visit/visit not conducted	X	x	x	x	x	x
	Other	X	x	x	x	x	x
Protocol procedure/assessment	Any type	X	x	x	x	x	x
	Incorrect version of ICF signed	X	x	x	x	x	x
	Blood not collected	X	x	x	x	x	x
	Other specimen not collected	X	x	x	x	x	x
	Too few aliquots obtained	X	x	x	x	x	x
	Specimen result not obtained	X	x	x	x	x	x
	Required procedure not conducted	X	x	x	x	x	x
	Required procedure done incorrectly	X	x	x	x	x	x
	Study product temperature excursion	X	x	x	x	x	x
	Specimen temperature excursion	X	x	x	x	x	x
	Other	X	x	x	x	x	x
Treatment administration	Any type	X	x	x	x	x	x
	Required procedure done incorrectly	X	x	x	x	x	x
	Study product temperature excursion	X	x	x	x	x	x
	Other	X	x	x	x	x	x

N= Number of subjects in the ITT Population.

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 3: Subject Disposition by Treatment Group

Subject Disposition	Dalbavancin (N=X)		Standard of Care (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	--	--	--	--	x	--
Enrolled	x	100	x	100	x	100
Randomized	x	xx	x	xx	x	xx
Received Treatment	x	xx	x	xx	x	xx
Completed All Scheduled Dalbavancin Treatments	x	xx	N/A	N/A	x	xx
Completed <4 Weeks of Standard of Care Treatment[a]	N/A	N/A	x	xx	x	xx
Completed 4 - <6 Weeks of Standard of Care Treatment[a]	N/A	N/A	x	xx	x	xx
Completed 6 - <8 Weeks of Standard of Care Treatment[a]	N/A	N/A	x	xx	x	xx
Completed ≥8 Weeks of Standard of Care Treatment[a]	N/A	N/A	x	xx	x	xx
Discontinued Treatment[b]	x	xx	x	xx	x	xx
Completed Day 8 Visit[b]	x	xx	x	xx	x	xx
Completed Day 22 Visit[b]	x	xx	x	xx	x	xx
Completed Day 42 Visit[b]	x	xx	x	xx	x	xx
Completed Day 70 Visit[b]	x	xx	x	xx	x	xx
Completed Day 180 Visit[c]	x	xx	x	xx	x	xx

N= Number of subjects in the ITT Population.
[a] Duration of standard of care treatment calculated from date of first negative blood culture to end date of last antibiotic received.
[b] Refer to Listing 16.2.1 for reasons subjects discontinued or terminated early.
[c] Day 180 Visit will only be completed by subjects with osteomyelitis.

Table 4: Analysis Populations by Treatment Group – ITT Population

Analysis Populations	Reason Subjects Excluded	Dalbavancin (N=X)		Standard of Care (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
ITT	Any Reason						
	Subject not randomized						
Safety	Any Reason						
	Subject not treated with at least one dose of study product						
Modified ITT	Any Reason						
	Subject was excluded from ITT population						
	Subject not treated with at least one dose of study product						
Clinically Evaluable at Day 42	Any Reason						
	Subject was excluded from mITT population						
	Subject had missing data or major protocol deviation at Day 42[a]						
Clinically Evaluable at Day 70	Any Reason						
	Subject was excluded from mITT population						
	Subject had missing data or major protocol deviation at Day 70[a]						

N= Number of subjects in the ITT Population.
[a] Major protocol deviation for analysis population purposes will be defined as those that prevent the adjudication committee from evaluating the outcomes at the given day.

Table 5: Dates of First Treatment by Site and Treatment Group

[Implementation note: Replace site numbers by site names and sort the site list alphabetically.]

Site	Treatment Group	February 2021- December 2021	January 2022-December 2022
Any Site	Any Treatment	x	x
Any Site	Dalbavancin	x	x
	Standard of Care	x	x
Site 1	Dalbavancin	x	x
	Standard of Care	x	x
Site 2	Dalbavancin	x	x
	Standard of Care	x	x
Site 3	Dalbavancin	x	x
	Standard of Care	x	x
Site 4	Dalbavancin	x	x
	Standard of Care	x	x
[Repeat for all sites that enrolled at least one subject.]			

Table 6: Treatment Compliance for the Dalbavancin Treatment Group – Safety Population

	Dalbavancin (N=X)	
	n	**%**
Received 1 Dose of Dalbavancin	x	x
Received 2 Doses of Dalbavancin	x	x
Lowered dose of Dalbavancin received[a]	x	x
Interrupted/Incomplete dose of Dalbavancin received	x	x

N = Number of subjects in the Safety Population who received at least one dose of Dalbavancin.
[a] Summarizes the number of subjects that received a lower dose of dalbavancin due to an absence of regular hemodialysis or peritoneal dialysis and CrCl < 30 mL/min.

Table 7: Treatment Compliance in the Standard of Care Treatment Group Measured by Number of Days – Safety Population

Standard of Care Antibiotics	Statistic	Standard of Care (N=X)		
		Duration from Date of First Positive Blood Culture (Days)	Duration from Date of First Negative Blood Culture (Days)	Duration from Date of Randomization (Days)
Any Standard of Care Antibiotic	N	x	x	x
	Mean	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Cefazolin	N	n	n	n
	Mean	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Nafcillin	N	x	x	x
	Mean	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Oxacillin	N	x	x	x
	Mean	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Vancomycin	N	x	x	x
	Mean	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Daptomycin	N	x	x	x
	Mean	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
[Create additional rows to add any other Standard of Care antibiotics administered in this study.]				
N = Number of subjects in the Safety Population in the standard of care arm. n = Number of subjects in the Safety Population who received the corresponding standard of care antibiotic.				

Table 8: Ineligibility Summary of Screen Failures

Inclusion/ Exclusion Category	Inclusion/ Exclusion Criterion	n[a]	%[b]
All Subjects	Total number of subjects failing any eligibility criterion or who were eligible but not randomized.	x	100
Inclusion and Exclusion	Number of subjects failing any eligibility criterion		
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
	…		
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx
	…		
Eligible but Not Enrolled	Any Reason	x	xx
	[Reason 1]	x	xx
	[Reason 2]	x	xx
	…		

[a] More than one criterion may be marked per subject.
[b] Denominator for percentages is the total number of subjects not enrolled in this study which include screen failures and subjects eligible but not enrolled.

14.1.2 Demographic Data by Study Group

Table 9: Summary of Categorical Demographic and Baseline Characteristics by Site – ITT Population

Demographic Category		Sex		Ethnicity				Race							Baseline Pathogen	
Characteristic		Male	Female	Not Hispanic or Latino	Hispanic or Latino	Not Reported	Unknown	American Indian or Alaska Native	Asian	Native Hawaiian or Other Pacific Islander	Black or African American	White	Multi-Racial	Unknown	MRSA	MSSA
[Site 1] (N=X)	n	x	x	x	x	x	X	x	x	x	x	x	x	x		
	%	x	x	x	x	x	X	x	x	x	x	x	x	x		
[Site 2] (N=X)	n	x	x	x	x	x	X	x	x	x	x	x	x	x		
	%	x	x	x	x	x	X	x	x	x	x	x	x	x		
All Subjects (N=X)	n	x	x	x	x	x	X	x	x	x	x	x	x	x		
	%	x	x	x	x	x	X	x	x	x	x	x	x	x		
N = Number of subjects in the ITT Population.																

Note: Will repeat for all sites.

Table 10: Summary of Categorical Demographic and Baseline Characteristics by Site – Safety Population

The table will repeat Table 9 limited to the safety population

Table 11: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group – ITT Population

Variable	Characteristic	Dalbavancin (N=X)		Standard of Care (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx
	Female						
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx
	Hispanic or Latino						
	Not Reported						
	Unknown						
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx
	Asian						
	Native Hawaiian or Other Pacific Islander						
	Black or African American						
	White						
	Multi-Racial						
	Unknown						
Baseline Pathogen	MRSA						
	MSSA						
PWID Status	PWID						
	Non-PWID						
Infectious Disease Consultation	Yes						
	No						
TEE Performed	Yes						
	No						
Underlying Site of Infection	Endovascular						
	Bone and Joint						
	Skin						
	Pulmonary						
	Other/Unknown						
Immunosuppression	Yes						
	No						
Duration of Initial Bacteremia (Days)	< 2						
	2-4						
	> 4						
	Other/Unknown						

Table 11: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group – ITT Population (continued)

Variable	Characteristic	Dalbavancin (N=X)		Standard of Care (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Pre-randomization Antibiotics	[Antibiotic 1]						
	[Antibiotic 2]						
	[Antibiotic 3]						
	…						
Comorbid Conditions	Heart failure						
	Chronic kidney disease						
	Diabetes						
	Liver disease						
	Cancer						
Baseline Infection Characteristics	Right-sided endocarditis						
	ABSSSI						
	Septic pulmonary emboli						
	Osteomyelitis, non-vertebral						
	Vertebral osteomyelitis						
	Septic arthritis						
	Catheter-associated bloodstream infection						
	Cardiac device infection						
	Intravascular graft infection						
	Prosthetic valve infection						
	Prosthetic joint infection						
	Pneumonia						

N = Number of subjects in the ITT Population.
PWID = Persons Who Inject Drugs.
TEE = Transesophageal Echocardiography.
ABSSSI = Acute Bacterial Skin and Skin Structure Infection.

Table 12: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group – Safety Population

This table will repeat Table 11 limited to the safety population.

Table 13: Summary of Continuous Demographic and Baseline Characteristics by Site – ITT Population

Variable	n	Mean	Standard Deviation	Median	Minimum	Maximum
[Site 1 (N=X)]						
Age (years)	x	x.x	x.x	x.x	x	x
BMI (kg/m^2)	x	x.xx	x.xx	x.xx	x.x	x.x
Height (cm)	x	x.xx	x.xx	x.xx	x.x	x.x
Weight (kg)	x	x.xx	x.xx	x.xx	x.x	x.x
Baseline QoL[a]	x	x.xx	x.xx	x.xx	x.x	x.x
Creatinine Clearance (mL/min)	x	x.xx	x.xx	x.xx	x.x	x.x
Duration of Bacteremia (days)	x	x.x	x.x	x.x	x	x
[Site 2 (N=X)]						
Age (years)	x	x.x	x.x	x.x	x	X
BMI (kg/m^2)	x	x.x	x.x	x.x	x	X
Height (cm)	x	x.x	x.x	x.x	x	X
Weight (kg)	x	x.x	x.x	x.x	x	X
Baseline QoL[a]	x	x.xx	x.xx	x.xx	x.x	x.x
Creatinine Clearance (mL/min)	x	x.xx	x.xx	x.xx	x.x	x.x
Duration of Bacteremia (days)	x	x.x	x.x	x.x	x	x
[Repeat for all sites and all subjects]						

N = Number of subjects in the ITT Population.
n = Number of subjects in the ITT Population with non-missing values for the corresponding baseline characteristic.
[a] Baseline QoL standardized score is obtained from the questions arising from the PROMIS physical function item bank (PROMIS Item Bank v2.0, short form 6b) item bank on the ARLG Bloodstream Infection QoL.

Table 14: Summary of Continuous Demographic and Baseline Characteristics by Site – Safety Population

This table will repeat Table 13 limited to the safety population.

Table 15: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group – ITT Population

Variable	Statistic	Dalbavancin (N=X)	Standard of Care (N=X)	All Subjects (N=X)
Age (years)	n	X	x	x
	Mean	x.x	x.x	x.x
	Standard Deviation	x.x	x.x	x.x
	Median	x.x	x.x	x.x
	Minimum	X	x	x
	Maximum	X	x	x
BMI (kg/m^2)	n	x.xx	x.xx	x.xx
	Mean	X	x	x
	Standard Deviation	x.xx	x.xx	x.xx
	Median	x.xx	x.xx	x.xx
	Minimum	x.x	x.x	x.x
	Maximum	x.x	x.x	x.x
Height (cm)	n	X	x	x
	Mean	x.xx	x.xx	x.xx
	Standard Deviation	x.xx	x.xx	x.xx
	Median	x.xx	x.xx	x.xx
	Minimum	X	x	x
	Maximum	X	x	x
Weight (kg)	n	X	x	x
	Mean	x.xx	x.xx	x.xx
	Standard Deviation	x.xx	x.xx	x.xx
	Median	x.xx	x.xx	x.xx
	Minimum	x.x	x.x	x.x
	Maximum	x.x	x.x	x.x
Baseline QoL[a]	n	X	x	x
	Mean	x.xx	x.xx	x.xx
	Standard Deviation	x.xx	x.xx	x.xx
	Median	x.xx	x.xx	x.xx
	Minimum	x.x	x.x	x.x
	Maximum	x.x	x.x	x.x

Table 15: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group – ITT Population (continued)

Variable	Statistic	Dalbavancin (N=X)	Standard of Care (N=X)	All Subjects (N=X)
Creatinine Clearance (mL/min)	n	X	x	x
	Mean	x.xx	x.xx	x.xx
	Standard Deviation	x.xx	x.xx	x.xx
	Median	x.xx	x.xx	x.xx
	Minimum	x.x	x.x	x.x
	Maximum	x.x	x.x	x.x
Duration of Bacteremia (days)	n	X	x	x
	Mean	x.xx	x.xx	x.xx
	Standard Deviation	x.xx	x.xx	x.xx
	Median	x.xx	x.xx	x.xx
	Minimum	x.x	x.x	x.x
	Maximum	x.x	x.x	x.x

N = Number of subjects in the ITT Population.
n = Number of subjects in the ITT Population with non-missing values for the corresponding baseline characteristic.
[a] Baseline QoL standardized score is obtained from the questions arising from the PROMIS physical function item bank (PROMIS Item Bank v2.0, short form 6b) item bank on the ARLG Bloodstream Infection QoL.

Table 16: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group – Safety Population

This table will repeat Table 15 limited to the safety population.

14.1.3 Prior and Concurrent Medical Conditions

Table 17: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group – ITT Population

MedDRA System Organ Class	Dalbavancin (N=X)		Standard of Care (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx
[SOC 1]	x	xx	x	xx	x	xx
[SOC 2]	x	xx	x	xx	x	xx
[repeat for all SOC]						

N = Number of subjects in the ITT population.
n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

14.2 Efficacy Data

Table 18: Percentage of Subjects with Missing Data by Study Endpoint, Timepoint, and Treatment Group – ITT Analysis Population

Endpoint	Dalbavancin (N=X)		Standard of Care (N=X)		All Subjects (N=X)	
	n	%	N	%	n	%
Day 42						
DOOR						
Clinical efficacy						
Microbiologic Success						
Clinical Failure						
Day 70						
DOOR						
Clinical efficacy						
Microbiologic Success						
Clinical Failure						

N = Number of subjects in the ITT population in the respective treatment group.
n = Number of subjects with missing data.

Table 19: Percentage of Subjects with Missing Data by Study Endpoint, Timepoint, and Treatment Group – mITT Analysis Population

This table will repeat Table 18 limited to the mITT population.

Table 20: Analysis of DOOR at Day 70 – ITT Analysis Population

[Implementation Note: This table will be included in the interim analysis.]

Model	Tie-Breaking[a]	Subjects with non-missing DOOR n (%)	Subjects with missing DOOR n (%)	Pr(Better DOOR in Dalbavancin Arm)[b] (95% CI)[c]
IPW	Tie-Breaking	x (x)	x (x)	x.xx (x.xx, x.xx)
	No Tie-Breaking	x (x)	x (x)	x.xx (x.xx, x.xx)
Multiple Imputation	Tie-Breaking	x (x)	x (x)	x.xx (x.xx, x.xx)
	No Tie-Breaking	x (x)	x (x)	x.xx (x.xx, x.xx)

[a]DOOR analysis with tie-breaking is the primary analysis.
[b]Probability of Better DOOR in Dalbavancin arm at Day 70 + 0.5 Probability of Equal DOOR.
[c]95% CI obtained using the method described in Halperin et. al. Superiority of Dalbavancin is concluded if the lower bound of the 95% CI for the DOOR probability is above 0.5.

Table 21: Analysis of DOOR at Day 70 – mITT Analysis Population

This table will repeat Table 20 limited to the mITT population.

Table 22: Analysis of DOOR at Day 42 – ITT Analysis Population

Model	Tie-Breaking[a]	Subjects with non-missing DOOR n (%)	Subjects with missing DOOR n (%)	Pr(Better DOOR in Dalbavancin Arm)[b] (95% CI)[c]
IPW	Tie-Breaking	x (x)	x (x)	x.xx (x.xx, x.xx)
	No Tie-Breaking	x (x)	x (x)	x.xx (x.xx, x.xx)
Multiple Imputation	Tie-Breaking	x (x)	x (x)	x.xx (x.xx, x.xx)
	No Tie-Breaking	x (x)	x (x)	x.xx (x.xx, x.xx)

[a] DOOR analysis with tie-breaking is the primary analysis.
[b] Probability of Better DOOR in Dalbavancin arm at Day 42 + 0.5 Probability of Equal DOOR.
[c] 95% CI obtained using the method described in Halperin et. al. Superiority of Dalbavancin is concluded if the lower bound of the 95% CI for the DOOR probability is above 0.5.

Table 23: Analysis of DOOR at Day 42 – mITT Analysis Population

This table will repeat Table 22 limited to the mITT population.

Table 24: Analysis of DOOR at Day 42 and Day 70 – CE Analysis Population

Timepoint	Tie-Breaking	N	Pr(Better DOOR)[a]	Halperin 95% CI[b]
Day 42	Tie-Breaking	x	x.xx	x.xx, x.xx
	No Tie-Breaking	x	x.xx	x.xx, x.xx
Day 70	Tie-Breaking	x	x.xx	x.xx, x.xx
	No Tie-Breaking	x	x.xx	x.xx, x.xx

N = Number of subjects with complete data in the given analysis population.
[a] Probability of Better DOOR in Dalbavancin Arm at Day 42 (or Day 70) + 0.5 Probability of Equal DOOR.
[b] 95% CI obtained using the method described in Halperin et. al.

Table 25: Subgroup Analysis of DOOR with Tie-Breaking by Timepoint – ITT Analysis Population

Timepoint	Variable	Level	N_d	N_s	DOOR Probability[a]	95% CI[b]
Day 42	Baseline Pathogen	MRSA	xx	xx	x.xx	x.xx, x.xx
		MSSA	xx	xx	x.xx	x.xx, x.xx
	PWID Status	PWID	xx	xx	x.xx	x.xx, x.xx
		Non-PWID	xx	xx	x.xx	x.xx, x.xx
	Infectious Disease Consultation	Yes	xx	xx	x.xx	x.xx, x.xx
		No	xx	xx	x.xx	x.xx, x.xx
	Underlying Site of Infection	Endovascular	xx	xx	x.xx	x.xx, x.xx
		Bone and Joint	xx	xx	x.xx	x.xx, x.xx
		Skin	xx	xx	x.xx	x.xx, x.xx
		Pulmonary	xx	xx	x.xx	x.xx, x.xx
	Immunosuppression	Yes	xx	xx	x.xx	x.xx, x.xx
		No	xx	xx	x.xx	x.xx, x.xx
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	x.xx	x.xx, x.xx
		2-4	xx	xx	x.xx	x.xx, x.xx
		> 4	xx	xx	x.xx	x.xx, x.xx
Day 70	Baseline Pathogen	MRSA	xx	xx	x.xx	x.xx, x.xx
		MSSA	xx	xx	x.xx	x.xx, x.xx
	PWID Status	PWID	xx	xx	x.xx	x.xx, x.xx
		Non-PWID	xx	xx	x.xx	x.xx, x.xx
	Infectious Disease Consultation	Yes	xx	xx	x.xx	x.xx, x.xx
		No	xx	xx	x.xx	x.xx, x.xx
	Underlying Site of Infection	Endovascular	xx	xx	x.xx	x.xx, x.xx
		Bone and Joint	xx	xx	x.xx	x.xx, x.xx
		Skin	xx	xx	x.xx	x.xx, x.xx
		Pulmonary	xx	xx	x.xx	x.xx, x.xx
	Immunosuppression	Yes	xx	xx	x.xx	x.xx, x.xx
		No	xx	xx	x.xx	x.xx, x.xx
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	x.xx	x.xx, x.xx
		2-4	xx	xx	x.xx	x.xx, x.xx
		> 4	xx	xx	x.xx	x.xx, x.xx

N_d = number of subjects in the ITT population who received dalbavancin within the subgroup category.
N_s = number of subjects in the ITT population who received standard of care within the subgroup category.
PWID = Persons Who Inject Drugs.
[a] Probability of Better DOOR in Dalbavancin arm compared to standard of care + 0.5 Probability of Equal DOOR. This analysis uses IPW to handle missing values of DOOR and change in QoL as a tie breaker.
[b] 95% CI obtained using the method described in Halperin et. al.

Table 26: Subgroup Analysis of DOOR with Tie-Breaking by Timepoint – mITT Analysis Population

This table will repeat Table 25 limited to the mITT population.

Table 27: Subgroup Analysis of DOOR with Tie-Breaking by Timepoint – CE Analysis Population

Timepoint	Variable	Level	N_d	N_s	DOOR Probability[a]	Halperin 95% CI[b]
Day 42	Baseline Pathogen	MRSA	xx	xx	x.xx	x.xx, x.xx
		MSSA	xx	xx	x.xx	x.xx, x.xx
	PWID Status	PWID	xx	xx	x.xx	x.xx, x.xx
		Non-PWID	xx	xx	x.xx	x.xx, x.xx
	Infectious Disease Consultation	Yes	xx	xx	x.xx	x.xx, x.xx
		No	xx	xx	x.xx	x.xx, x.xx
	Underlying Site of Infection	Endovascular	xx	xx	x.xx	x.xx, x.xx
		Bone and Joint	xx	xx	x.xx	x.xx, x.xx
		Skin	xx	xx	x.xx	x.xx, x.xx
		Pulmonary	xx	xx	x.xx	x.xx, x.xx
	Immunosuppression	Yes	xx	xx	x.xx	x.xx, x.xx
		No	xx	xx	x.xx	x.xx, x.xx
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	x.xx	x.xx, x.xx
		2-4	xx	xx	x.xx	x.xx, x.xx
		> 4	xx	xx	x.xx	x.xx, x.xx
Day 70	Baseline Pathogen	MRSA	xx	xx	x.xx	x.xx, x.xx
		MSSA	xx	xx	x.xx	x.xx, x.xx
	PWID Status	PWID	xx	xx	x.xx	x.xx, x.xx
		Non-PWID	xx	xx	x.xx	x.xx, x.xx
	Infectious Disease Consultation	Yes	xx	xx	x.xx	x.xx, x.xx
		No	xx	xx	x.xx	x.xx, x.xx
	Underlying Site of Infection	Endovascular	xx	xx	x.xx	x.xx, x.xx
		Bone and Joint	xx	xx	x.xx	x.xx, x.xx
		Skin	xx	xx	x.xx	x.xx, x.xx
		Pulmonary	xx	xx	x.xx	x.xx, x.xx
	Immunosuppression	Yes	xx	xx	x.xx	x.xx, x.xx
		No	xx	xx	x.xx	x.xx, x.xx
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	x.xx	x.xx, x.xx
		2-4	xx	xx	x.xx	x.xx, x.xx
		> 4	xx	xx	x.xx	x.xx, x.xx

N_d = number of subjects in the CE population who received dalbavancin within the subgroup category.
N_s = number of subjects in the CE population who received standard of care within the subgroup category.
PWID = Persons Who Inject Drugs.
[a] Probability of Better DOOR in Dalbavancin Arm + 0.5 Probability of Equal DOOR.
[b] 95% CI obtained using the method described in Halperin et. al.

Table 28: Analysis of DOOR Categories – ITT Analysis Population

[Implementation Note: This table will be included in the interim analysis.]

Timepoint	DOOR Category	Dalbavancin (N=X)		Standard of Care (N=X)	
		n	% (95% CI)[a]	n	% (95% CI)[a]
Day 42	Alive with no events	xx	xx (xx, xx)	xx	xx (xx, xx)
	Alive with 1 event	xx	xx (xx, xx)	xx	xx (xx, xx)
	Alive with 2 events	xx	xx (xx, xx)	xx	xx (xx, xx)
	Alive with 3 events	xx	xx (xx, xx)	xx	xx (xx, xx)
	Death	xx	xx (xx, xx)	xx	xx (xx, xx)
	Missing	xx	xx (xx, xx)	xx	xx (xx, xx)
Day 70	Alive with no events	xx	xx (xx, xx)	xx	xx (xx, xx)
	Alive with 1 event	xx	xx (xx, xx)	xx	xx (xx, xx)
	Alive with 2 events	xx	xx (xx, xx)	xx	xx (xx, xx)
	Alive with 3 events	xx	xx (xx, xx)	xx	xx (xx, xx)
	Death	xx	xx (xx, xx)	xx	xx (xx, xx)
	Missing	xx	xx (xx, xx)	xx	xx (xx, xx)

N = Number of subjects in the ITT Population in the given treatment group.
n = Number of subjects in the corresponding analysis population, treatment group, and DOOR category
[a] 95% CI estimated using the Wilson Method.
Note: Events that are both infectious complications and SAEs or AEs leading to study drug discontinuation count twice towards the DOOR.

Table 29: Analysis of DOOR Categories – mITT Analysis Population

This table will repeat Table 28 limited to the mITT population.

Table 30: Analysis of DOOR Categories – CE Analysis Population

This table will repeat Table 28 limited to the CE population.

[Implementation note: The missing category is removed from this analysis since the CE population has complete data.]

Table 31: Cumulative Proportions of DOOR - ITT Analysis Population

[Implementation Note: This table will be included in the interim analysis.]

Timepoint	DOOR Category	Dalbavancin			Standard of Care			Cumulative DOOR Probability
		N	n[a]	%[a]	N	n[a]	%[a]	% (95% CI)[b]
Day 42	Alive with no events	xx	xx	xx	xx	xx	xx	xx (x.x, x.x)
	Alive with less than 2 events	xx	xx	xx	xx	xx	xx	xx (x.x, x.x)
	Alive with less than 3 events	xx	xx	xx	xx	xx	xx	xx (x.x, x.x)
	Alive or Dead	xx	xx	xx	xx	xx	xx	xx (x.x, x.x)
Day 70	Alive with no events	xx	xx	xx	xx	xx	xx	xx (x.x, x.x)
	Alive with less than 2 events	xx	xx	xx	xx	xx	xx	xx (x.x, x.x)
	Alive with less than 3 events	xx	xx	xx	xx	xx	xx	xx (x.x, x.x)
	Alive or Dead	xx	xx	xx	xx	xx	xx	xx (x.x, x.x)

N = Number of subjects in the ITT Population in the given treatment group with non-missing cumulative DOOR category at the corresponding timepoint.
n = Number of subjects in the given cumulative DOOR category.
[a] n and % represent cumulative numbers.
[b] 95% CI for cumulative DOOR probability obtained using the method described in Halperin et. al.
Note: Events that are both infectious complications and SAEs or AEs leading to study drug discontinuation count twice towards the DOOR.

Table 32: Cumulative Proportions of DOOR – mITT Analysis Population

This table will repeat Table 31 limited to the mITT population.

Table 33: Cumulative Proportions of DOOR – CE Analysis Population

This table will repeat Table 31 limited to the CE population.

Table 34: Summary of Expected Numbers Gained Loss at Day 42 and Day 70 by Analysis Population

Analysis Population	Timepoint	DOOR Category	Dalbavancin				Standard of Care				Gained Loss[a] (95% CI)
			N	n	%	Expected Number	N	n	%	Expected Number	
ITT	Day 42	Alive with no events	xx	xx	xx	xxx	xx	xx	xx	xxx	xx(xx, xx)
		Alive with 1 event	xx	xx	xx	xxx	xx	xx	xx	xxx	xx
		Alive with 2 events	xx	xx	xx	xxx	xx	xx	xx	xxx	xx
		Alive with 3 events	xx	xx	xx	xxx	xx	xx	xx	xxx	xx
		Death	xx	xx	xx	xxx	xx	xx	xx	xxx	xx
	Day 70	Alive with no events	xx	xx	xx	xxx	xx	xx	xx	xxx	xx
		Alive with 1 event	xx	xx	xx	xxx	xx	xx	xx	xxx	xx
		Alive with 2 events	xx	xx	xx	xxx	xx	xx	xx	xxx	xx
		Alive with 3 events	xx	xx	xx	xxx	xx	xx	xx	xxx	xx
		Death	xx	xx	xx	xxx	xx	xx	xx	xxx	xx
[Repeat for mITT and CE analysis populations]											

N = Number of subjects in the corresponding analysis population and treatment group with non-missing DOOR category at the corresponding timepoint.
n = Number of subjects in the corresponding analysis population, treatment group, and DOOR category.
[a] The gained loss is calculated as the difference in expected numbers, dalbavancin relative to standard of care.
Note: Events that are both infectious complications and SAEs or AEs leading to study drug discontinuation count twice towards the DOOR.

Table 35: Analysis of Clinical Efficacy at Day 70 Using ITT and mITT Analysis Populations

Analysis Population	Model	Statistic	Dalbavancin (N=X)	Standard of Care (N=X)
ITT	IPW	Subjects with non-missing clinical efficacy on Day 70 – n (%)	x (x)	x (x)
		Subjects with missing clinical efficacy on Day 70– n (%)	x (x)	x (x)
		Percent rate of clinical efficacy at Day 70 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
		Difference in rates (percent) of clinical efficacy, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-
		Conclusion of non-inferiority of dalbavancin to standard of care[b]	Yes/No	-
		Conclusion of superiority of dalbavancin to standard of care[c]	Yes/No	-
	Multiple Imputation	Subjects with non-missing clinical efficacy on Day 70 – n (%)	x (x)	x (x)
		Subjects with missing clinical efficacy on Day 70– n (%)	x (x)	x (x)
		Percent rate of clinical efficacy at Day 70 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
		Difference in rates (percent) of clinical efficacy, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-
		Conclusion of non-inferiority of dalbavancin to standard of care[b]	Yes/No	-
		Conclusion of superiority of dalbavancin to standard of care[c]	Yes/No	-
mITT	IPW	Subjects with non-missing clinical efficacy on Day 70 – n (%)	x (x)	x (x)
		Subjects with missing clinical efficacy on Day 70– n (%)	x (x)	x (x)
		Percent rate of clinical efficacy at Day 70 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
		Difference in rates (percent) of clinical efficacy, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-
		Conclusion of non-inferiority of dalbavancin to standard of care[b]	Yes/No	-
		Conclusion of superiority of dalbavancin to standard of care[c]	Yes/No	-
	Multiple Imputation	Subjects with non-missing clinical efficacy on Day 70 – n (%)	x (x)	x (x)
		Subjects with missing clinical efficacy on Day 70– n (%)	x (x)	x (x)
		Percent rate of clinical efficacy at Day 70 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
		Difference in rates (percent) of clinical efficacy, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-
		Conclusion of non-inferiority of dalbavancin to standard of care[b]	Yes/No	-
		Conclusion of superiority of dalbavancin to standard of care[c]	Yes/No	-

N = Number of subjects in the corresponding analysis Population. Multiple imputation was used to impute missing values.
[a] 95% CIs were obtained from linear regression model following multiple imputation adjusting for study day of Day 70.
[b] Non-inferiority of dalbavancin was concluded if the lower bound of the 95% CI for the difference in proportions is greater than -20%.
[c] Superiority of dalbavancin was concluded if the 95% CI for the difference in proportions does not contain 0.

Table 36: Analysis of Clinical Efficacy at Day 42 Using ITT and mITT Analysis Populations

This table will repeat Table 35 using Day 42.

Table 37: Analysis of Clinical Efficacy at Day 42 and Day 70 Using CE Analysis Population

[Implementation note: If the lower bound of 95% CI for the difference in rates of clinical efficacy is greater than -20%, annotate the interval with footnote b that states 'Lower bound of confidence interval greater than -20% (non-inferiority margin).']

Timepoint	Treatment Group	Rate of Clinical Efficacy			Difference in Rates		
		n	%	95% CI[a]	%	95% CI[a]	Miettinen–Nurminen 95% CI
Day 42	Dalbavancin (N=X)	x	xx	xx, xx	xx	xx, xx	xx, xx
	Standard of Care (N=X)	x	xx	xx, xx	Reference	-	-
Day 70	Dalbavancin (N=X)	x	xx	xx, xx	xx	xx, xx	xx, xx
	Standard of Care (N=X)	x	xx	xx, xx	Reference	-	-

N = Number of subjects in the CE analysis population at the corresponding timepoint.
n = Number of subjects in CE population with clinical efficacy at the corresponding timepoint.
[a] 95% CI obtained from linear regression.

Table 38: Subgroup Analysis of Clinical Efficacy by Timepoint – ITT Analysis Population

			Dalbavancin			Standard of Care			
Timepoint	**Variable**	**Level**	**N**	**n**	**Proportion % (95% CI)[a]**	**N**	**n**	**Proportion % (95% CI)[a]**	**Difference in Proportion % (95% CI)[a]**
Day 42	Baseline Pathogen	MRSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		MSSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	PWID Status	PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Non-PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Infectious Disease Consultation	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Underlying Site of Infection	Endovascular	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Bone and Joint	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Skin	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Pulmonary	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Immunosuppression	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		2-4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		>4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
Day 70	Baseline Pathogen	MRSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		MSSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	PWID Status	PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Non-PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Infectious Disease Consultation	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Underlying Site of Infection	Endovascular	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Bone and Joint	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Skin	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Pulmonary	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Immunosuppression	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		2-4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		>4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)

N = Number of subjects in the ITT analysis population, treatment group and subgroup category
n = Number of subjects in the corresponding analysis population and treatment group who achieved clinical efficacy.
PWID = Persons Who Inject Drugs.
[a]95% CIs were obtained from linear regression model with IPW.
Note: IPW was used to handle missing values of clinical efficacy.

Table 39: Subgroup Analysis of Clinical Efficacy by Timepoint – mITT Analysis Population

This table will repeat Table 38 limited to the mITT population.

Table 40: Subgroup Analysis of Clinical Efficacy by Timepoint – CE Analysis Population

Timepoint	Variable	Level	Dalbavancin			Standard of Care			
			N	n	Proportion % (95% CI)[a]	N	n	Proportion % (95% CI)[a]	Difference in Proportion % (95% CI)[a]
Day 42	Baseline Pathogen	MRSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		MSSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	PWID Status	PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Non-PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Infectious Disease Consultation	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Underlying Site of Infection	Endovascular	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Bone and Joint	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Skin	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Pulmonary	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Immunosuppression	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		2-4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		>4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
Day 70	Baseline Pathogen	MRSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		MSSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	PWID Status	PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Non-PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Infectious Disease Consultation	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Underlying Site of Infection	Endovascular	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Bone and Joint	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Skin	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Pulmonary	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Immunosuppression	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		2-4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		>4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)

N = Number of subjects in the CE analysis population, treatment group and subgroup category.
PWID = Persons Who Inject Drugs.
[a] 95% CIs were obtained from linear regression model.

Table 41: Summary of Clinical DOOR Components at Day 70 – ITT Analysis Population

DOOR Component	Dalbavancin			Standard of Care			DOOR Probability
	N	n	%	N	n	%	% (95% CI)[a]
Clinical Failure	x	x	x	x	x	x	xx (x.x, x.x)
Infectious Complication	x	x	x	x	x	x	xx (x.x, x.x)
SAEs	x	x	x	x	x	x	xx (x.x, x.x)
AEs Leading to Study Drug Discontinuation	x	x	x	x	x	x	xx (x.x, x.x)
All-cause Mortality	x	x	x	x	x	x	xx (x.x, x.x)

N = Number of subjects in the ITT population with non-missing values for the corresponding DOOR component.
n = Number of subjects with who experienced the corresponding DOOR component.
[a] 95% CI for DOOR Probability obtained through method described in Halperin et. al.

Table 42: Summary of Clinical DOOR Components at Day 70 – mITT Analysis Population

This table will repeat Table 41 limited to the mITT population.

Table 43: Summary of Clinical DOOR Components at Day 70 – CE Analysis Population

This table will repeat Table 41 limited to the CE population.

Table 44: Summary of Clinical DOOR Components at Day 42 – ITT Analysis Population

This table will repeat Table 41 limited to the ITT population at Day 42.

Table 45: Summary of Clinical DOOR Components at Day 42 – mITT Analysis Population

This table will repeat Table 41 limited to the mITT population at Day 42.

Table 46: Summary of Clinical DOOR Components at Day 42 – CE Analysis Population

This table will repeat Table 41 limited to the CE population at Day 42.

Table 47: Summary of DOOR by Component at Day 70 – ITT Analysis Population

DOOR	Clinical Failure	Infectious Complication	SAEs or AEs Leading to Study Drug Discontinuation	Dalbavancin (N=X)		Standard of Care (N=X)	
				n	%	N	%
1 - Alive with No Events	-	-	-				
2 - Alive with One Event	Yes	-	-				
	-	Yes	-				
	-	-	Yes				
3 - Alive with Two Events	Yes	Yes	-				
	Yes	-	Yes				
	-	Yes	Yes				
4 - Alive with Three Events	Yes	Yes	Yes				
5 - Death	-	-	-				
	Yes	-	-				
	-	Yes					
	-	-	Yes				
	Yes	Yes	-				
	Yes	-	Yes				
	-	Yes	Yes				
	Yes	Yes	Yes				

Note: Events that are both infectious complications and SAEs or AEs leading to study drug discontinuation count twice towards the DOOR.

Table 48: Summary of DOOR by Component at Day 42 – ITT Analysis Population

This table will repeat Table 47 at Day 42.

Table 49: Analysis of Clinical Failure at Day 70 Using Weighted GEE and Weighted GLMM Models- ITT Analysis Population

Model	Dalbavancin		Standard of Care			
	%	95% CI	%	95% CI	Difference (95% CI)	P-Value
Weighted GEE	x.xxx	(x.xxx, x.xxx)	x.xx	(x.xx, x.xx)	(x.xxx, x.xxx)	x.xxx
Weighted GLMM	x.xxx	(x.xxx, x.xxx)	x.xx	(x.xx, x.xx)	(x.xxx, x.xxx)	x.xxx

Table 50: Analysis of Microbiologic Success Using ITT or mITT Analysis Populations

Timepoint	Analysis Population	Model	Statistic	Dalbavancin (N=X)	Standard of Care (N=X)
Day 42	ITT	IPW	Subjects with non-missing microbiologic success on Day 42– n (%)	x (x)	x (x)
			Subjects with missing microbiologic success on Day 42 – n (%)	x (x)	x (x)
			Percent rate of microbiologic success at 42 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
			Difference in rates (percent) of microbiologic success, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-
		Multiple Imputation	Subjects with non-missing microbiologic success on Day 42– n (%)	x (x)	x (x)
			Subjects with missing microbiologic success on Day 42 – n (%)	x (x)	x (x)
			Percent rate of microbiologic success at 42 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
			Difference in rates (percent) of microbiologic success, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-
	mITT	IPW	Subjects with non-missing microbiologic success on Day 42– n (%)	x (x)	x (x)
			Subjects with missing microbiologic success on Day 42 – n (%)	x (x)	x (x)
			Percent rate of microbiologic success at 42 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
			Difference in rates (percent) of microbiologic success, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-
		Multiple Imputation	Subjects with non-missing microbiologic success on Day 42– n (%)	x (x)	x (x)
			Subjects with missing microbiologic success on Day 42 – n (%)	x (x)	x (x)
			Percent rate of microbiologic success at 42 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
			Difference in rates (percent) of microbiologic success, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-
Day 70	ITT	IPW	Subjects with non-missing microbiologic success on Day 70– n (%)	x (x)	x (x)
			Subjects with missing microbiologic success on Day 70 – n (%)	x (x)	x (x)
			Percent rate of microbiologic success at Day 70 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
			Difference in rates (percent) of microbiologic success, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-
		Multiple Imputation	Subjects with non-missing microbiologic success on Day 70– n (%)	x (x)	x (x)
			Subjects with missing microbiologic success on Day 70 – n (%)	x (x)	x (x)
			Percent rate of microbiologic success at Day 70 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
			Difference in rates (percent) of microbiologic success, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-

Table 50: Analysis of Microbiologic Success Using ITT or mITT Analysis Populations (continued)

	mITT	IPW	Subjects with non-missing microbiologic success on Day 70– n (%)	x (x)	x (x)
			Subjects with missing microbiologic success on Day 70 – n (%)	x (x)	x (x)
			Percent rate of microbiologic success at 70 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
			Difference in rates (percent) of microbiologic success, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-
		Multiple Imputation	Subjects with non-missing microbiologic success on Day 70– n (%)	x (x)	x (x)
			Subjects with missing microbiologic success on Day 70 – n (%)	x (x)	x (x)
			Percent rate of microbiologic success at Day 70 (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
			Difference in rates (percent) of microbiologic success, dalbavancin relative to standard of care (95% CI)[a]	xx (xx, xx)	-

N = Number of subjects in the corresponding analysis Population. Multiple imputation and IPW were used to handle missing values of microbiological success.
[a] 95% CIs were obtained from linear regression model following multiple imputation or IPW.

Table 51: Analysis of Microbiologic Success at Day 42 and Day 70 Using CE Analysis Population

Timepoint	Treatment Group	Proportion of Microbiologic Success			Difference in Proportion		
		n	%	95% CI[a]	%	95% CI[a]	Miettinen–Nurminen 95% CI
Day 42	Dalbavancin (N=X)	x	xx	xx, xx	xx	xx, xx	xx, xx
	Standard of Care (N=X)	x	xx	xx, xx	Reference	-	-
Day 70	Dalbavancin (N=X)	x	xx	xx, xx	xx	xx, xx	xx, xx
	Standard of Care (N=X)	x	xx	xx, xx	Reference	-	-

N = Number of subjects in the CE analysis population at the corresponding timepoint.
n = Number of subjects in CE population with microbiologic success at the corresponding timepoint.
[a] 95% CI obtained from linear regression.

Table 52: Subgroup Analysis of Microbiologic Success by Timepoint – ITT Analysis Population

Timepoint	Variable	Level	Dalbavancin			Standard of Care			Difference in Proportion % (95% CI)[a]
			N	n	Proportion % (95% CI)[a]	N	n	Proportion % (95% CI)[a]	
Day 42	Baseline Pathogen	MRSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		MSSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	PWID Status	PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Non-PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Infectious Disease Consultation	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Underlying Site of Infection	Endovascular	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Bone and Joint	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Skin	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Pulmonary	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Immunosuppression	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		2-4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		>4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
Day 70	Baseline Pathogen	MRSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		MSSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	PWID Status	PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Non-PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Infectious Disease Consultation	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Underlying Site of Infection	Endovascular	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Bone and Joint	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Skin	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Pulmonary	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Immunosuppression	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		2-4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		>4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)

N = Number of subjects in the ITT analysis population, treatment group and subgroup category. IPW was used to handle missing values of microbiological success.
PWID = Persons Who Inject Drugs.
[a] 95% CIs were obtained from linear regression model with IPW.

Table 53: Subgroup Analysis of Microbiologic Success by Timepoint – mITT Analysis Population

This table will repeat Table 52 limited to the mITT population.

Table 54: Subgroup Analysis of Microbiologic Success by Timepoint – CE Analysis Population

Timepoint	Variable	Level	Dalbavancin			Standard of Care			Difference in Proportions % (95% CI)[a]
			N	n	Proportion % (95% CI)[a]	N	n	Proportion % (95% CI)[a]	
Day 42	Baseline Pathogen	MRSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		MSSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	PWID Status	PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Non-PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Infectious Disease Consultation	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Underlying Site of Infection	Endovascular	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Bone and Joint	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Skin	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Pulmonary	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Immunosuppression	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		2-4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		>4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
Day 70	Baseline Pathogen	MRSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		MSSA	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	PWID Status	PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Non-PWID	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Infectious Disease Consultation	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Underlying Site of Infection	Endovascular	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Bone and Joint	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Skin	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		Pulmonary	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Immunosuppression	Yes	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		No	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
	Duration of Initial Bacteremia (Days)	< 2	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		2-4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)
		>4	xx	xx	xx (xx, xx)	xx	xx	xx (xx, xx)	xx (xx, xx)

N = Number of subjects in the CE analysis population, treatment group and subgroup category.
PWID = Persons Who Inject Drugs.
[a] 95% CIs were obtained from linear regression model without multiple imputation.

Table 55: Distribution of DOOR at Day 42 by Subgroup Categories – ITT Analysis Population

Subgroup	Subgroup Category	DOOR Category	Dalbavancin (N=X)		Standard of Care (N=X)		All Subjects (N=X)	
			n	%	n	%	n	%
Baseline Pathogen	MRSA	Any DOOR Category	x	xx	x	xx	**x**	**100**
		Alive with no events	x	xx	x	xx	x	xx
		Alive with 1 event						
		Alive with 2 events						
		Alive with 3 events						
		Death						
	MSSA	Any DOOR Category						
		Alive with no events						
		Alive with 1 event						
		Alive with 2 events						
		Alive with 3 events						
		Death						
PWID Status	PWID	Repeat for all DOOR as above						
	Non-PWID							
Infectious Disease Consultation	Yes							
	No							
Underlying Site of Infection	Endovascular							
	Bone and Joint							
	Skin							
	Pulmonary							
Immunosuppression	Yes							
	No							
Duration of Initial Bacteremia (Days)	< 2							
	2-4							
	>4							

N = Number of subjects in the ITT analysis population.
n = Number of subjects in the given ITT population with non-missing values of DOOR.
Note: Events that are both infectious complications and SAEs or AEs leading to study drug discontinuation count twice towards the DOOR.

Table with similar format:

Table 56: Distribution of DOOR at Day 70 by Subgroup Categories – ITT Analysis Population

Table 57: Summary Statistics of QoL Scores from the ARLG Bloodstream Infection QoL Measure at Day 42 and Day 70 Using ITT, mITT, and CE Analysis Populations

			QoL Score					Change from Baseline				
Analysis Population	Time Point	Treatment Group	n	Mean	Standard Deviation	Median	Min, Max	n	Mean	Standard Deviation	Median	Min, Max
ITT	Baseline	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	NA	NA	NA	NA	NA
		Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	NA	NA	NA	NA	NA
	Day 42	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 70	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
mITT	Baseline	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	NA	NA	NA	NA	NA
		Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	NA	NA	NA	NA	NA
	Day 42	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 70	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
CE	Baseline	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	NA	NA	NA	NA	NA
		Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	NA	NA	NA	NA	NA
	Day 42	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Day 70	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
		Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x

N = Number of subjects in the given analysis population.
n = Number of subjects in the given analysis population with non-missing QoL score values at the timepoint of interest. For the change from baseline, n represents the number of subjects in the given analysis population with non-missing values at baseline and at the timepoint being assessed.
Note: Baseline QoL standardized score is obtained from the questions arising from the PROMIS physical function item bank (PROMIS Item Bank v2.0, short form 6b) item bank on the ARLG Bloodstream Infection QoL.

Table 58: Summary Statistics of QoL Scores Using the EQ-5D-5L Instrument at Day 42 and Day 70 Using ITT, mITT, and CE Analysis Populations

This table will be similar to Table 57.

Table 59: Summary Statistics of QoL Scores Using the PROMIS Global Health Short Form at Day 42 and Day 70 Using ITT, mITT, and CE Analysis Populations

This table will be similar to Table 57.

Table 60: Predictive Interval Plots (PIPS) Statistics for the Probability of Higher DOOR in the Dalbavancin Group at Day 70 – ITT Analysis Population

[Implementation Note: this table will only be included in the interim analysis.]

Assumption	Current 95% CI	Width of Current 95% CI	Width of Predicted 95% CI Median [Q1, Q3]	Probability to Reject Null Hypothesis[a]
Observed Trend	(x.xx – x.xx)	x.xx	x.xx (x.xx – x.xx)	x.xx
Null Hypothesis	(x.xx – x.xx)	x.xx	x.xx (x.xx – x.xx)	x.xx
Alternative Hypothesis	(x.xx – x.xx)	x.xx	x.xx (x.xx – x.xx)	x.xx
Best case scenario for remaining outcome	(x.xx – x.xx)	x.xx	x.xx (x.xx – x.xx)	x.xx
Best case scenario for remaining outcome	(x.xx – x.xx)	x.xx	x.xx (x.xx – x.xx)	x.xx

Q1 = 25th percentile. Q3 = 75th percentile.
[a] Probability to Reject Null Hypothesis = proportion of PIs simulated that have a lower bound greater than 0.50.
Note: Statistics related to the PIPS are also presented in Figure 26.

Table 61: Predictive Interval Plots (PIPS) Statistics for the Rates of Clinical Efficacy at Day 70 – ITT Analysis Population

This table will be similar to Table 60.

Implementation Note: this table will only be included in the interim analysis.

Table 62: Number and Percentage of Subjects with Late Recurrence - Osteomyelitis Population

Analysis Group	Statistic	Dalbavancin (N=X)	Standard of Care (N=X)
Osteomyelitis Population	Number of subjects with late recurrence	x	x
	Percent rate of late recurrence (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
	Difference in rates (percent) late recurrence, dalbavancin relative to standard of care (95% CI)[b]	xx (xx, xx)	-
Sensitivity Osteomyelitis Population	Number of subjects with late recurrence	x	x
	Percent rate of late recurrence (95% CI)[a]	xx (xx, xx)	xx (xx, xx)
	Difference in rates (percent) late recurrence, dalbavancin relative to standard of care (95% CI)[b]	xx (xx, xx)	-

N = Number of subjects in the diagnosed with osteomyelitis.
[a] 95% CI for proportions calculated using the Wilson method.
[b] 95% CI for the difference in proportions, dalbavancin relative to standard of care, calculated using the Miettinen–Nurminen method.
Note: The osteomyelitis population includes subjects in the ITT population diagnosed with osteomyelitis for whom consent and data were obtained for Visit 7. The sensitivity osteomyelitis population excludes subjects from the Osteomyelitis Population those subjects for whom consent was obtained retroactively. XX (of NN) and YY (of MM) subjects with osteomyelitis in the Dalbavancin and Standard of Care Arms, respectively, became eligible for Visit 7 data collection under protocol version 3.0 and re-consented to Visit 7 data collection.

Programming Note: In the Note above:

XX = subjects treated with Dalbavancin who became eligible for Visit 7 data collection under protocol version 3.0 **and** re-consented Visit 7 data collection.

NN = subjects treated with Dalbavancin who became eligible for Visit 7 data collection under protocol version 3.0.

YY = subjects treated with Standard of Care who became eligible for Visit 7 data collection under protocol version 3.0 **and** re-consented Visit 7 data collection.

MM = subjects treated with Standard of Care who became eligible for Visit 7 data collection under protocol version 3.0.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 63: Number and Percentage of Subjects reporting SAEs, AEs Leading Discontinuation, Grade 3 or Higher AEs, AESIs, and ALT/AST Elevations by Treatment Group - Safety Population

[Implementation note: Sort this table by decreasing frequency for the treatment group.]

Adverse Event Type	Dalbavancin (N=X)			Standard of Care (N=X)			All Subjects (N=X)		
	n	%	Events	n	%	Events	n	%	Events
SAEs	x	x	x	x	x	x	x	x	x
AE Leading to Study Drug Discontinuation	x	x	x	x	x	x	x	x	x
Grade 3 or Higher AEs	x	x	x	x	x	x	x	x	x
AESIs	x	x	x	x	x	x	x	x	x
AST/ALT Elevation[a]	x	x	x	x	x	x	x	x	x

N = Number of subjects in the Safety Population.
[a] Occurrence of AST/ALT elevations >3x upper limit of normal (ULN) from first dose of study product through follow-up period.

Table 64: Number and Percentage of subjects reporting SAEs, AEs Leading Discontinuation, Grade 3 or Higher AEs, AESIs, and ALT/AST Elevations by Standard of Care Antibiotics – Standard of Care Arm, Safety Population

[Implementation note: If any other standard of care antibiotics not listed here are administered, extend the table to add more columns for new SOC antibiotics.]

Adverse Event Type	Cefazolin (N=X)			Nafcillin (N=X)			Oxacillin (N=X)			Vancomycin (N=X)			Daptomycin (N=X)		
	n	%	Events	n	%	Events	n	%	Events	n	%	Events	n	%	Events
SAEs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AE Leading to Study Drug Discontinuation	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Grade 3 or Higher AEs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AESIs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AST/ALT Elevation[a]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

N = Number of subjects in the Safety Population who received standard of care antibiotics.
[a] Occurrence of AST/ALT elevations >3x upper limit of normal (ULN) from first dose of study product through follow-up period.

14.3.1.2 Unsolicited Adverse Events

Table 65: Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term, Relationship, and Treatment Group

MedDRA System Organ Class	Preferred Term	Dalbavancin (N=X)						Standard of Care (N=X)						All Subjects (N=X)					
		Related		Not Related		Total		Related		Not Related		Total		Related		Not Related		Total	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	PT 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	PT 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
…	…																		
N = Number of subjects in the Safety Population.																			

Table 66: Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Treatment Group

MedDRA System Organ Class	Preferred Term	Severity	Dalbavancin (N=X)						Standard of Care (N=X)						All Subjects (N=X)					
			Related		Not Related		Total		Related		Not Related		Total		Related		Not Related		Total	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Not Reported	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 3	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 4	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 5	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	PT 1	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Not Reported	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 3	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 4	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 5	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	PT 2	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Not Reported	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 3	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 4	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 5	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
…	…																			

N = Number of subjects in the Safety Population.

Table 67: Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and High Level Group Term, Relationship, and Treatment Group

MedDRA System Organ Class	High Level Group Term	Dalbavancin (N=X)						Standard of Care (N=X)						All Subjects (N=X)					
		Related		Not Related		Total		Related		Not Related		Total		Related		Not Related		Total	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any HLGT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	HLGT 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	HLGT 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	…																		
	Repeat for applicable HLGT																		
SOC 1	Any HLGT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	HLGT 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	HLGT 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	…																		
	Repeat for applicable HLGT																		
SOC2	Any HLGT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	HLGT 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	HLGT 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	…																		
	Repeat for applicable HLGT																		
….	….																		

N = Number of subjects in the Safety Population.

Table 68: Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and High Level Group Term, Maximum Severity, Relationship, and Treatment Group

MedDRA System Organ Class	High Level Group Term	Severity	Dalbavancin (N=X)						Standard of Care (N=X)						All Subjects (N=X)					
			Related		Not Related		Total		Related		Not Related		Total		Related		Not Related		Total	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any HLGT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Not Reported	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 3	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 4	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 5	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	HLGT 1	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Not Reported	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 3	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 4	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 5	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	HLGT 2	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Not Reported	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 3	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 4	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Grade 5	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
….	….																			

N = Number of subjects in the Safety Population.

Table 69: Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Maximum Severity, Relationship, and Treatment Group

MedDRA System Organ Class	Severity	Dalbavancin (N=X)						Standard of Care (N=X)						All Subjects (N=X)					
		Related		Not Related		Total		Related		Not Related		Total		Related		Not Related		Total	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Not Reported	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 3	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 4	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 5	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Not Reported	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 3	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 4	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 5	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 2	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Not Reported	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 1	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 2	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 3	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 4	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Grade 5	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
….																			

N = Number of subjects in the Safety Population.

Table 70: Summary of AESIs by MedDRA System Organ Class, Maximum Severity, Relationship, and Treatment Group

This table will be similar to Table 69.

Table 71: Summary of Treatment-Emergent AEs, On-therapy SAEs, AESIs, and AEs Leading Discontinuation Occurring in 2% of Subjects in Any Treatment Group by MedDRA Preferred Term, and Treatment Group – Safety Population

[Implementation note: Sort this table by decreasing frequency for the treatment group.]

Preferred Term	Dalbavancin (N=X)			Standard of Care (N=X)			All Subjects (N=X)		
	n	%	Events	n	%	Events	n	%	Events
Any PT	x	x	x	x	x	x	x	x	x
PT1	x	x	x	x	x	x	x	x	x
PT2	x	x	x	x	x	x	x	x	x
Etc									
N = Number of subjects in the Safety Population.									

Table 72: Summary of Fatal on-Therapy SAEs by MedDRA Preferred Term, and Treatment Group – Safety Population

Preferred Term	Dalbavancin (N=X)			Standard of Care (N=X)			All Subjects (N=X)		
	n	%	Events	n	%	Events	n	%	Events
Any PT	x	x	x	x	x	x	x	x	x
PT1	x	x	x	x	x	x	x	x	x
PT2	x	x	x	x	x	x	x	x	x
…									
N = Number of subjects in the Safety Population.									

Table 73: Summary of Fatal on-Therapy SAEs by MedDRA High Level Group Term, and Treatment Group – Safety Population

High Level Group Term	Dalbavancin (N=X)			Standard of Care (N=X)			All Subjects (N=X)		
	n	%	Events	n	%	Events	n	%	Events
Any HLGT	x	x	x	x	x	x	x	x	x
HLGT1	x	x	x	x	x	x	x	x	x
HLTG2	x	x	x	x	x	x	x	x	x
…									
N = Number of subjects in the Safety Population.									

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 74: Listing of Serious Adverse Events

Adverse Event	Study Day of AE Onset	Duration (Days)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA High Level Group Term	MedDRA Preferred Term
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Note: For additional details about SAEs, see Table: xx.											

Table 75: Listing of Adverse Events of Special Interest

This table will be similar to Table 74.

Table 76: Listing of Adverse Events Leading to Discontinuation

This table will be similar to Table 74.

Table 77: Listing of Subjects whose Outcome was Fatal During the Study

This table will be similar to Table 74.

Table 78: Listing of Treatment-Emergent Adverse Events

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Group Term
Subject ID: , Treatment Group: , AE Number:											
Comments:											
Subject ID: , Treatment Group: , AE Number:											
Comments:											

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

(Not included in SAP, but this is a placeholder for the CSR.)

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 79: Listing of Potentially Clinically Significant Laboratory Results – Chemistry

Treatment Group	Subject ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)

Notes: All laboratory results for a parameter are displayed for subjects with at least one PCS result for that parameter.
PCS Criteria is defined as follows for each parameter: Sodium (<130 mmol/L OR >150 mmol/L), Potassium (<3.0 mmol/L OR >5.5 mmol/L), Glucose (<55 mg/dL), Creatinine (Serum creatinine >1.5x baseline), Albumin (<3 g/dL), Alkaline phosphatase (>ULN if baseline was normal; >2.0 x baseline if baseline was abnormal), Total bilirubin (>ULN if baseline was normal; > 1.0 x baseline if baseline was abnormal), AST (>ULN if baseline was normal; >1.5 x baseline if baseline was abnormal), ALT (>ULN if baseline was normal; >1.5 x baseline if baseline was abnormal).

Programming Notes: sort by treatment group (dalbavancin first), then subject ID.

[Implementation Note: **If a subject has at least one PCS, list all their laboratory results for that laboratory parameter.** The criteria for PCS will be defined below. Laboratory parameters not included in this table will be ignored.

- Laboratory parameter (Potentially Clinically Significant Result Criteria)
- Sodium (<130 mmol/L OR >150 mmol/L)
- Potassium (<3.0 mmol/L OR >5.5 mmol/L)
- Glucose (<55 mg/dL)
- Creatinine (Serum creatinine >1.5x baseline)
- Albumin (<3 g/dL)
- Alkaline phosphatase (>ULN if baseline was normal; >2.0 x baseline if baseline was abnormal)
- Total bilirubin (>ULN if baseline was normal; > 1.0 x baseline if baseline was abnormal)
- AST (>ULN if baseline was normal; >1.5 x baseline if baseline was abnormal)
- ALT (>ULN if baseline was normal; >1.5 x baseline if baseline was abnormal)]

Table 80: Listing of Potentially Clinically Significant Laboratory Results – Hematology

If a subject has at least one PCS, list all their laboratory results for that laboratory parameter.]

Treatment Group	Subject ID	Sex	Age (years)	Planned Time Point	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)

Notes: All laboratory results for a parameter are displayed for subjects with at least one PCS result for that parameter.
PCS Criteria is defined as follows for each parameter: Hemoglobin (<10 g/dL), Platelets (<75 /µL), White blood cell count (<3.0 x 10e9), Absolute neutrophil count (ANC) (<1500 x 10e9), Absolute lymphocyte count (ALC) (<800 x 10e9).

Programming Note: sort by treatment group (dalbavancin first), then subject ID.

[Implementation Note: **If a subject has at least one PCS, list all their laboratory results for that laboratory parameter.** The criteria for PCS will be defined as follows:

- Laboratory parameter (Potentially Clinically Significant Result Criteria)
- Hemoglobin (<10 g/dL)
- Platelets (<75 /µL)
- White blood cell count (<3.0 x 10e9)
- Absolute neutrophil count (ANC) (<1500 x 10e9)
- Absolute lymphocyte count (ALC) (<800 x 10e9)

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 81: Number and Percentage of Subjects with Potentially Clinically Significant Post-Baseline Laboratory Values by Parameter and Treatment Group – Chemistry Parameters

Serum Chemistry Parameter	Dalbavancin			Standard of Care		
	N	n	%	N	n	%
Any Serum Chemistry Parameter	x	x	xx	x	x	xx
Sodium	x	x	xx	x	x	xx
Potassium	x	x	xx	x	x	xx
Glucose	x	x	xx	x	x	xx
Creatinine	x	x	xx	x	x	xx
Alkaline Phosphatase	x	x	xx	x	x	xx
Albumin	x	x	xx	x	x	xx
Total bilirubin	x	x	xx	x	x	xx
AST	x	x	xx	x	x	xx
ALT	x	x	xx	x	x	xx

PCS = Potentially Clinically Significant. PCS Criteria is defined as follows for each parameter: Sodium (<130 mmol/L OR >150 mmol/L), Potassium (<3.0 mmol/L OR >5.5 mmol/L), Glucose (<55 mg/dL), Creatinine (Serum creatinine >1.5x baseline), Albumin (<3 g/dL), Alkaline phosphatase (>ULN - 2.5 x ULN if baseline was normal; >2.0 - 2.5 x baseline if baseline was abnormal), Total bilirubin (>ULN – 1.5 x ULN if baseline was normal; > 1.0 – 1.5 x baseline if baseline was abnormal), AST (>ULN - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal), ALT (>ULN if baseline was normal; >1.5 x baseline if baseline was abnormal).
N = Number of subjects in the Safety Population with available non-PCS baseline values and at least 1 post-baseline assessment.
n = Number of subjects with at least one PCS post-baseline laboratory value.

Table 82: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Sodium

[Implementation Note: The number of decimals for the minimum and maximum will be the same as the original values, while the number of decimals for the mean, standard deviation, and median will add an extra decimal point to that of the original values.]

		Laboratory Value					Change from Baseline				
Time Point	**Treatment Group**	**n**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**	**n**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**
Baseline	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	NA	NA	NA	NA	NA
	Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	NA	NA	NA	NA	NA
Day 8	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
Day 22	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
Day 42	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x

N = Number of subjects in the Safety Population.
n = Number of subjects in the Safety Population with non-missing laboratory values at the timepoint of interest. For the change from baseline, n represents the number of subjects in the Safety population with non-missing values at baseline and at the timepoint being assessed.

Tables with similar format to Table 82:

Table 83: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Potassium

Table 84: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Calcium

Table 85: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Chloride

Table 86: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Bicarbonate

Table 87: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Glucose

Table 88: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Blood Urea Nitrogen

Table 89: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Creatinine

Tables with similar format to Table 82 *(continued)*

Table 90: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Total Protein

Table 91: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Alkaline Phosphatase

Table 92: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Albumin

Table 93: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, Total Bilirubin

Table 94: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, AST

Table 95: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Serum Chemistry, ALT

14.3.5.2 Hematology Results

Table 96: Number and Percentage of Subjects with Potentially Clinically Significant Post-Baseline Laboratory Values by Parameter and Treatment Group – Hematology Parameters

Serum Chemistry Parameter	Dalbavancin			Standard of Care		
	N	n	%	N	n	%
Any Hematology Parameter	x	x	xx	x	x	xx
Absolute WBC	x	x	xx	x	x	xx
Hemoglobin	x	x	xx	x	x	xx
Platelet Count	x	x	xx	x	x	xx
Absolute Neutrophil Count	x	x	xx	x	x	xx
Absolute Lymphocyte Count	x	x	xx	x	x	xx

PCS = Potentially Clinically Significant. PCS Criteria is defined as follows for each parameter: Hemoglobin (<10 g/dL), Platelets (<75 /µL), White blood cell count (<3.0 x 10e9), Absolute neutrophil count (ANC) (<1500 x 10e9), Absolute lymphocyte count (ALC) (<800 x 10e9).
N = Number of subjects in the Safety Population with available non-PCS baseline values and at least 1 post-baseline assessment.
n = Number of subjects with at least one PCS post-baseline laboratory value.

Table 97: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hematology, Absolute WBC

[Implementation Note: The number of decimals for the minimum and maximum will be the same as the original values, while the number of decimals for the mean, standard deviation, and median will add an extra decimal point to that of the original values.]

		Laboratory Value					Change from Baseline				
Time Point	**Treatment Group**	**n**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**	**n**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**
Baseline	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	NA	NA	NA	NA	NA
	Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	NA	NA	NA	NA	NA
Day 8	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
Day 22	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
Day 42	Dalbavancin (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Standard of Care (N=X)	x	xx.x	xx.x	xx.x	xx.x, xx.x	x	xx.x	xx.x	xx.x	xx.x, xx.x

N = Number of subjects in the Safety Population.
n = Number of subjects in the Safety Population with non-missing laboratory values at the timepoint of interest. For the change from baseline, n represents the number of subjects in the Safety population with non-missing values at baseline and at the timepoint being assessed.

Tables with similar format to Table 97:

Table 98: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hematology, Erythrocyte

Table 99: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hematology, Hemoglobin

Table 100: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hematology, Hematocrit

Table 101: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hematology, Platelet Count

Table 102: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hematology, Neutrophils

Table 103: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hematology, Lymphocytes

Table 104: Laboratory Summary Statistics by Parameter, Time Point, and Treatment Group – Hematology, Monocytes

14.3.6 Displays of Vital Signs

Table 105: Summary of Vital Signs Values by Vital Sign Parameter, Visit, and Treatment Group

[Implementation Note: The number of decimals for the minimum and maximum will be the same as the original values, while the number of decimals for the mean, standard deviation, and median will add an extra decimal point to that of the original values.]

Vital Sign	Time Point	Dalbavancin (N=X)					Standard of Care (N=X)				
		n	Mean	Standard Deviation	Median	Min, Max	n	Mean	Standard Deviation	Median	Min, Max
Temperature (°F)	Visit 1 (Screening)	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Visit 2 (Baseline)										
	Visit 3 (Day 8)										
	Visit 4 (Day 22)										
	Visit 5 (Day 42)										
	Visit 6 (Day 70)										
	Visit 7 (Day 180)										
	Early Termination Visit										
Systolic Blood Pressure (mmHg)	Visit 1 (Screening)	x	xx.x	xx.x	xx.	xx, xx	x	xx.x	xx.x	xx.x	xx, xx
	Visit 2 (Baseline)										
	Visit 3 (Day 8)										
	Visit 4 (Day 22)										
	Visit 5 (Day 42)										
	Visit 6 (Day 70)										
	Visit 7 (Day 180)										
	Early Termination Visit										
Diastolic Blood Pressure (mmHg)	Visit 1 (Screening)	x	xx.x	xx.x	xx.x	xx, xx	x	xx.x	xx.x	xx.x	xx, xx
	Visit 2 (Baseline)										
	Visit 3 (Day 8)										
	Visit 4 (Day 22)										

Table 105: Summary of Vital Signs Values by Vital Sign Parameter, Visit, and Treatment Group (continued)

Vital Sign	Time Point	Dalbavancin (N=X)					Standard of Care (N=X)				
		n	Mean	Standard Deviation	Median	Min, Max	n	Mean	Standard Deviation	Median	Min, Max
	Visit 5 (Day 42)										
	Visit 6 (Day 70)										
	Visit 7 (Day 180)										
	Early Termination Visit										
Respiratory Rate (breaths/min)	Visit 1 (Screening)	x	xx.x	xx.x	xx.x	xx, xx	x	xx.x	xx.x	xx.x	xx, xx
	Visit 2 (Baseline)										
	Visit 3 (Day 8)										
	Visit 4 (Day 22)										
	Visit 5 (Day 42)										
	Visit 6 (Day 70)										
	Visit 7 (Day 180)										
	Early Termination Visit										
Pulse (beats/min)	Visit 1 (Screening)	x	xx.x	xx.x	xx.x	xx, xx	x	xx.x	xx.x	xx.x	xx, xx
	Visit 2 (Baseline)										
	Visit 3 (Day 8)										
	Visit 4 (Day 22)										
	Visit 5 (Day 42)										
	Visit 6 (Day 70)										
	Visit 7 (Day 180)										
	Early Termination Visit										

N = Number of subjects in the Safety Population.
n = Number of subjects in the Safety Population with non-missing values for the corresponding vital sign at the given timepoint.

Table 106: Summary of Change from Baseline Vital Signs Values by Vital Sign Parameter, Visit, and Treatment Group

[Implementation Note: The number of decimals for the minimum and maximum will be the same as the original values, while the number of decimals for the mean, standard deviation, and median will add an extra decimal point to that of the original values.]

		Dalbavancin (N=X)					Standard of Care (N=X)				
Vital Sign	**Time Point**	**n**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**	**n**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**
Temperature (°F)	Visit 3 (Day 8)	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x	x	xx.xx	xx.xx	xx.xx	xx.x, xx.x
	Visit 4 (Day 22)										
	Visit 5 (Day 42)										
	Visit 6 (Day 70)										
	Visit 7 (Day 180)										
	Early Termination Visit										
Systolic Blood Pressure (mmHg)	Visit 3 (Day 8)	x	xx.x	xx.x	xx.	xx, xx	x	xx.x	xx.x	xx.x	xx, xx
	Visit 4 (Day 22)										
	Visit 5 (Day 42)										
	Visit 6 (Day 70)										
	Visit 7 (Day 180)										
	Early Termination Visit										
Diastolic Blood Pressure (mmHg)	Visit 3 (Day 8)	x	xx.x	xx.x	xx.x	xx, xx	x	xx.x	xx.x	xx.x	xx, xx
	Visit 4 (Day 22)										
	Visit 5 (Day 42)										
	Visit 6 (Day 70)										
	Visit 7 (Day 180)										
	Early Termination Visit										

Table 106: Summary of Change from Baseline Vital Signs Values by Vital Sign Parameter, Visit, and Treatment Group (continued)

		Dalbavancin (N=X)					Standard of Care (N=X)				
Vital Sign	**Time Point**	**n**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**	**n**	**Mean**	**Standard Deviation**	**Median**	**Min, Max**
Respiratory Rate (breaths/min)	Visit 3 (Day 8)										
	Visit 4 (Day 22)										
	Visit 5 (Day 42)										
	Visit 6 (Day 70)										
	Visit 7 (Day 180)										
	Early Termination Visit										
Pulse (beats/min)	Visit 3 (Day 8)										
	Visit 4 (Day 22)										
	Visit 5 (Day 42)										
	Visit 6 (Day 70)										
	Visit 7 (Day 180)										
	Early Termination Visit										

N = Number of subjects in the Safety Population.
n = Number of subjects in the Safety Population with non-missing values for the corresponding vital sign at both baseline and given timepoint.

14.4 Summary of Concomitant Medications and Nondrug Interventions

Table 107: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Dalbavancin (N=X)		Standard of Care (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						
[ATC Level 1 – 2]	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						

N = Number of subjects in the Safety Population.
n = Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

Table 108: Number and Percentage of Subjects with Nondrug Interventions by MedDRA System Organ Class and Treatment Group – ITT Population

MedDRA System Organ Class	Dalbavancin (N=X)		Standard of Care (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx
[SOC 1]						
[SOC 2]						

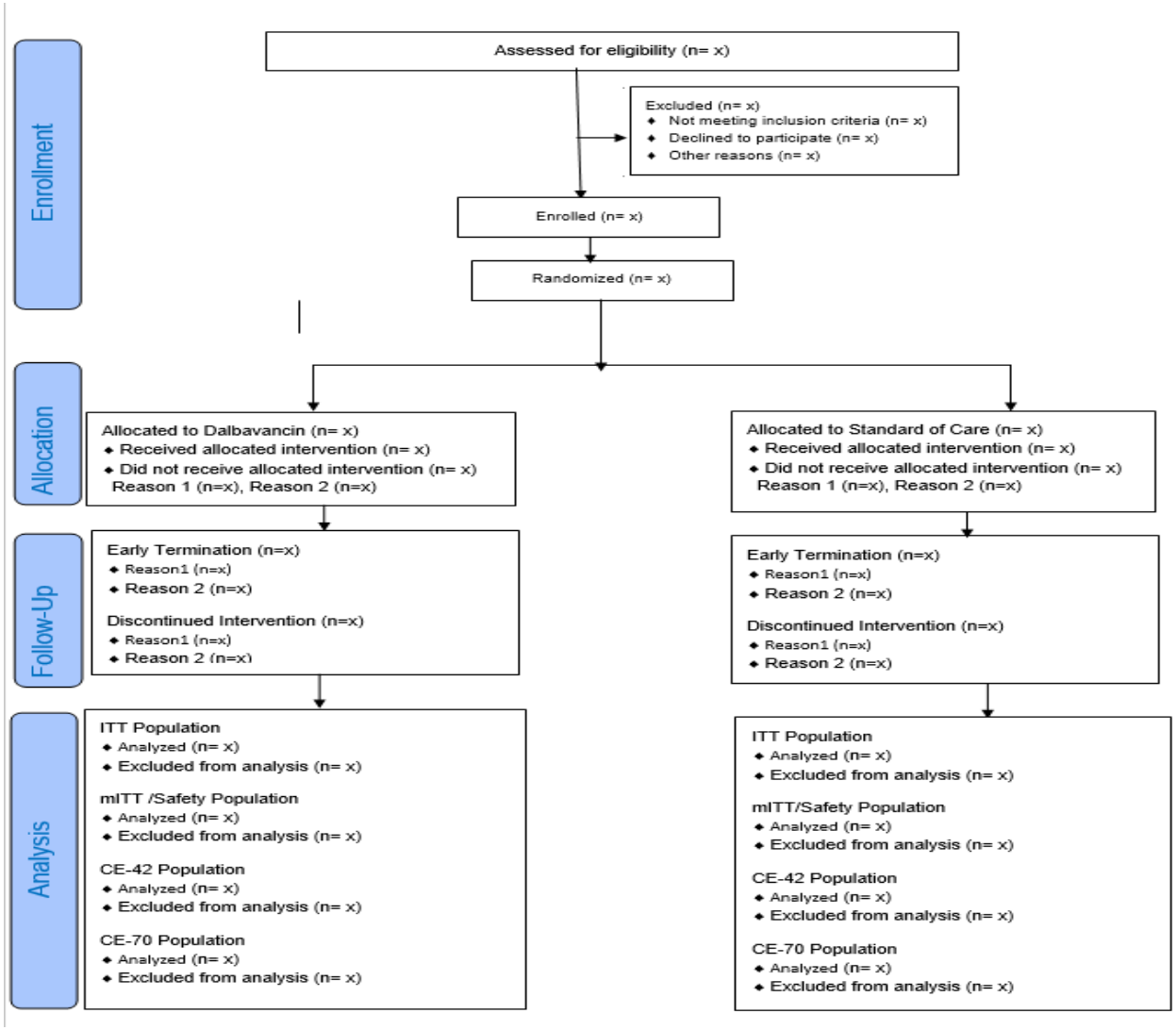
N = Number of subjects in the ITT population.
n = Number of subjects reporting a nondrug intervention within the specified SOC. A subject is only counted once per SOC.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

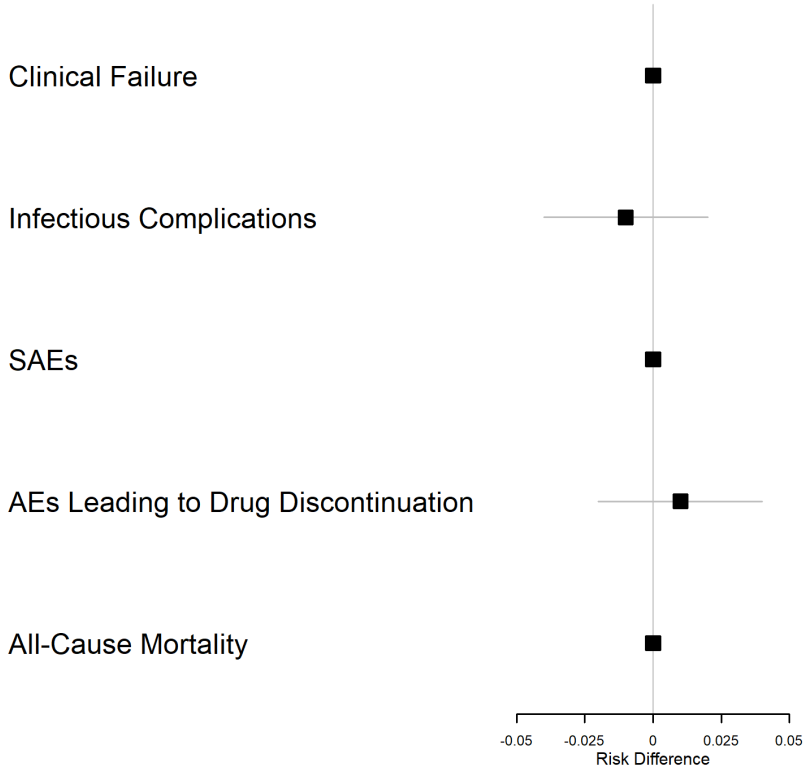
10.1 Disposition of Subjects

Figure 1: CONSORT Flow Diagram



14.2.2 Efficacy Response Figures by Measure, Treatment, and Time Point

Figure 2: Forest Plot of DOOR Probability, Dalbavancin Relative to Standard of Care, of Clinical DOOR Components at Day 70 – ITT Population



Programming Note: Include n (%) of subjects by arm as additional columns – next to description of each DOOR component. Additionally, change "Risk Difference" to DOOR Probability.

Figures similar to Figure 2:

Figure 3: Forest Plot of DOOR Probability, Dalbavancin Relative to Standard of Care, of Clinical DOOR Components at Day 70 – mITT Population

Figure 4: Forest Plot of DOOR Probability, Dalbavancin Relative to Standard of Care, of Clinical DOOR Components at Day 70 – CE Population

Figure 5: Forest Plot of DOOR Probability, Dalbavancin Relative to Standard of Care, of Clinical DOOR Components at Day 42 – ITT Population

Figure 6: Forest Plot of DOOR Probability, Dalbavancin Relative to Standard of Care, of Clinical DOOR Components at Day 42 – mITT Population

Figure 7: Forest Plot of DOOR Probability, Dalbavancin Relative to Standard of Care, of Clinical DOOR Components at Day 42 – CE Population

Figure 8: Distribution of DOOR at Day 70 – ITT Population

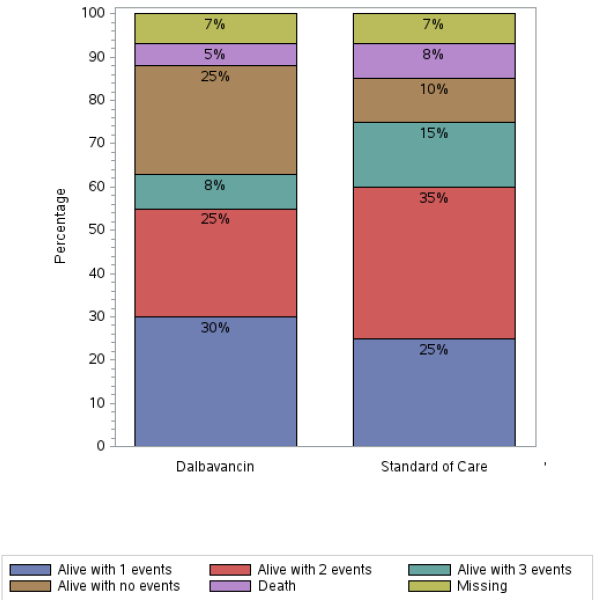


Figure 9: Distribution of DOOR at Day 70 – mITT Population

Figure will be similar to Figure 8.

Figure 10: Distribution of DOOR at Day 70 – CE Population

Figure will be similar to Figure 8.

[Implementation note: The missing category is removed from this analysis since the CE population has complete data.]

Figure 11: Distribution of DOOR at Day 42 – ITT Population

Figure will be similar to Figure 8.

Figure 12: Distribution of DOOR at Day 42 – mITT Population

Figure will be similar to Figure 8.

Figure 13: Distribution of DOOR at Day 42 – CE Population

Figure will be similar to Figure 8.

[Implementation note: The missing category is removed from this analysis since the CE population has complete data.]

Figure 14: Distribution of DOOR at Day 70 by Baseline Pathogen – ITT Population

Figure similar to Figure 8.

[Implementation note: Create two separate panels for MRSA and MSSA]

Figure 15: Distribution of DOOR at Day 70 by PWID Status – ITT Population

Figure similar to Figure 8.

[Implementation note: Create two separate panels for PWID and non-PWID]

Figure 16: Distribution of DOOR at Day 70 by Infectious Disease Consultation – ITT Population

Figure similar to Figure 8.

[Implementation note: Create two separate panels for Yes and No]

Figure 17: Distribution of DOOR at Day 70 by Underlying Site of Infection – ITT Population

Figure similar to Figure 8.

[Implementation note: Create four separate panels for the 4 different sites.]

Figure 18: Distribution of DOOR at Day 70 by Immunosuppression – ITT Population

[Implementation note: Create two separate panels for Yes and No]

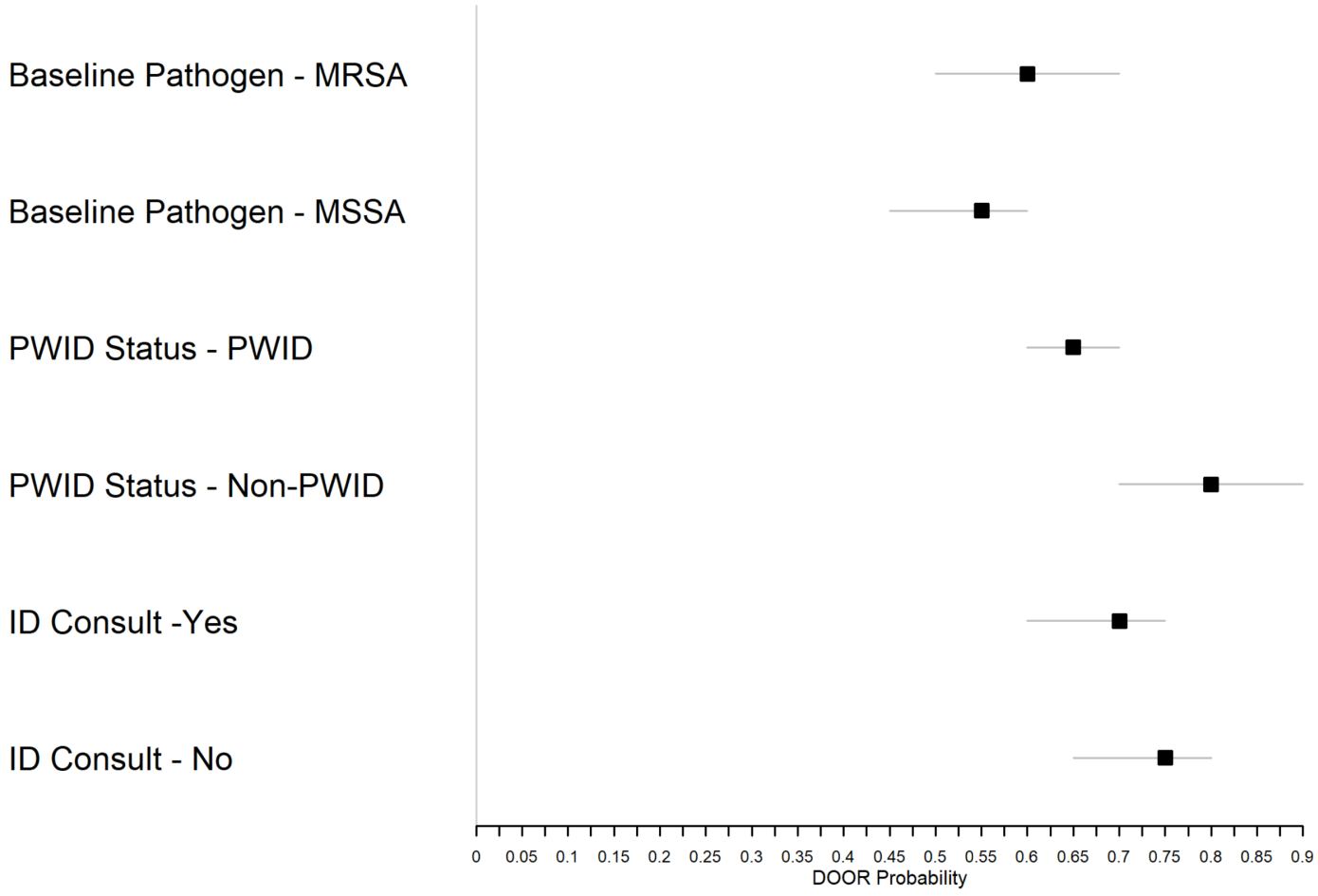
Figure 19: Distribution of DOOR at Day 70 by Duration of Initial Bacteremia – ITT Population

Figure similar to Figure 8.

[Implementation note: Create three separate panels for <2, 2-4, >4 days]

Figure 20: Forest Plot of DOOR Probabilities at Day 70 – ITT Population

[Implementation note: This figure will be updated using SAS to add the rest of the subgroups and reformat the Y axis values as: Baseline Pathogen as title with indented categories MRSA, MSSA. Similar format update will be done for the rest of the subgroup categories. Caps will also be added to the error bars.]



Similar to Figure 2.

Programming note: Include n (%) as columns.

Figure 21: Forest Plot of DOOR Probabilities at Day 42 – ITT Population

Figure similar to Figure 20.

Figure 22: Difference in Cumulative Proportions of DOOR Along with 95% CI

[Implementation note: Make a figure with 6 panels (2 rows representing Day 42 and Day 70; 3 columns representing the 3 analysis populations.]

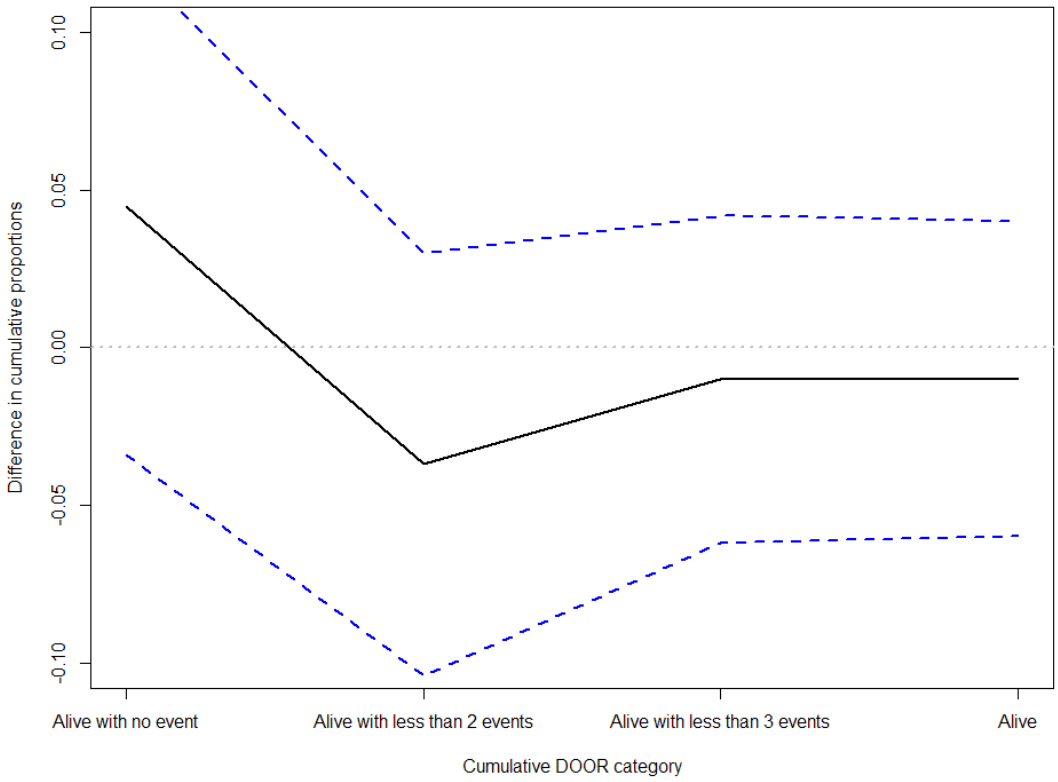


Figure 23: Difference in Means of Partial Credit Score by Timepoint and Analysis Population

[Implementation note: The figure will have 6 panels with two rows for Day 42 and Day 70 and two columns representing ITT, mITT, and CE analysis populations.]

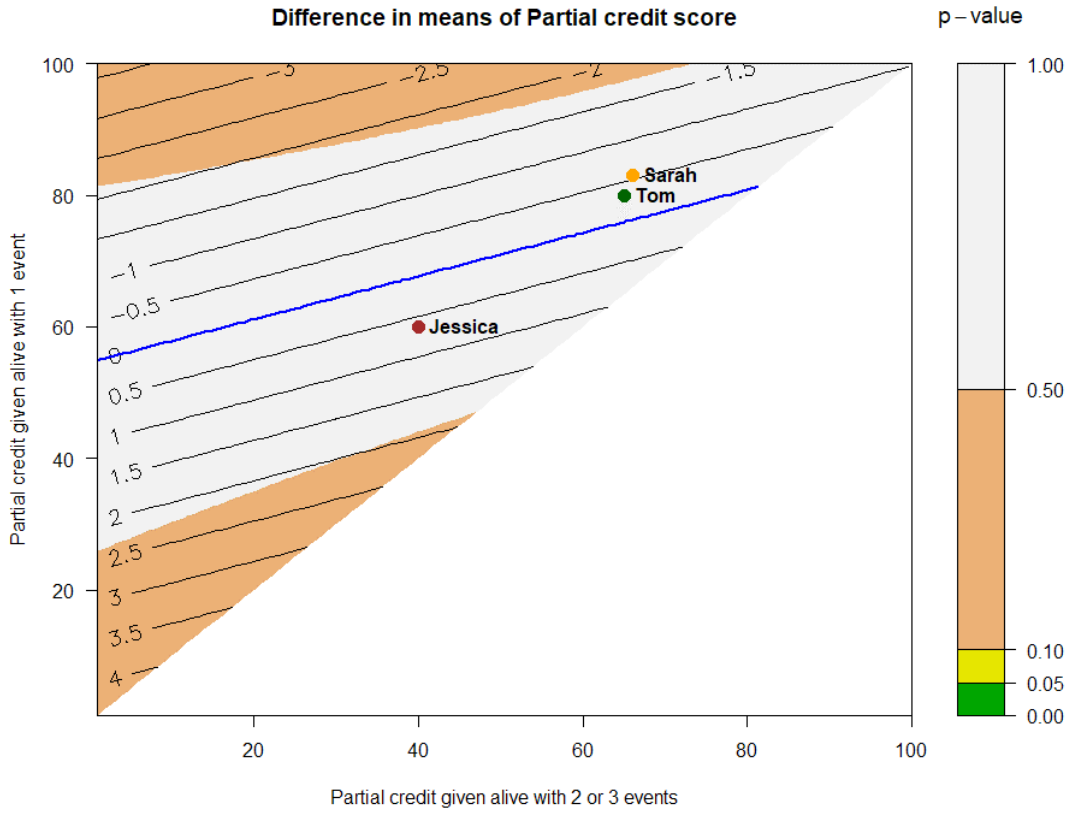


Figure 24: Bivariate Analysis of DOOR Probability vs Difference in Mean of Change in QoL Score from Baseline at Day 70 – ITT Analysis Population

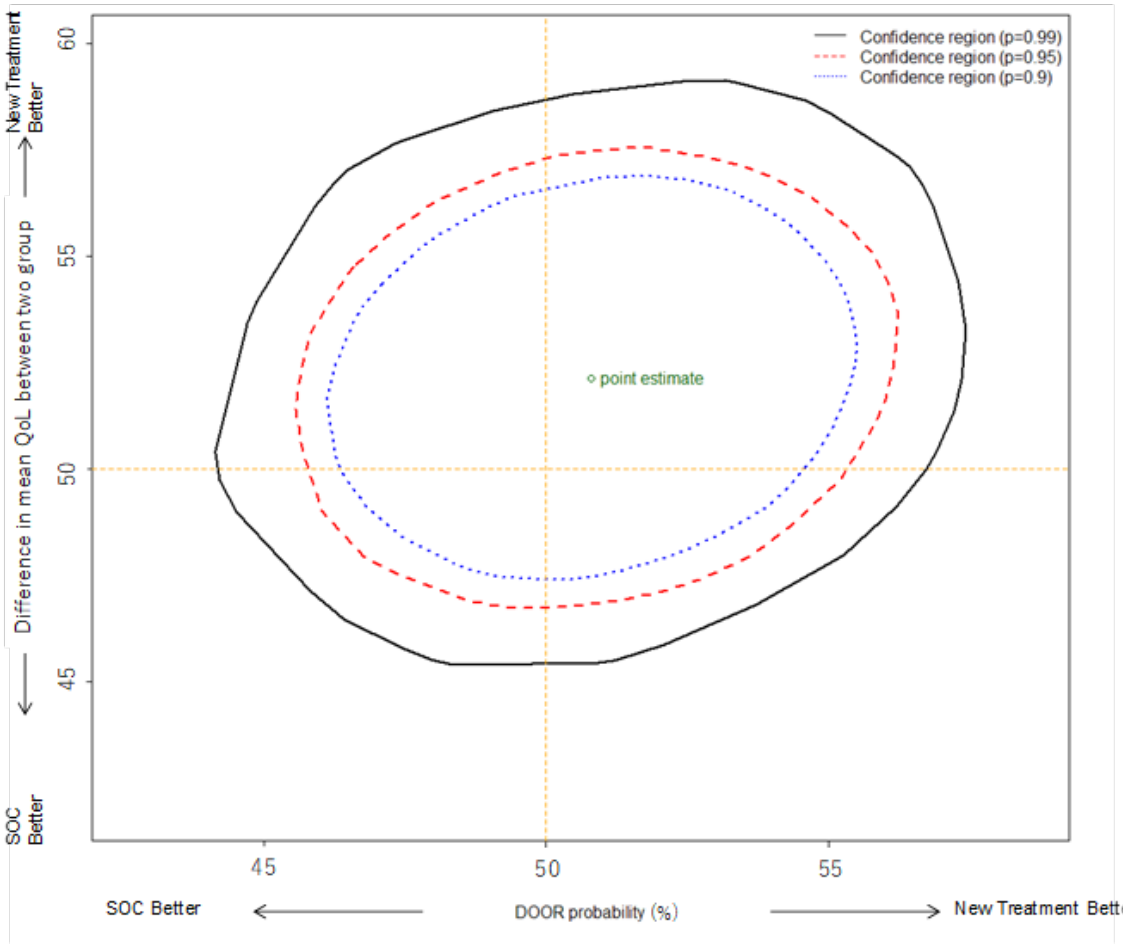


Figure 25: Bivariate Analysis of DOOR Probability vs Difference in Mean of Change in QoL Score from Baseline at Day 42 – ITT Analysis Population

Figure will be similar to Figure 24.

Figure 26: Predictive Interval Plots for the Probability of Higher DOOR in the Dalbavancin Group at Day 70 – ITT Analysis Population

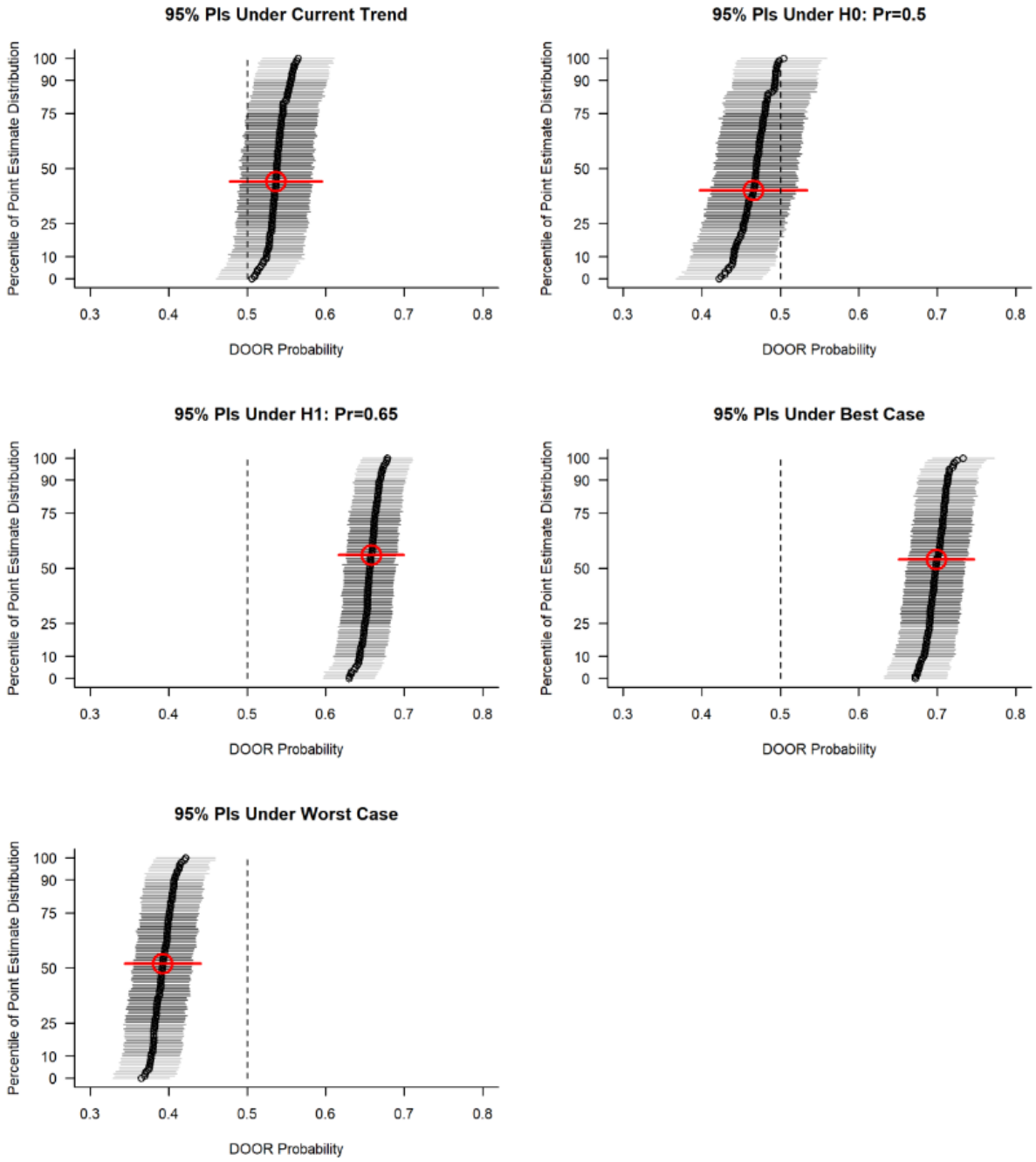


Figure with similar format:

Figure 27: Predictive Interval Plots Statistics for the Rates of Clinical Efficacy at Day 70 – ITT Analysis Population*

[Implementation note: Regenerate the figure for rates of clinical efficacy. Provide results for current trend, under null H0 with rate =0.5, under alternative H0 with rate=0.4, under best case and under worst case scenario.]

14.3.1.2 Unsolicited Adverse Events

Figure 28: Frequency of Related Adverse Events by MedDRA System Organ Class, Severity, and Treatment Group

[Implementation note: Panels for Dalbavancin and Standard of Care subjects will be presented. Grade 3 or higher will be reported for all AEs except AESIs which will include lower severities 1 and Grade 2.]

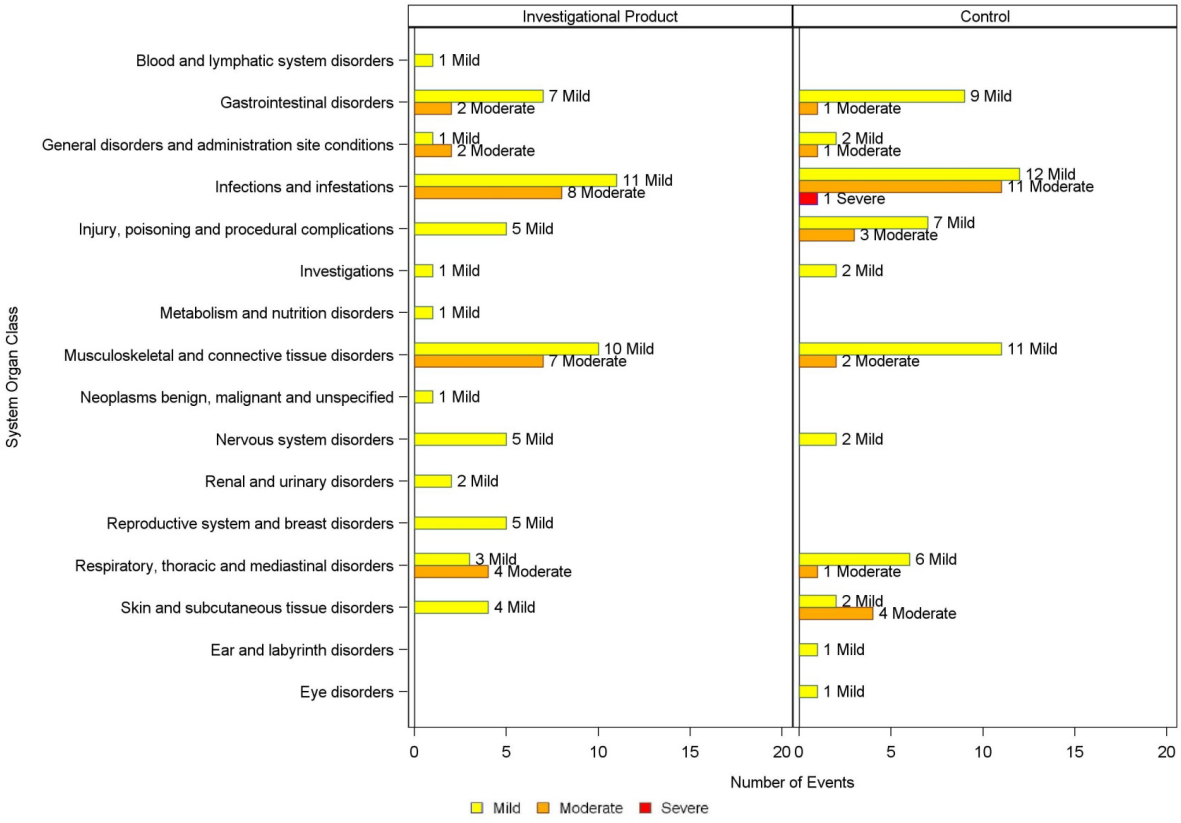
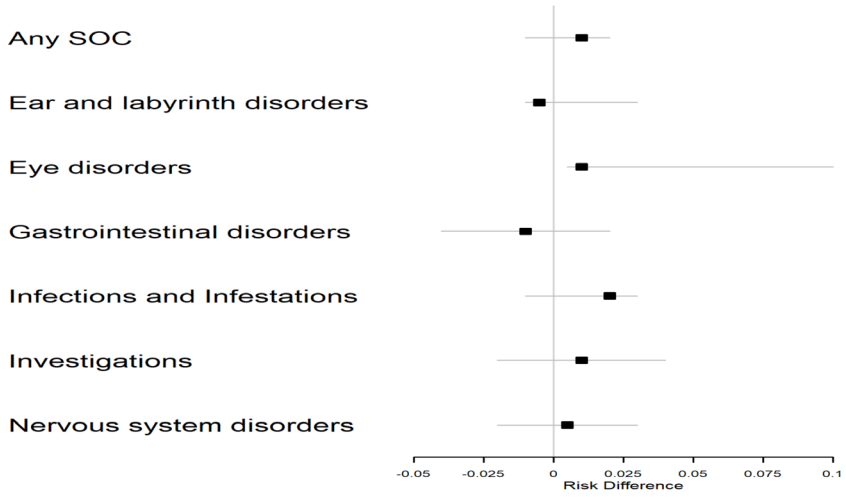


Figure 29: Frequency of Related Adverse Events by MedDRA High Level Group Term, Severity, and Treatment Group

Figure will be similar to Figure 28.

Figure 30: Forest Plot of Risk Differences of All Adverse Events by MedDRA System Organ Class

[Implementation note: The 95% CI for the risk difference will be computed using the Miettinen-Nurminen method.]



Implementation Note: Include n (%) as columns. See Figure 2 for example.

Figure 31: Forest Plot of Risk Differences of All Adverse Events by MedDRA High Level Group Term

Figure will be similar to Figure 30.

Implementation Note: Include n (%) as columns. See Figure 2 for example.

14.3.5 Displays of Laboratory Results

Figure 32: Forest Plot of Risk Differences of Experiencing a Clinical Laboratory Abnormality by Laboratory Parameter – Hematology Parameters

[Implementation note: Create separate panels for each visit. 95% confidence intervals for the risk differences will be computed using the Miettinen-Nurminen method.]

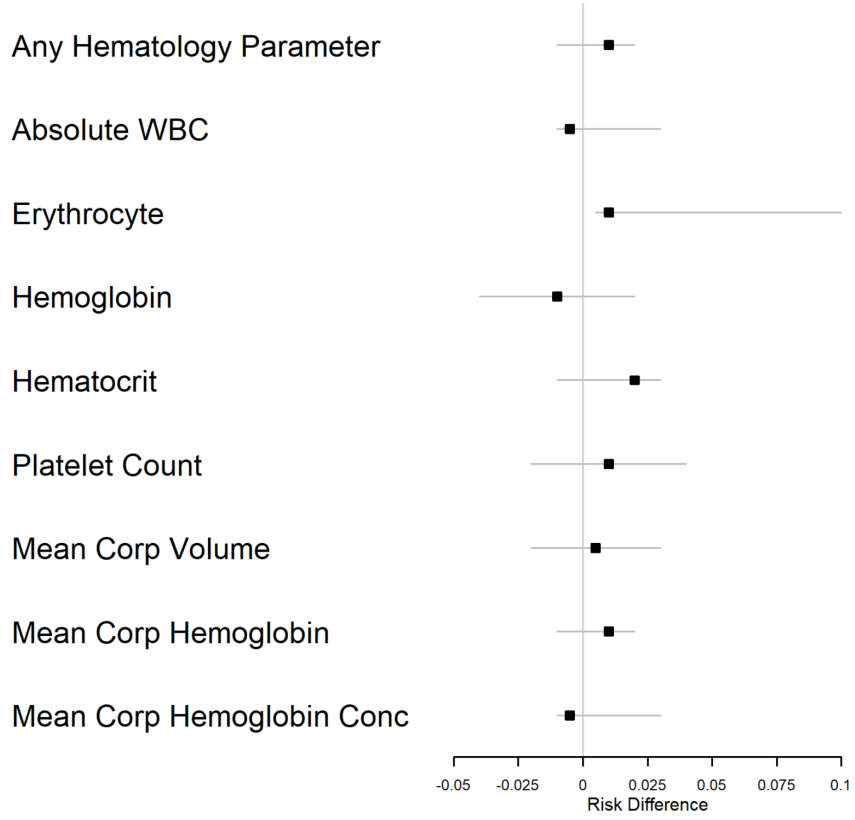
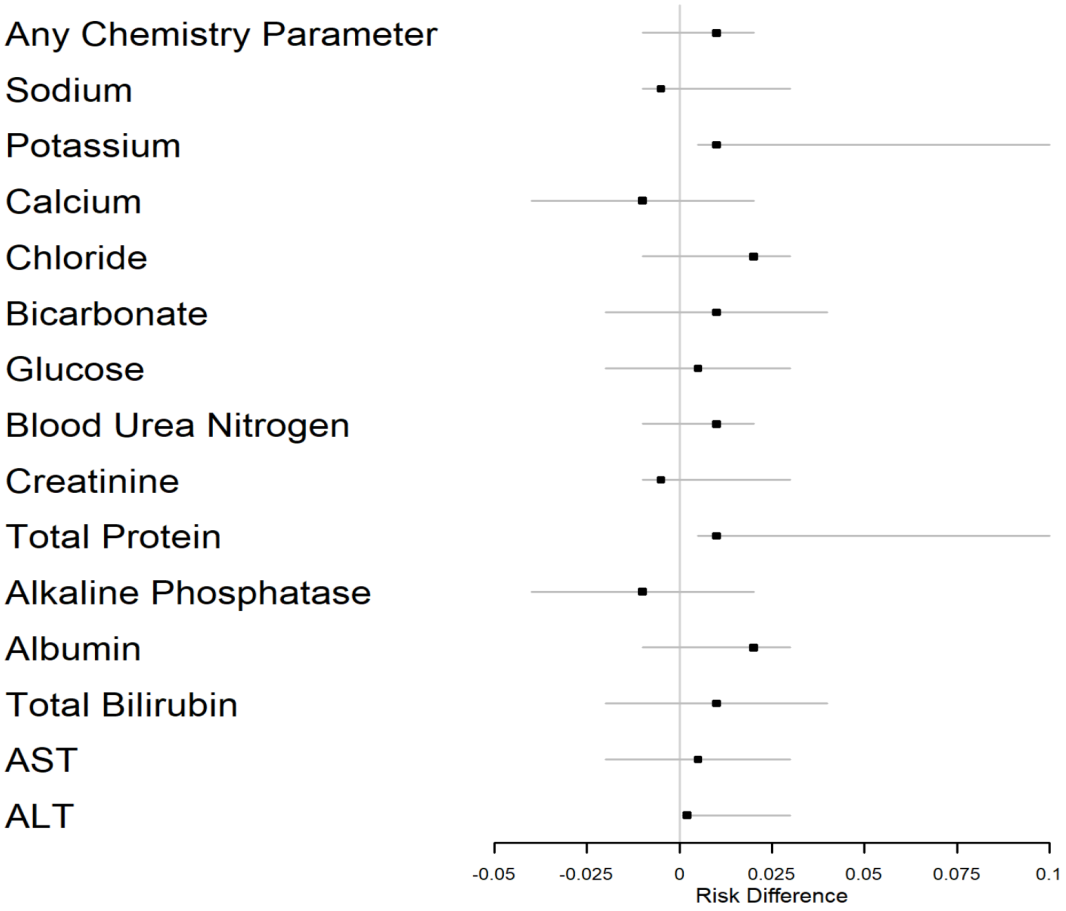


Figure 33: Forest Plot of Risk Differences of Experiencing a Clinical Laboratory Abnormality by Laboratory Parameter – Serum Chemistry Parameters

[Implementation note: Create separate panels for each visit. 95% confidence intervals for the risk differences will be computed using the Miettinen-Nurminen method.]



APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

Listing 1: **16.1.6: Listing of Subjects Receiving Investigational Product**

(Not included in SAP, but this is a placeholder for the CSR)

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 2: 16.2.1: Early Terminations or Discontinued Subjects

Treatment Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1: Subject-Specific Protocol Deviations

Treatment Group	Subject ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

Listing 4: 16.2.2.2: Non-Subject-Specific Protocol Deviations

Site	Start Date	Deviation	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 5: 16.2.3: Subjects Excluded from Analysis Populations

Treatment Group	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Reason Subject Excluded
Dalbavancin	SST.XXXX	[e.g., Safety, ITT, mITT]	CE42	
Dalbavancin	SST.XXXX		CE70	

16.2.4 Demographic Data

Listing 6: 16.2.4.1: Demographic Data

Treatment Group	Subject ID	Sex	Age (years)	Ethnicity	Race	Height (cm)	Weight (kg)	BMI (kg/m^2)	Baseline Pathogen	Baseline QoL Score

Listing 7: 16.2.4.2: Pre-Existing and Concurrent Medical Conditions

Treatment Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Group Term

Listing 8: 16.2.4.3: Investigator Assessment of Baseline *S. aureus* Bacteremia Diagnoses

Treatment Group	Subject ID	*S. aureus* Infectious Complication	Evidence of Infectious Complication?
Dalbavancin	SST.XXXX	Acute bacterial skin and skin structure infection (ABSSSI)	Yes/No
Dalbavancin	SST.XXXX	Other (Abcess)	Yes

16.2.5 Compliance and/or Drug Concentration Data (if available)

Listing 9: 16.2.5: Compliance and/or Drug Concentration Data

[Implementation note: Sort by Treatment group and subject ID.]

Treatment Group	Subject ID	Dose Amount	Treatment Duration[a]	Creatinine Clearance[b]

[a] Treatment duration is defined as the number of doses for dalbavancin while it is defined as the duration between start and end dates for standard of care.
[b] Only included for subjects treated with Dalbavancin.

16.2.6 Individual Efficacy Response Data

Listing 10: 16.2.6.1: Individual DOOR Response Data

[Implementation note: Sort by treatment group, subject ID, and Planned Time Point.]

Treatment Group	Subject ID	Planned Time Point	Clinical Failure	Infectious Complications	SAEs	AEs Leading to Study Drug Discontinuation	All-cause Mortality	DOOR Category	Change in QoL from Baseline	DOOR	Clinical Efficacy	Microbiological Success
Dalbavancin	SST.XXXX	Day 42	Yes	No	No	No	No	2	40	120	No	Yes
Dalbavancin	SST.XXXX	Day 70	No	No	No	No	No	1	60	20	Yes	Yes

Listing 11: 16.2.6.1: Investigator Assessment of Efficacy – Clinical Success

[Implementation note: Sort by treatment group, subject ID, and Planned Time Point.]

Treatment Group	Subject ID	Planned Time Point	Has the Subject Died?	Have additional antibiotics not specified by the protocol been required for the treatment of *S. aureus* bacteremia?	How many antibiotics have been used?	Is it anticipated that additional antibiotic therapy beyond that specified by the protocol will be required for the treatment of *S. aureus* bacteremia?
Dalbavancin	SST.XXXX	Day 42	Yes	No	N/A	No
Dalbavancin	SST.XXXX	Day 70	No	Yes	3	N/A

Listing 12: 16.2.6.1: Investigator Assessment of Efficacy – Infectious Complications

[Implementation note: Sort by treatment group, subject ID, and Planned Time Point.]

Treatment Group	Subject ID	Planned Time Point	Is the subject experiencing clinical failure?	Has the subject had endocarditis since randomization/ last assessment?	Has the subject had new evidence of metastatic foci of infection since randomization/ last assessment?	Has the subject relapsed since randomization/ last assessment?	Has the subject been re-hospitalized since randomization/last assessment for subsequent care of indication under study?	Has the subject had an additional unplanned source control procedure since randomization/last assessment?	Has the subject had a change in antibiotic therapy due to inadequate clinical response?	Has the subject achieved clinical success?
Dalbavancin	SST.XXXX	Day 42	Yes	No	No	No	No	No	Yes	No
Dalbavancin	SST.XXXX	Day 70	No	No	No	No	No	No	No	Yes

Listing 13: 16.2.6.2: Listing of Culture Results

Treatment Group	Subject ID	Culture Site	Collection Date	Actual Study Day	Collection Time	Culture Result	Pathogen Detected
Dalbavancin	SST.XXXX	Blood or Urine or Sputum, …	XXMMMYYYY		HH:MM	Positive or Negative	

Listing 14: 16.2.6.2: Individual QoL Data

Treatment Group	Subject ID	Planned Time Point	QoL Score Using ARLG Bloodstream Infection[a]	QoL Score Using PROMIS Global Health Short Form	QoL Score Using EQ-5D-5L instrument
Dalbavancin	SST.XXXX	Baseline			
Dalbavancin	SST.XXXX	Day 42			
Dalbavancin	SST.XXXX	Day 70			

[a] Standardized score is obtained from the items selected from the PROMIS physical function item bank (PROMIS Item Bank v2.0, short form 6b) item bank on the ARLG Bloodstream Infection QoL

16.2.7 Adverse Events

Listing 15: 16.2.7.3: Listing of Treatment-Emergent Adverse Events

Adverse Event	Study Day of AE Onset	Duration (Days)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Group Term
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Treatment Group: , Subject ID: , AE Number:											
Comments:											

Listing 16: 16.2.7.3: Listing of All Adverse Events for Subjects with Potentially Clinically Significant Post-Baseline Clinical Laboratory or Vital Sign Values

Adverse Event	Study Day of AE Onset	Duration (Days)	Severity	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term	MedDRA High Level Group Term
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Treatment Group: , Subject ID: , AE Number:											
Comments:											

16.2.8 Individual Laboratory Measurements

Listing 17: 16.2.8.1: Clinical Laboratory Results – Chemistry

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

Listing 18: 16.2.8.2: Clinical Laboratory Results – Hematology

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

16.2.9 Vital Signs and Physical Exam Findings

Listing 19: 16.2.9.1: Vital Signs

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Temperature (°F)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Pulse (beats/min)	Respiratory Rate (breaths/min)

Listing 20: 16.2.9.2: Physical Exam Findings

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.10 Concomitant Medications

Listing 21: 16.2.10.1: Concomitant Medications

Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)

Listing 22: 16.2.10.1: Nondrug Interventions

Treatment Group	Subject ID	ND Number	Surgery/Procedure	Date of Procedure	Indication

Listing 23: 16.2.10.1: Echocardiogram Results

Treatment Group	Subject ID	Date of Procedure	Procedure Type	Result
			Transthoracic	Normal
			Transesophageal	Abnormal, not clinically significant
			Transthoracic	Abnormal, with evidence of left-sided endocarditis
			Transthoracic	Abnormal, with other clinically significant findings: specify

Listing 24: 16.2.10.2: Hospitalization Events

Treatment Group	Subject ID	Date of Admission	Reason for Admission	Date of Discharge	Discharge Status	Discharge Diagnosis

16.2.11 Pregnancy Reports

Listing 25: 16.2.11.1: Pregnancy Reports – Maternal Information

Treatment Group	Subject ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?

Note: Maternal Complications are included in the Adverse Event listing. Medications taken during pregnancy are included in the Concomitant Medications Listing.

Listing 26: 16.2.11.2: Pregnancy Reports – Gravida and Para

			Live Births												
Subject ID	Pregnancy Number	Gravida	Extremely PB[a]	Very Early PB[a]	Early PB[a]	Late PB[a]	Early TB[b]	Full TB[b]	Late TB[b]	Post TB[b]	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?

Note: Gravida includes the current pregnancy, para events do not.

[a] Preterm Birth
[b] Term Birth

Listing 27: 16.2.11.3: Pregnancy Reports – Live Birth Outcomes

Subject ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?

Note: Congenital Anomalies are included in the Adverse Event listing.

Listing 28: 16.2.11.4: Pregnancy Reports – Still Birth Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 29: 16.2.11.5: Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion