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Study ID: DAL-MD-04

Title: A Phase 2, Single-center, Open-label, Randomized, Comparator-Controlled Trial of
the Safety and Efficacy of Dalbavancin versus Active Comparator in Adult Patients
with Osteomyelitis Known or Suspected to be due to Gram-Positive Organisms

Statistical Analysis Plan Amendment 1 Date: 16 Jan 2018

Please note: The original Statistical Analysis Plan (pages 44-81) was removed from this document, since
the summary of changes for Amendment 1 are included.

1.0   **TITLE PAGE**

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DAL-MD-04

A Phase 2, Single-center, Open-label, Randomized, Comparator-Controlled Trial of the Safety and Efficacy of Dalbavancin versus Active Comparator in Adult Patients with Osteomyelitis Known or Suspected to be due to Gram-Positive Organisms

STATISTICAL ANALYSIS PLAN

Final: August 29, 2016
Amendment #1: January 16, 2018

<u>2.0</u>   <u>TABLE OF CONTENTS</u>

3.0   **LIST OF ABBREVIATIONS**

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
bmp	beats per minute
BUN	blood urea nitrogen
CE	clinically evaluable
CI	confidence interval
CRP	C-reactive protein
eCRF	electronic case report form
ESR	erythrocyte sedimentation rate
GGT	gamma-glutamyl transpeptidase
HCO3	bicarbonate
ITT	intent to treat
IV	intravenous
LDH	lactate dehydrogenase
LLN	lower limit of normal value
ME	microbiologically evaluable
mITT	modified intent-to-treat
micro-mITT	microbiological modified intent-to-treat
mL	milliliter
PCS	potentially clinically significant
PID	patient identification
RBC	red blood cell

SAE	serious adverse event
SAP	statistical analysis plan
SI	*Le Système International d'Unités* (International System of Units)
SOC	standard of care
TEAE	treatment-emergent adverse event
ULN	upper limit of normal value
WBC	white blood cell

4.0   <u>**INTRODUCTION**</u>

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the final protocol of Study DAL-MD-04 (version dated June 23, 2015). Specifications of tables, figures, and data listings are contained in a separate document. The SAP for pharmacokinetic/pharmacodynamic data will be prepared separately.

This is a Phase 2, single-center, open-label, randomized, comparator -controlled, parallel-group trial of the safety and efficacy of dalbavancin versus active comparator in adult subjects with osteomyelitis known or suspected to be due to Gram-positive organisms. The study center will be located at Ukraine. Eligible subjects are male or female patients who are at least18 years of age that meet the diagnostic criteria for osteomyelitis defined as pain or point tenderness upon palpation or probing to bone, and either radiological findings consistent with a diagnosis of osteomyelitis or a bone specimen with Gram-positive cocci on a baseline Gram-stain.

Signed informed consent from the patient or the patient's legally authorized representative will be obtained before any study-related procedures are begun. Patients meeting the inclusion criteria will be randomized (7:1 ratio) to one of the 2 open-label treatment groups: dalbavancin treatment group or the comparator treatment group. Patients randomized to the dalbavancin treatment group will receive dalbavancin IV over 30 (+/-5) minutes on Day 1 and Day 8 (1500 mg for patients with normal renal function or 1000 mg for patients with chronic renal insufficiency) and patients in the comparator treatment group will receive oral or IV SOC antibiotic for osteomyelitis based on investigator judgment for 4-6 weeks. The patients will then be followed up for a period of 365 days.

Aztreonam may be administered at randomization for presumed co-infection with a Gram-negative pathogen and could be discontinued if a Gram-negative pathogen is not documented by culture results. A switch to an oral antibiotic for coverage of Gram-negative pathogens is allowed once evidence of clinical improvement has been established. Metronidazole (IV or oral) or oral vancomycin may be used for Clostridium difficile infections.

In the case of renal impairment, at any time, the dose of dalbavancin (including the initial dose) may be adjusted by the pharmacist or designee per the dosage regimen in Table 4-1 below. At any time, the dose of dalbavancin may be readjusted to the appropriate dosage when renal function improves.

Table 4-1. **Dalbavancin Dosage Adjustments for Renal Impairment**

Estimated Creatinine Clearance (mL/min)[a]	Recommended Dosage Regimen
≥ 30 and patients receiving regular hemodialysis or peritoneal dialysis	No adjustment: 1500 mg IV (over 30 minutes) on Day 1 and Day 8
< 30	1000 mg IV (over 30 minutes) on Day 1 and Day 8

a As calculated using the Cockcroft-Gault formula.

IV = intravenously.

Receipt of more than 24 hours of potentially effective intravenous antibacterial therapy for osteomyelitis within 96 hours of randomization is not allowed (unless the pathogen isolated was documented to be MRSA that was resistant to the administered antibiotic). Treatment with an investigational drug within 30 days prior to the first dose of study medication is not allowed. A patient who has had a prior failed course of therapy for osteomyelitis should not be enrolled.

Efficacy and safety assessments will be conducted at the clinic on Day 1, 8, 21, 28, 42, 180 and 365. Patients prematurely discontinuing from the study drug, regardless of cause, will be seen for premature discontinuation assessments. A patient who is withdrawn from the study should be encouraged to undergo the assessments for premature discontinuation on the day of withdrawal. Patients who do not complete all scheduled visits/procedures must be requested in writing to come in for a premature discontinuation visit and to return any unused investigational product. Randomized patients who are withdrawn will not be replaced.

The schedule of evaluations for Study DAL-MD-04 is presented in Table 4- below.
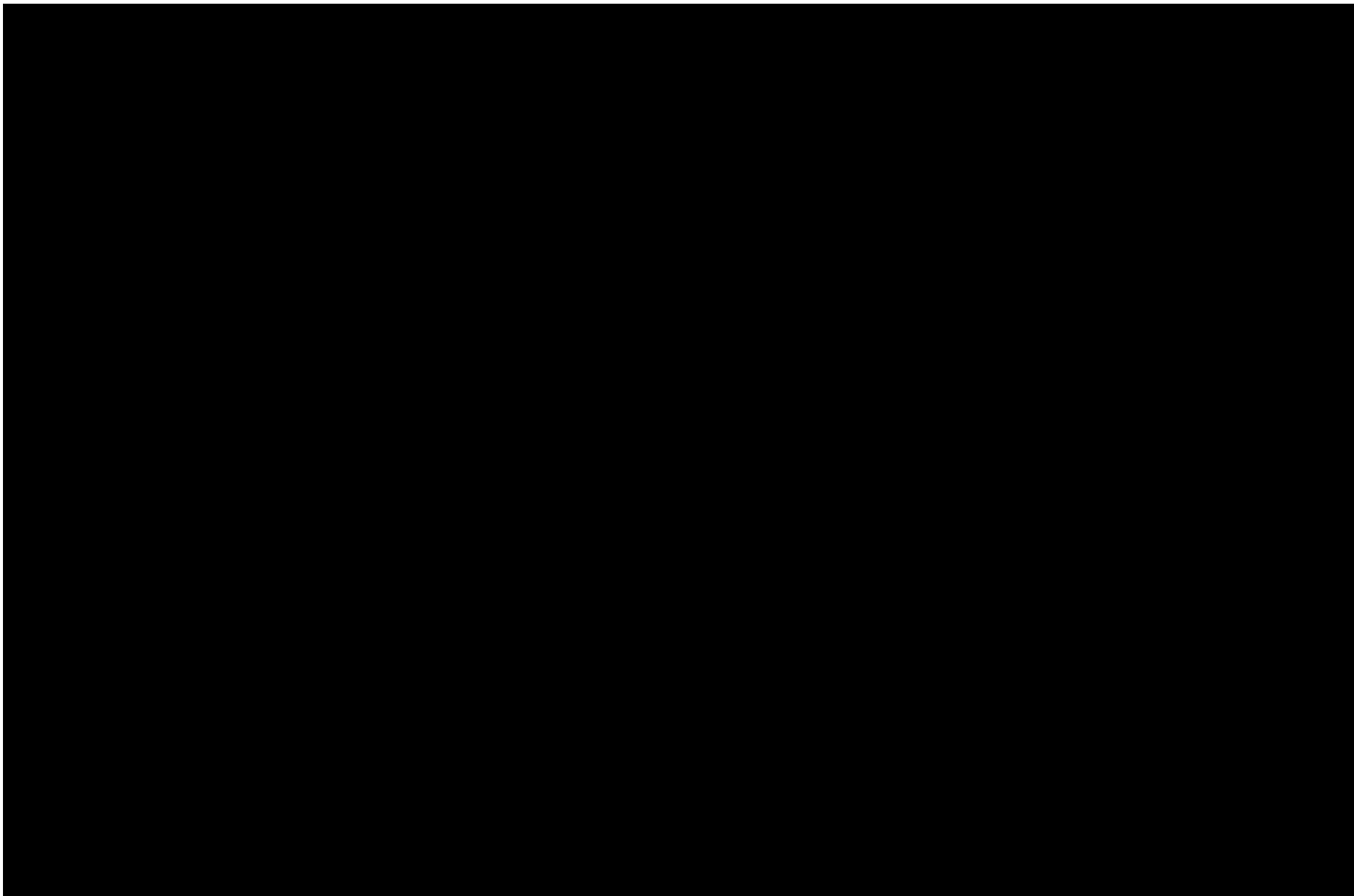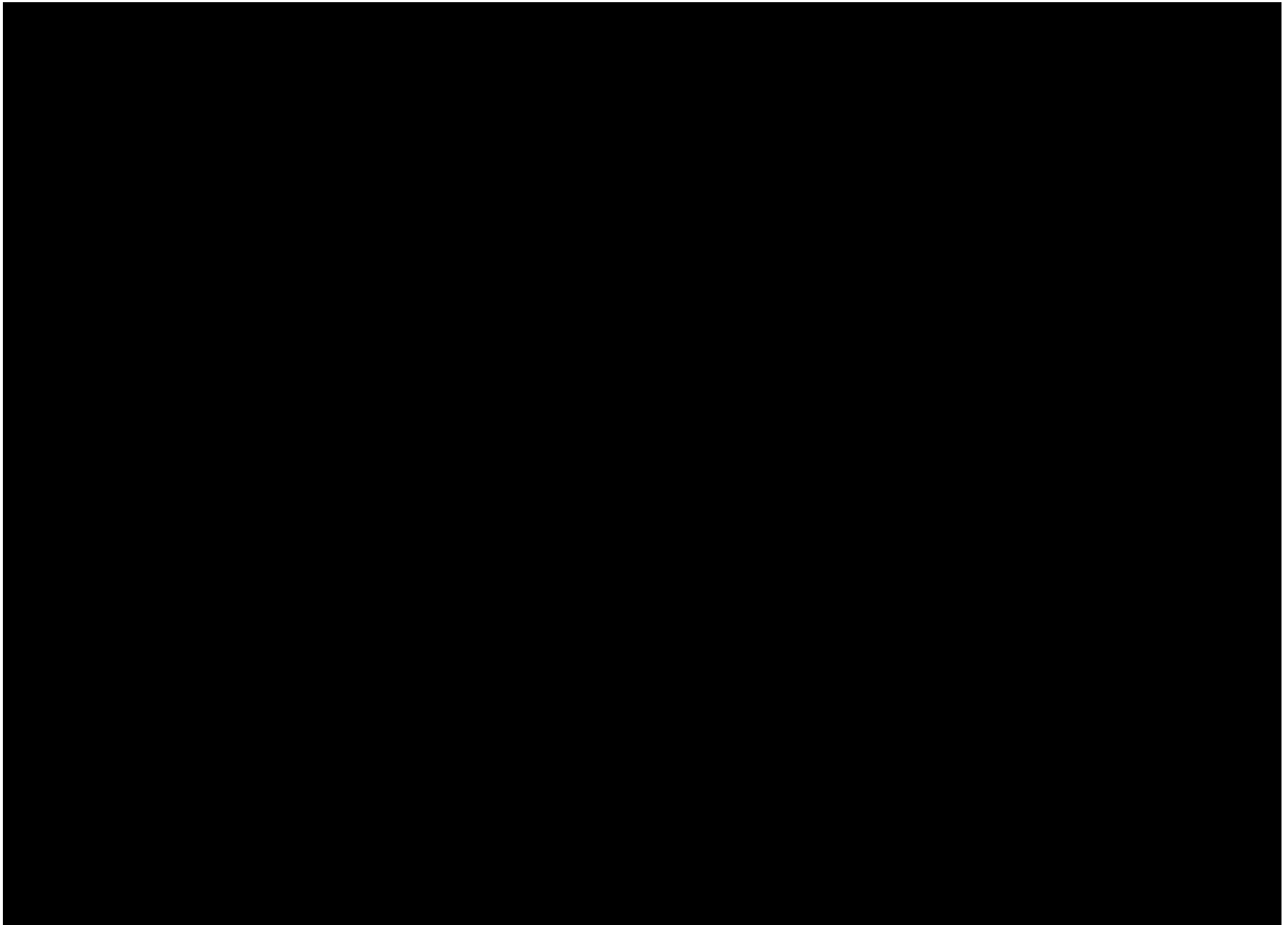
5.0   OBJECTIVES

The primary objective of this study is to determine the efficacy of dalbavancin for the treatment of the first episode of osteomyelitis known or suspected to be caused by Gram-positive pathogens in adults.

The secondary objectives of this study are:

- To assess the safety and tolerability of dalbavancin in adult patients with osteomyelitis;

- To estimate the clinical response rate per pathogen in the dalbavancin group at the end of therapy (Day 42) and Day 180;

- To estimate the clinical response rate in the dalbavancin group at Day 21, Day 180 and Day 365;

- To collect healthcare resource utilization in dalbavancin-treated and comparator-treated regimens.

6.0   PATIENT POPULATIONS

6.1   SCREENED POPULATION

The Screened Population will consist of all patients who undergo the Baseline Visit and receive a patient identification (PID) number.

6.2   INTENT-TO-TREAT POPULATION

The Intent-to-Treat Population will consist of all patients in the Screened Population who are randomized to a treatment group in the study.

6.3   SAFETY POPULATON

The Safety Population will consist of all patients in the ITT Population who receive any amount of randomized medication. Patients will be analyzed according to the treatment actually received.

6.4   MODIFIED INTENT-TO-TREAT POPULATION

The Modified Intent-to-treat (mITT) Population will consist of all patients in the ITT Population who receive any amount of randomized medication and meet the criteria for known or suspected Gram-positive osteomyelitis. Patients from whom only a Gram-negative pathogen is isolated from blood and/or bone culture will be excluded from the mITT. Patients whose cultures include both a Gram-positive and a Gram-negative pathogen will remain in the mITT. Patients will be analyzed according to randomized treatment group, regardless of treatment received.

6.5   CLINICALLY EVALUABLE POPULATIONS

The Clinically Evaluable (CE) Populations will be subsets of the mITT Population and will include patients who meet both of the following specific conditions for evaluability. Four CE populations will be defined based on the timing of the outcome assessment, CE-D21, CE-D42, CE-D180, and CE-D365.

- For patients randomized to receive dalbavancin, received at least 1 dose of active study medication. For patients randomized to comparator, received at least 2 weeks of study medication;

- Received no more than one dose of another (non-study) systemic antibacterial therapy with documented activity against the causative organism, from study drug initiation until the outcome assessment visit, for an indication other than osteomyelitis. [Note: patients receiving a non-study systemic antibacterial treatment for the treatment of osteomyelitis from initiation of study drug through the outcome assessment visit will be assessed as EVALUABLE FAILURES].

6.6   MICROBIOLOGICAL MODIFIED INTENT-TO-TREAT POPULATION

The Microbiological mITT (micro-mITT) Population will consist of all patients in the mITT Population with a Gram-positive pathogen isolated from blood and/or bone specimen. Patients whose cultures include both a Gram-positive and a Gram-negative pathogen will remain in the micro-mITT.

Figure 6–1.   Analysis Populations for Study DAL-MD-04
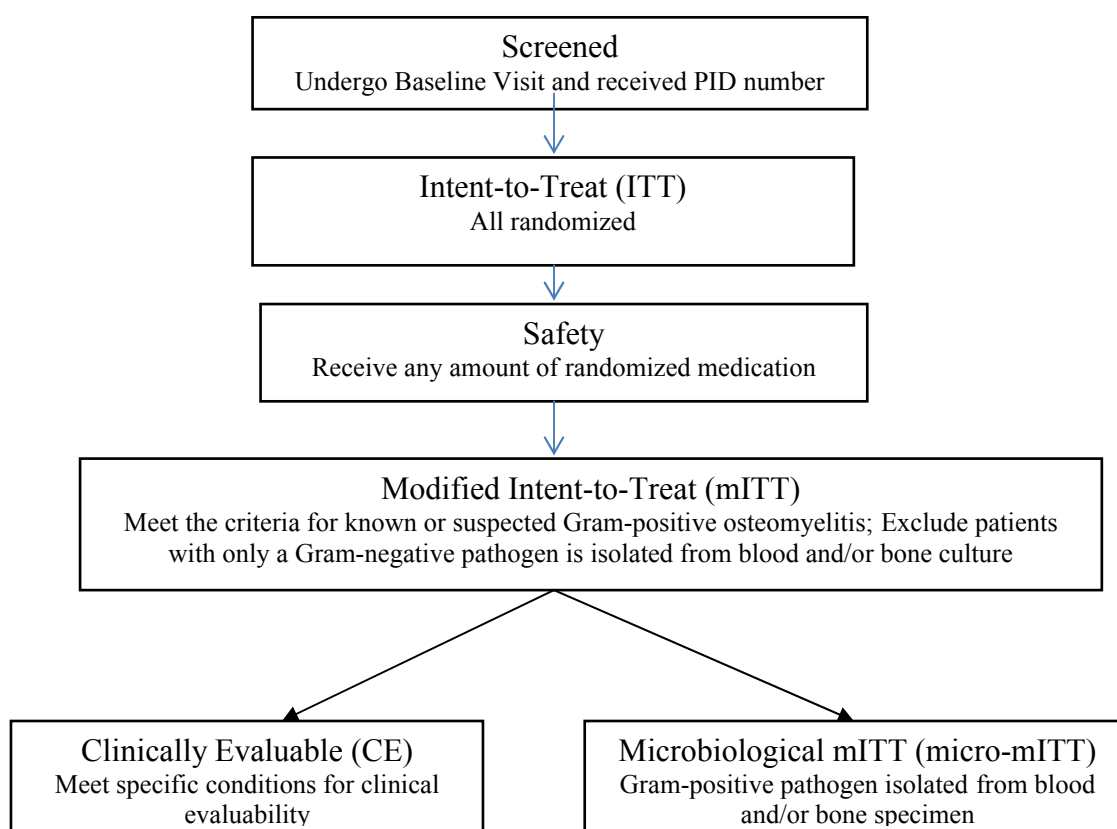
7.0   PATIENT DISPOSITION

The number of patients in each of the study population (ITT, Safety, mITT, CE-D21, CE-D42, CE-D180, CE-D365, and micro-mITT) will be summarized by treatment group and overall; the Screened Population will be summarized overall only.

Screen-failure patients (ie, patients screened but not randomized) and the associated reasons for failure to randomize will be tabulated overall for the Screened Population.

Patient disposition (enrollment, discontinuations from study drug and the study) by treatment group will be provided based on the ITT Population. Reasons for exclusion from study populations (Safety, mITT, CE-D21, CE-D42, CE-D180, CE-D365, and micro-mITT) will be summarized for the ITT Population.

The number and percentage of patients who complete the treatment period and of patients who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for the ITT Population. The reasons for premature discontinuation from the treatment period as recorded on the termination pages of the electronic case report form (eCRF) will be summarized (number and percentage) by treatment group for all randomized patients. All patients who prematurely discontinue during the treatment period will be listed by discontinuation reason for the ITT Population.

The number and percentage of patients with any significant protocol deviation, as well as each individual protocol deviation (including enrollment of a subject who did not meet all inclusion and exclusion criteria; wrong investigational product; investigational product dosing non-compliance; and prohibited concomitant medication), will be summarized and listed by treatment group for the ITT Population.

8.0   DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; race; sex; weight; height; and body mass index (BMI), calculated as weight [kg]/(height [m])^2) will be summarized by treatment group in the mITT and safety Population. Other baseline characteristics, including description of the osteomyelitis current episode at baseline, renal impairment status [creatinine clearance <30 mL/min or ≥ 30 mL/min]), and radiographic assessment will be summarized by treatment group in the mITT Population. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

Abnormalities in patients' medical and surgical histories will be coded using the *Medical Dictionary for Regulatory Activities,* version 19.0. The number and percentage of patients with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized by treatment group for the Safety Population.

Prior medication is defined as any medication taken before the date of the first dose of study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of study treatment. Medications that are ongoing at the time of first dose of randomized medication will be counted both as prior and concomitant.

Both prior and concomitant medications will be coded by drug name and therapeutic class. The use of prior and concomitant medications will be summarized by the number and percentage of patients in each treatment group for the Safety Population and micro-mITT population. If a patient took a specific medication multiple times or took multiple medications within a specific therapeutic class, that patient would be counted only once for the coded drug name or therapeutic class. Formulations (including salts, esters, etc) containing the same active ingredient will be pooled under the coded drug name of the base compound. Medications containing multiple active ingredients of different coded drug names will be reviewed during the course of the study and may be pooled under a single coded drug name for analyses. The proportion of patients who receive prior and concomitant use of antibiotics, analgesics and/or anti-inflammatory drugs, other drugs and non-drug therapy will be summarized by treatment group for the Safety and micro-mITT Population.

The WHO Drug Dictionary (WHODDMAR14) or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

8.1   MICROBIOLOGICAL ASSESSMENT

The microbiological assessment from blood and bone specimens will be summarized by treatment group for the mITT, CE-D42 and micro-mITT Population. A frequency distribution of the type of specimen, the result of the local Gram's stain, including organism characteristics will be presented. The number and percentage of patients with no growth/contaminant and positive for a pathogen will also be presented. The bacterial pathogens identified from the baseline blood culture will be presented as will the bacterial pathogens from only bone culture. The number and percentage of patients with isolated gram-positive pathogens (aerobes and anaerobes) and with isolated gram-negative pathogens (aerobes and anaerobes) will be presented by genus and species for the micro-mITT Population. The same pathogen identified from both the blood and the bone culture will be counted only once in the summary. In addition, the number and percentage of patients with mono-microbial and poly-microbial infections (gram-positive only and mixed infections [gram-positive and gram-negative]) will be provided overall and by infection type. A listing will be provided that includes all baseline and postbaseline isolates obtained from the blood and bone specimens and will indicate the type of specimen, and whether or not the isolate is considered the pathogenic organism. Microbiological assessment will be adjudicated and the summary table will be based on adjudicated data.

9.0   EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1   EXTENT OF EXPOSURE

Exposure to study drug will be summarized by treatment group for the Safety, mITT, CE-D42 and micro-mITT Population. For patients on dalbavancin treatment, the number and percent of patients receiving 1 or 2 doses will be tabulated. The dalbavancin dose received will be summarized based on baseline creatinine clearance ($\geq$30 mL/min or dialysis and <30 mL/min without dialysis) for Day 1 and based on most recent creatinine clearance for Day 8. For the comparator treatment, calendar days of exposure will be calculated as the number of calendar days on study drug. Calendar days on adjunctive IV therapy (Aztreonam) will also be summarized. For each type of exposure descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) will be presented.

9.2   TREATMENT COMPLIANCE

Each patient's compliance with study therapy will be calculated based on the number of doses of study drug the patient would have been expected to receive based on the number of treatment days, the specific dosing regimen indicated for the given drug, and the start and stop date and times of the first and last dose of each study drug. Treatment compliance is defined as the number of doses actually received divided by the number of doses expected ($\times$ 100) multiplied by 100.

Any partial infusion will be considered as a complete infusion for the purpose of compliance, and the relevant details will be listed. For each compliance measure, descriptive statistics (number of patients, mean, SD, minimum, median, and maximum value) and the number and percentage of patients whose compliance is < 80%, 80% - 100% and > 100% will be presented by treatment group for the Safety, mITT, CE-D42 and micro-mITT population.

10.0   EFFICACY ANALYSES

Baseline for efficacy analyses is defined as the last nonmissing efficacy measurement collected before the first dose of study treatment. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

For each efficacy parameter listed below, number and proportion of patients with categories of clinical responses will be presented by treatment groups, and the 2-sided 95% confidence intervals for the percentage of patients with favorable response will be obtained using the Clopper-Pearson method (Clopper and Pearson, 1934) for each treatment group unless stated otherwise. Due to the small sample size of comparator treatment arm, the between treatment comparison will not be provided.

For primary and secondary efficacy parameters, missing data will be imputed as failure.

10.1   PRIMARY EFFICACY PARAMETER

The primary efficacy parameter is the clinical response at Day 42 in the CE-D42 Population.
Clinical response can be either cure, failure, or indeterminate, as determined by investigator at Day 42:

- Cure is defined as recovery without need for additional antibiotic therapy.

- Failure is defined as:

  ○ Requirement of additional antibiotic therapy for no response or worsening after improvement

  ○ New purulence

  ○ Amputation due to progression of infection (from initiation of study drug to outcome assessment visit).

  ○ Requiring > 6 weeks of antibiotic therapy for patients in the comparator arm

  ○ Death (for any reason).

- Indeterminate is defined as:

  ○ Lost to follow-up

  ○ Amputation due to vascular insufficiency (from initiation of study drug to outcome assessment visit).

The number and percentage of clinical cure, clinical failure and indeterminate will be tabulated by treatment group. The 95% confidence interval for the percentage of clinical cure will be calculated using the method of Clopper-Pearson method (Clopper and Pearson, 1934).

10.2   SECONDARY EFFICACY PARAMETERS

The following are the secondary efficacy parameters:

* Clinical improvement at Day 21 in the mITT and CE-D21 Populations Clinical improvement is defined as no worsening of pain from baseline (if present at baseline) (subjective pain and/or point tenderness [categorized as absent, mild, moderate, severe]) and improvement in inflammation (as measured by decreased CRP at Day 28). Clinical improvement will be determined by investigator at Day 21.

* Clinical response (cure, failure, or indeterminate) at Day 42 in the mITT and micro-mITT Populations

* Clinical response (cure, failure, or indeterminate) at Day 180 in the mITT and CE-D180 Population

* Clinical response (cure, failure, or indeterminate) at Day 365 in the mITT and CE-D365 Population

* Clinical response (cure, failure, or indeterminate) by pathogen at Day 42 and Day 180 in the corresponding CE Population.

For all the secondary parameters listed above, the number of percentage of patients within each category will be summarized by treatment group. The 95% confidence interval for the percentage of patients with outcome of cure will be calculated using the method of Clopper-Pearson method (Clopper and Pearson, 1934). For clinical response by pathogen, 95% confidence intervals will be calculated only for pathogens for which sample sizes are greater than 10 in the dalbavancin group.

11.0   SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs) and clinical laboratory, vital sign, plain film radiography, and microbiology. For each safety parameter of the clinical laboratory, the last nonmissing safety assessment before the first dose of study treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

11.1   ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities,* version 19.0 or newer.

An AE will be considered a treatment-emergent adverse event (TEAE) if it was present after the initiation of the first dose of study treatment or was present before the initiation of the first dose of study treatment and increased in severity after the first dose of study treatment. If more than 1 AE was reported before the first dose of study treatment and coded to the same preferred term, the AE with the greatest severity will be used for comparison with the AEs occurring during the study.

Overall summary of AEs will be provided on a per-patient basis for categories of all TEAEs, treatment-related TEAEs, serious adverse events (SAEs), deaths, AEs leading to study discontinuation, and AEs leading to discontinuation of the study treatment.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by descending percentage in any group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study treatment. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.

The incidence of common ($\geq 2\%$ of patients in any treatment group) TEAEs will be summarized by system organ class, preferred term, and treatment group.

The total number of TEAEs by severity and causal relationship to the study treatment will be summarized by treatment group.

The number and percentage of patients who have SAEs will be summarized by preferred term and treatment group. In addition, the incidence of on-therapy SAEs that led to death will be summarized separately by preferred term for each treatment group.

The number and percentage of patients in the Safety Population who have treatment related TEAEs leading to premature discontinuation of the study treatment will be summarized by preferred term and treatment.

For the all screened patients, separate tabular displays will be presented for patients who died, patients with SAEs, and patients with AEs leading to premature discontinuation of the study.

11.2   CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for the following continuous laboratory parameters:

Hematology: Basophils (absolute count and %), eosinophils (absolute count and %), erythrocyte count, hematocrit, hemoglobin, lymphocytes (absolute count and %), monocytes (absolute count and %), neutrophils (absolute count and %), immature neutrophils (bands; %), platelet count. Hematology test will be performed at Baseline, Day 8, Day 28 (+/- 2 days), and at time of premature discontinuation.

Serum Chemistry: Albumin, ALP, AST, ALT, bilirubin (total and direct), blood urea nitrogen, calcium, creatinine, electrolytes (ie, bicarbonate, chloride, potassium, sodium), gamma-glutamyl transferase, glucose (nonfasting), lactate dehydrogenase, magnesium, protein (total). Chemistry test will be performed at Baseline, Day 8, Day 28 (+/- 2 days), and at time of premature discontinuation.

CRP: Baseline, Day 8, Day 28 (+/- 2 days), Day 42 (+/- 3 days), Day 180 (+/- 7 days), and at time of premature discontinuation.

ESR: Baseline, Day 8, Day 28 (+/- 2 days), Day 42 (+/- 3 days), Day 180 (+/- 7 days), and at time of premature discontinuation.

Pregnancy Test will be performed only on female patients of childbearing potential only, including those who are fewer than 2 years postmenopausal. Blood or urine sample at baseline, Day 28 (+/- 2 days), Day 42 (+/- 3 days) and at time of premature discontinuation will be obtained.

Detailed patient listings of all the laboratory data collected during the study will be provided.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11.2-1. The number and percentage of patients who have PCS postbaseline clinical laboratory values will be tabulated by treatment group for the treatment period. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind treatment period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value for the treatment period. A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, study center number, and baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all AEs that occurred in patients who had PCS postbaseline clinical laboratory values will be provided.

Table 11.2–1.   **Criteria for Potentially Clinically Significant Laboratory Results**

Laboratory Group	Parameter	SI Unit	PCS Low Limit	PCS High Limit
Hematology	Band Neutrophils Percent	%	NA	> 4.0 × ULN
	Basophils Absolute Cell Count	10^9/L	NA	> 4.0 × ULN
	Basophils Percent	%	/	> 4.00×ULN
	Eosinophils Absolute Cell Count	10^9/L	NA	> 4.0 × ULN
	Eosinophils Percent	%	NA	> 4.0 × ULN
	Hematocrit	%	< 0.6 × baseline	> 1.3 × ULN
	Hemoglobin	g/L	< 0.6 × baseline	> 1.3 × ULN
	Lymphocytes Absolute Cell Count	10^9/L	< 0.2 × LLN	> 2.2 × ULN
	Lymphocytes Percent	%	< 0.2 × LLN	> 2.2 × ULN
	Monocytes Absolute Cell Count	10^9/L	NA	>4.00×ULN
	Monocytes Percent	%	NA	>4.00×ULN
	Neutrophill Absolute Cell Count	10^9/L	< 0.5 × LLN	> 2.2 × ULN
	Neutrophils Percent	%	< 0.5 × LLN	> 2.2 × ULN
	Immature Neutrophill Bands	10^9/L	NA	>3 x ULN

Laboratory Group	Parameter	SI Unit	PCS Low Limit	PCS High Limit
	Immature Neutrophils Percent	%	NA	>3 x ULN
	Platelet Count (thrombocytes)	10^9/L	< 0.4 × LLN	> 2.0 × ULN
	Red Blood Cell Count	10^{12}/L	< 0.8 × LLN	> 1.3 × ULN
	White Blood Cell Count	10^9/L	< 0.5 × LLN	> 2.0 × ULN
Chemistry	Alanine Aminotransferase (ALT)	U/L	NA	> 3 × ULN
	Albumin	g/L	< 0.8 × LLN	NA
	Alkaline Phosphatase	U/L	NA	> 3 × ULN
	Aspartate Aminotransferase (AST)	U/L	NA	> 3 × ULN
	Bicarbonate (HCO3)	mmol/L	< 0.7 × LLN	> 1.3 × ULN
	Bilirubin, Direct (Conjugated)	μmol/L	NA	> 2.5 × ULN
	Bilirubin, total	μmol/L	/NA	> 2.0 × ULN
	Blood Urea Nitrogen	mmol/L	NA	> 1.3 × ULN
	Calcium	mmol/L	< 0.9 x LLN	>1.1 x ULN
	Chloride	mmol/L	< 0.80×LLN	NA
	Creatinine	μmol/L	< 0.6 x LLN	> 1.3 × ULN
	Gamma Glutamyl Transferase (GGT)	U/L	NA	> 3 × ULN
	Glucose	mmol/L	< 0.6 x LLN	> 2.5 x ULN
	Lactate Dehydrogenase	U/L	NA	> 3 × ULN
	Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Protein, Total	g/L	< 0.8 x LLN	NA
	Sodium	mmol/L	< 0.95 × LLN	> 1.1 × ULN

LLN = lower limit of normal value provided by the laboratory; SI = Le Système International d'Unités (International System of Units); ULN = upper limit of normal value provided by the laboratory.

11.3   VITAL SIGNS

Descriptive statistics for vital signs (systolic and diastolic blood pressures, respiration rate, temperature and pulse rate) and changes from baseline values at each visit and at the end of study will be presented by treatment group.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 11.3–1. The number and percentage of patients with PCS postbaseline values will be tabulated by treatment group. The percentages will be calculated relative to the number of patients with available baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available baseline values and at least 1 PCS postbaseline value. A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, baseline and postbaseline values.

In addition, a tabular display showing all AEs that occurred in patients who had PCS postbaseline vital sign values will be provided.

Table 11.3–1.   *Criteria for Potentially Clinically Significant Vital Signs*

| *Parameter* | *Flag* | *Criteria[a]* | |
		Observed Value	*Change From Baseline*
systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 30
	Low	≤ 90	Decrease of ≥ 30----
diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 20
	Low	≤ 50	Decrease of ≥ 20
Respiration Rate	High	>20	---
	Low	<12	---
Temperature	High	>39	----
	Low	< 36	---
pulse rate, bpm	High	≥ 130	
	Low	≤ 40	

a. A postbaseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.
bpm = beats per minute.

11.4   OTHER SAFETY PARAMETERS

11.4.1   Physical Examination

A complete physical examination (including targeted examination of the infection site) will be conducted at Baseline by a professionally trained physician or health professional licensed to perform physical examinations which includes: head, eyes, ears, nose, throat, neck, skin, heart, lungs, abdomen, neurologic system, extremities, height, and body weight. If height or weight is not obtainable (eg, patient is immobilized), the last known or stated height and weight may be used. Abnormal physical examination findings will be presented as data listings.

A targeted examination of the infection site will be performed on Day 8, 21, 28, 42, 180, and 365 as well as upon premature discontinuation. Any abnormal findings will be presented in the data listing.

11.4.2   Plain Film Radiography

A detailed listing of the radiograph and MRI of extremity under study at baseline and at each follow-up visit or time of discontinuation will be provided.

11.4.3   Potential Hy's Law

Criteria for potential Hy's Law cases are as follows:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 3 \times$ ULN AND

- Total bilirubin $\geq 2 \times$ ULN AND

- Alkaline phosphatase (ALP) $< 2 \times$ ULN

Patients who meet the potential Hy's Law criteria will be summarized for the Safety Population. Supportive tabular displays will also be provided.

13.0   <u>INTERIM ANALYSIS</u>

No interim analysis is planned for this study.

### 14.0   DETERMINATION OF SAMPLE SIZE

The study is not powered for comparative inferential statistical analyses.

The planned enrollment of 70 patients in the dalbavancin treatment arm will result in a 2-sided 95% confidence interval with the approximate half-width of 11% for the proportion of patients with a clinical cure when the expected proportion is 65%. Higher observed favorable response rates will result in improved precision. The precision for the comparator arm is not estimated due to the small sample size. The comparator arm is intended to provide information on SOC treatment regimens and overall generalizability of study findings, and is not intended to provide a statistically powered comparison of efficacy.

15.0   STATISTICAL SOFTWARE

Statistical analyses will be performed using version ▮▮▮▮▮▮▮▮▮▮▮▮▮
▮▮▮▮▮▮▮▮

16.0   DATA HANDLING CONVENTIONS
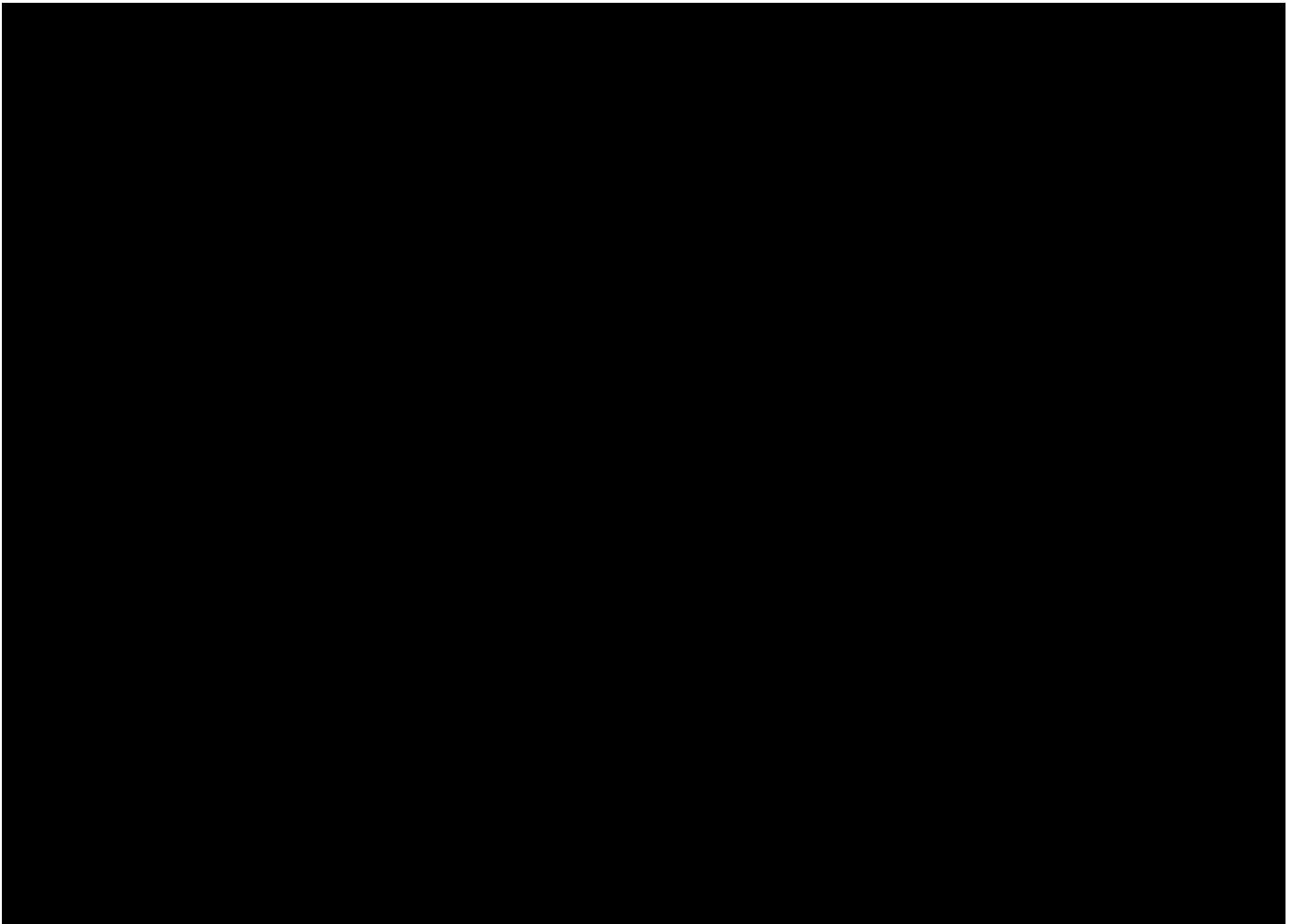
If the assessment date (if the assessment date is unavailable, use visit date instead) is on or after the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment + 1. If the assessment date is before the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment. Therefore, a negative day indicates a day before the start of the study treatment.

If a patient has 2 or more visits within the same window, the visit closest to the targeted visit date and with a nonmissing value will be used for analysis.

16.2   REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated assessments before the start of the first treatment, the results from the final nonmissing assessment made prior to the start of the study treatment will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

16.3   MISSING DATE OF THE LAST DOSE OF INVESTIGATIONAL PRODUCT

When the date of the last dose of study treatment is missing for a patient in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date.

16.4   MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.5   MISSING CAUSAL RELATIONSHIP TO STUDY TREATMENT FOR ADVERSE EVENTS

If the relationship to the study treatment is missing for an AE that started on or after the date of the first dose of study treatment, a causality of "related" will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.6   MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment , the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only
- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study treatment, the date of the first dose of study treatment will be assigned to the missing start date

- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date

16.7 **MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS**

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

16.7.1 **Incomplete Start Date**

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day
- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only
- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

16.7.2   Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, impute it as described in Section 16.4. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

Missing month and day
- If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only
- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study treatment, the first day of the month will be assigned to the missing day

17.0   DATA COLLECTED BUT NOT ANALYZED

None.

18.0   CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

None.

19.0   REFERENCES

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934; 26:404–13.

20.0   HISTORY OF CHANGES

Amendment: #1

Date	Section(s)	Description
3/13/2017	16.1	• In Table 16.1-1 the phrase "and Safety" is added to the title to read "Visit Time Windows for Efficacy and Safety Analysis", as this. • In Table 16.1-1 the typographical error for the baseline window is corrected - from 2 to 24 - to read "Within 24 hours prior to first dose (Day -1 to 1)".
12/15/2017	16.1	• In Table 16.1-1 the analysis windows are broadened to avoid leaving observations in gaps.
12/21/2017	6.5	• Four clinical evaluable (CE) populations are defined according to when the outcome measure occurs.
12/21/2017	7	• CE populations are updated in the disposition analysis
12/21/2017	10	• Appropriate CE populations for specific visit are updated
12/21/2017	8	• Limitations for prior medication and concomitant medications being presented in the summary tables are deleted
12/21/2017	11.1	• AE leading to discontinuation of study and study drug are clarified
12/21/2017	Multiple places	• Typo micro-ITT has been corrected to micro-mITT
1/16/2018	10.3	• Repetitive wordings are deleted

1.0   TITLE PAGE

Durata Therapeutics International BV (an Allergan Affiliate)
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DAL-MD-04

A Phase 2, Single-center, Open-label, Randomized, Comparator-Controlled Trial of the Safety and Efficacy of Dalbavancin versus Active Comparator in Adult Patients with Osteomyelitis Known or Suspected to be due to Gram-Positive Organisms

STATISTICAL ANALYSIS PLAN ADDENDUM

SAP Approval: August 29, 2016
SAP Amendment #1: January 16, 2018
Addendum: April 13, 2018

2.0   <u>**TABLE OF CONTENTS**</u>

3.0   LIST OF ABBREVIATIONS

AE   adverse event

4.0   SUMMARY OF CHANGES

Here are the changes to analysis tables and listings:

1, Add new table 14.2.10D "Monomicrobial and Polymicrobial Infections at Baseline by Infection Type" to summarize baseline characteristic for Monomicrobial and Polymicrobial infections.

2, Add new table 14.3.1.2E "Total IV Infusion Duration" to summarize average IV infusion time at patient level over mITT population for both Comparator arm and Dalbavancin arm.

3, Add new listing 16.2.4.2B "Comparator Dosing Data" to summarize IV infusion time at patient level for comparator arm.

4, Add new listing 16.2.4.2C "Aztreonam Dosing Data by Treatment Group" to summarize Aztreonam IV infusion time at patient level for Dalbavancin arm.

1. Title Page

HEALTH ECONOMICS AND OUTCOMES RESEARCH

STATISTICAL ANALYSIS PLAN

A Phase 2, Single-center, Open-label, Randomized, Comparator-Controlled Trial of the Safety and Efficacy of Dalbavancin versus Active Comparator in Adult Patients with Osteomyelitis Known or Suspected to be due to Gram-Positive Organisms

Draft 1.0: 2017-09-08

Protocol Number:	DAL-MD-04
Development Phase:	2
Product Name:	Dalbavancin
Study Statistician:	███████████
HO-SAP Statistician:	████████
Sponsor:	Allergan, plc.

2. Table of Contents

2.1 List of Tables

3.   List of Abbreviations

Table 3-1   **Abbreviations and Definitions of Terms**

Abbreviation/Term	Definition
CE	clinically evaluable
eCRF	Electronic case report form
ER	Emergency room
IV	Intravenous
HEOR	health economics and outcomes research
HRU	health resource utilization
PID	patient identification
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
ITT	intent-to-treat
mITT	modified intent-to-treat
mg	milligram
LOS	length of stay

4. Introduction

This health economics and outcomes research (HEOR) statistical analysis plan (HO-SAP) details the statistical analyses of the health outcomes data specified in the final protocol of Study DAL-MD-04 (version dated June 23, 2015). Specifications of tables, figures, and data listings are contained in a separate document. The SAPs for efficacy, safety, and pharmacokinetics/pharmacodynamics data will be prepared separately.

Information regarding patient satisfaction with dalbavancin and Standard of Care (SOC) comparators is collected through the patient satisfaction questionnaire. Healthcare resource utilization in dalbavancin-treated and comparator-treated subjects are also collected in the study to reflect the way patients interact with health care providers and provide information on the health status of the analysis population under examination and availability of resources. The health outcome assessments are performed according to the schematic presented in the study protocol Table 2-1 (Schedule of Evaluations).

4.1 Study Design

This is a Phase 2, single-center, randomized, open-label, active-controlled, parallel-group study comparing dalbavancin to SOC therapy in adult subjects with osteomyelitis known or suspected to be due to Gram-positive organisms. Patients meeting the inclusion criteria will be randomized with 7:1 ratio to one of the 2 open-label treatment groups: dalbavancin treatment group or the comparator treatment group. Patients randomized to the dalbavancin treatment group will receive dalbavancin IV on Day 1 and Day 8 (1500 mg for patients with normal renal function or 1000 mg for patients with chronic renal insufficiency). Patients in the SOC treatment group will receive oral or IV SOC antibiotic for osteomyelitis based on investigator judgment for 4 to 6 weeks. The patients will then be followed up for a period of 365 days.

4.2 Study Objectives and Primary Endpoints

The primary study objective is to determine the efficacy of dalbavancin for the treatment of the first episode of osteomyelitis known or suspected to be caused by Gram-positive pathogens in adults.

The secondary study objectives are:

- To assess the safety and tolerability of dalbavancin in adult patients with osteomyelitis;
- To estimate the clinical response rate per pathogen in the dalbavancin group at the end of therapy (Day 42) and Day 180;
- To estimate the clinical response rate in the dalbavancin group at Day 21, Day 180 and Day 365; and
- To collect healthcare resource utilization in dalbavancin-treated and comparator-treated regimens.

The primary efficacy parameter is the clinical response at Day 42 in the Clinically Evaluable (CE) Population. Clinical response can be either cure, failure, or indeterminate, as determined by investigator at Day 42. Please refer to the clinical SAP Section 10.1 for additional details.

5. Objectives

The objectives of the statistical analyses of HEOR parameters are:

- To assess patients' satisfaction and preference for the treatment of dalbavancin and active comparator in patients with osteomyelitis known or suspected to be due to Gram-Positive organisms; and

- To characterize health resource utilization for the antibiotic treatment of dalbavancin and SOC comparator.

6.2   Healthcare Resource Utilization

Healthcare resource utilization in cases where the primary reason for the consumption of the identified healthcare resource is the treatment of osteomyelitis, or any related complications will be assessed. The following resource utilization data will be analyzed.

Care pathway
- Number admitted to the hospital (received the first dose of IV study drug as an inpatient) versus treated in outpatient setting (i.e., emergency room/department), defined as receiving the first dose of IV study drug in an emergency room/department outpatient setting.

Counts of visit types:

- Number of composite visits (i.e. all types of visits including all ER visits, unplanned physician visits);
- Number of ER visits for emergency room or department to receive IV study drug infusion;
- Number of unplanned visits to use the emergency room or department for the indication under study;
- Number (and percentage) of patients experiencing worsening, AE and other among those who had at least 1 unplanned visit to the emergency room;
- Number of unplanned visits to a physician's office for the indication under study;
- Number (and percentage) of patients experiencing worsening, AE or other among those who had unplanned visit to the physician's office; and
- Number of patients receiving indwelling venous catheter.

Duration of care:

- Days of IV antibiotic treatment for the indication under study;
- Days of antibiotic treatment (i.e. any route, including IV antibiotic or oral antibiotic treatment) of antibiotic therapy for the indication under study;
- Days of hospitalization (length of stay), calculated as the date of hospital discharge – date of admission + 1. In case that a patient has more than one episodes of hospitalization, days of hospitalization is the average length of stay in days, calculated by dividing the sum of inpatient days by the number of admissions;
- Hospital admissions
  - Summary statistics (mean, median, etc.):
    - Length of stay (LOS) of initial hospitalization;
    - LOS of all hospitalizations, including initial hospitalization (all-cause);

- o Distribution of admissions (i.e. number of patients with 0, 1, 2, 3, >3 admissions)
- Duration of catheter placement, calculated as catheter end date – catheter start date + 1; and

- Hospital readmission rate, calculated as the percentage of patients with hospital readmission. Hospital readmission is defined as patient admission to a hospital within 30 days after being discharged from the initial hospital stay (if admitted initially)

- Hospital readmission rate, calculated as the percentage of patients with hospital readmission. Hospital readmission is defined as patient admission to a hospital within 60 days after being discharged from the initial hospital stay (if admitted initially)

7. Statistical and Analytical Plan

7.1 Determination of Sample Size for Health Outcome Parameters

The study sample size justification is not based on the health outcomes parameters. However, the analysis population for health outcomes parameters is determined by the nature of the purpose of the collection of data which will be described in Section 7.5.2.

7.2 Software

Statistical analyses will be conducted using ████████████████████████████████ ██████████████ .

7.3 Subgroup Analyses

Two subgroups will be used for the analysis of the patient satisfaction questionnaire data:

- Subgroup of 'Currently hospitalized' includes any subjects in the mITT Population (defined in Section 7.5.2) who respond *Yes* to the sub-question 'Are you currently hospitalized?' on the questionnaire; and

- Subgroup of 'Not currently hospitalized' includes any subjects in the mITT Population who respond *No* to the sub-question 'Are you currently hospitalized?' on the questionnaire.

7.4 Interim Analyses

Not applicable.

7.5 Common Conventions

7.5.1 Analysis Visit Windows

The visit time windows specified in Section 16.1 of the clinical SAP will be applied to the analyses of the patient satisfaction questionnaire.

7.5.2 Analysis Populations

The Screened Population will consist of all patients who undergo the Baseline Visit and receive a patient identification (PID) number.

The Intent-to-Treat Population will consist of all patients in the Screened Population who are randomized to a treatment group in the study.

The Modified Intent-to-treat (mITT) Population will consist of all patients in the ITT Population who receive any amount of randomized medication and meet the criteria for known or suspected Gram-positive osteomyelitis. Patients from whom only a Gram-negative pathogen is isolated from blood and/or bone culture will be excluded from the mITT. Patients whose cultures include both a Gram-positive and a Gram-negative pathogen will remain in the mITT. Patients will be analyzed according to randomized treatment group, regardless of treatment received. All of the analyses in this plan are based on the mITT Population.

7.5.3 Imputation of Missing Values

All the analyses addressed in this plan will be based on the observed data without imputation, unless otherwise specified.

7.5.4 Study Treatments

The following treatment groups are defined for this study:

- Dalbavancin

- SOC Comparator

7.5.5 Baseline and Change from Baseline

Not applicable.

7.5.6 Statistical Methodology

The methodologies defined below apply as specified to individual endpoints defined in this SAP.

Table 7-1   Statistical Methodology

Methodology	Description
Categorical descriptive	- Number and percentage of patients in individual categories - Patients with ≥ 1 qualifying event counted once per individual category - Add a missing category if missing exists (i.e., if percentage denominator ≠ number of patients in the population (standard percentage denominator)
Continuous descriptive	- N1, mean, standard deviation (SD), median, minimum, maximum - Add lower and upper quartiles (i.e., 25th and 75th percentiles) as appropriate - N1 = number of patients with non-missing value

7.6   Analysis of Health Outcomes Endpoints

Summary statistics as described in Table 7-1 will be presented for each treatment group as well as the overall population for each health outcome endpoint. For the patient satisfaction questionnaire, frequency and percentage of item responses will also be summarized by visit (Day

8, 21, 28 and 42) for the subgroups of 'Currently hospitalized' (items 1, 4-10) and 'Not currently hospitalized', separately. The healthcare resource utilization parameters described in Section 6.2 will be summarized by treatment group as appropriate. In addition, the proportion of patients who utilize each healthcare resource will be summarized by treatment group.

7.7   Multiple Comparisons Procedure

Not applicable.

8. References

[text redacted]