1. Title Page

STATISTICAL ANALYSIS PLAN

A Phase 3, Multicenter, Open-Label, Randomized, Comparator Controlled Trial of the Safety and Efficacy of Dalbavancin versus Active Comparator in Pediatric Subjects with Acute Bacterial Skin and Skin Structure Infections

Final: 2020-11-06

Protocol Number:	DUR001-306
Development Phase:	3
Product Name:	Dalbavancin
Study Statistician:	[redacted] PhD; [redacted] MS
Sponsor:	Allergan Sales, LLC and Allergan Ltd.

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3. List of Abbreviations and Definition of Terms

Table 3-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
ABSSSI	acute bacterial skin and skin structure infections
AE	adverse event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood Urea Nitrogen
CE	Clinically Evaluable
CFB	change from baseline
eCRF	electronic case report form
EOT	End of Treatment Visit
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transpeptidase
hs-CRP	High-sensitivity C-reactive Protein
ICH	International Conference on Harmonisation
ITT	intent-to-treat
IV	Intravenous
IWRS	Interactive Web Randomization System
LDH	Lactate Dehydrogenase
ME	Microbiologically Evaluable
MedDRA	Medication Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRSA	Methicillin-resistant Staphylococcus aureus
PCS	potentially clinically significant
PK	pharmacokinetic
PID	patient identification
PP	per-protocol
PT	preferred term
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SI	Le Système International d'Unités (International System of Units)
SOC	system organ class
TEAE	treatment-emergent adverse event
TOC	Test of Cure (visit)
VRE	vancomycin-resistant enterococci
WBC	White Blood Cell
WHO	World Health Organization

4. Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy and safety data outlined and/or specified in the final protocol of Study DUR001-306 and the most recent amendment (Amendment 6, dated 26 April 2018). [redacted] Specifications of tables, figures, and data listings are contained in a separate document. The details of the analysis of pharmacokinetic (PK) and health outcome data collected as part of this protocol are not the scope of this SAP and will be detailed in separate analysis documents.

This document is organized into 3 main sections:

1. Study Overview
2. Statistical Methodology and Study Endpoints
3. Data Handling and Analysis Conventions

4.1 Study Design Summary

This is a Phase 3, multicenter, open-label, randomized, comparator controlled trial evaluating the safety and efficacy of a single dose of intravenous (IV) dalbavancin and a two-dose regimen of once weekly IV dalbavancin (for a total of 14 days of coverage) for the treatment of acute bacterial skin and skin structure infections known or suspected to be due to susceptible Gram-positive organisms in children, from birth to 17 years (inclusive). The comparators are either IV vancomycin (for methicillin-resistant Gram-positive infections) or IV oxacillin or flucloxacillin (for methicillin-susceptible Gram-positive infections) for 10-14 days. Patients may be switched from IV oxacillin or flucloxacillin to oral cefadroxil after at least 72 hours of study drug treatment, if they meet specified criteria for oral therapy. Similarly, if infection with methicillin-resistant *S. aureus* (MRSA) is documented, then patients may be switched from IV vancomycin to oral clindamycin after at least 72 hours of parenteral antibiotic therapy, if they meet specified criteria for oral therapy. If an alternate comparator regimen is indicated by local susceptibility patterns, this must be discussed with the medical monitor. In Cohort 5 (birth to < 3 months) only the single-dose regimen of dalbavancin (22.5 mg/kg) will be evaluated. At the discretion of the investigator, concomitant therapy based on local standard of care may be added to the single-dose regimen of dalbavancin, as clinically indicated, in Cohort 5. Cohort 5 will be initiated based on review of initial results from patients > 28 days to < 3 months in study DAL-PK-02 (DUR001-107).
Eligible patients from birth to 17 years of age (inclusive) with acute bacterial skin and skin structure infection will be enrolled. Approximately 188 patients will be enrolled, with 178 patients 3 months or older randomized to receive dalbavancin (single-dose or two-dose regimen) or comparator, in a 3:3:1 randomization scheme: 76 patients will be randomized to dalbavancin (single dose IV), 76 patients will be randomized to dalbavancin (2 IV doses one week apart), and 26 patients will be randomized to comparator (IV vancomycin or IV oxacillin or flucloxacillin). The randomization scheme will not include the youngest age cohort (birth to < 3 months of age),

as all 10 patients in this cohort will receive the single-dose regimen of dalbavancin, bringing the total number of patients enrolled in the study to approximately 188 patients. No patient in Cohort 5 (birth to < 3 months) will be randomized to the comparator arm. The enrollment target of 10 patients for Cohort 5 includes at least 5 patients ≤ 28 days (including pre-term neonates).

There will be 5 age cohorts:

- Cohort 1--12 years to 17 years old, inclusive;
- Cohort 2--6 years to < 12 years old,
- Cohort 3--2 years to < 6 years old,
- Cohort 4--3 months to < 2 years old, and
- Cohort 5--birth to < 3 months of age (including pre-term neonates with gestational age ≥ 32 weeks).

With the exception of Cohort 5, patients will be randomized 3:3:1 to each of the three treatment groups. In Cohorts 3 and 4 (enrolling patients aged 2 years to < 6 years old, and 3 months to < 2 years old, respectively), there will be approximately 15 patients in each dalbavancin arm, and 5 patients in each comparator arm. In Cohorts 1 and 2 (enrolling patients 12 years to 17 years old, inclusive and 6 years to < 12 years old, respectively), there will be approximately 23 patients in each dalbavancin arm, and 8 patients in each comparator arm.

4.2 Study Objectives and Endpoints

Each study objective is presented with corresponding endpoint(s) below:

Objectives	Endpoints
Primary • To determine the safety and descriptive efficacy of dalbavancin for the treatment of acute bacterial skin and skin structure infections in children, from birth to 17 years (inclusive), known or suspected to be caused by susceptible Gram-positive organisms, including methicillin- resistant strains of *Staphylococcus aureus* **Secondary** • To assess clinical response at 48-72 hours post randomization (defined as ≥ 20% reduction in lesion size compared to baseline) measured in patients who did not receive rescue therapy and are alive (Cohorts 1 – 4), In Cohort 5 (birth to < 3 months), clinical response in patients with ABSSSI at 48-72 hours post-randomization is defined as cessation	**Safety Assessments** • Physical examination, vital signs, adverse events, deaths (Cohort 5 only), and clinical laboratory tests • Audiologic testing at Day 28 (± 2 days) compared to Baseline in children < 12 years old • The impact of dalbavancin on bowel flora at Day 28 (± 2 days) compared to Baseline in patients from birth to < 2 years **Efficacy Endpoints** • Temperature, as a physical sign consistent with systemic inflammation at Day 1, 48-72 hours post randomization, Day 8 (± 1 day), Day 14 (± 2 days), Day 28 (± 2 days), and Day 54 (± 7 days) compared to Baseline • Laboratory measurements including high-sensitivity C-reactive protein (hs-CRP),

Objectives	Endpoints
of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions. In patients diagnosed with sepsis in Cohort 5, clinical response at 48-72 hours post-randomization is defined as improvement of at least one abnormal clinical and laboratory parameter related to sepsis. Clinical response, in each of the 5 cohorts, will be assessed in patients who did not receive rescue therapy and are alive (in Cohort 5, rescue therapy is defined as additional antibiotic therapy initiated after at least 48 hours of start of study treatment). Clinical response based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of therapy), at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy). • To assess clinical response by baseline pathogen at 48-72 hours post randomization (defined as ≥ 20% reduction in lesion size compared to baseline (Cohorts 1 – 4), In Cohort 5 (birth to < 3 months), clinical response by baseline pathogen in patients with ABSSSI at 48-72 hours post-randomization is defined as cessation of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions. In patients diagnosed with sepsis in Cohort 5, clinical response at 48-72 hours post-randomization is defined as improvement of at least one abnormal clinical and laboratory parameter related to sepsis. Clinical response, in each of the 5 cohorts, will be assessed in patients who did not receive rescue therapy and are alive (in Cohort 5,	WBC count, and manual differential, as markers of systemic infection • Infection site assessment at 48-72 hours post randomization, Day 8 (± 1 day), Day 14 (± 2 days), and Day 28 (± 2 days) compared to Baseline • Clinical response at 48-72 hours after randomization • Clinical response by investigator and by sponsor at the EOT visit • Clinical response by investigator and by sponsor at the TOC visit and at the follow-up visit • Clinical response by investigator and by sponsor (as applicable) by baseline pathogen at 48-72 hours post randomization, EOT, TOC, and last follow-up visit • Microbiological response at 48-72 hours post randomization, EOT, TOC, and last follow-up visit • Resource utilization at Day 14 (± 2 days) and Day 28 (± 2 days) • Patient and parent/guardian satisfaction with therapy at Day 14 (± 2 days) • Concordance analysis of clinical response at 48-72 hours post randomization and clinical response at EOT • Resolution of local signs and ABSSSI lesion measurements

Objectives	Endpoints
rescue therapy is defined as additional antibiotic therapy initiated after at least 48 hours of start of study treatment).For later timepoints, clinical response by baseline pathogen is based on the global clinical assessment by the investigator at end of treatment (14 ± 2 days after start of therapy), at test of cure visit (28 ± 2 days after start of therapy), and at last follow-up visit (54 ± 7 days after start of therapy). • Cohort 5 (birth to < 3 months): to assess all-cause mortality at test of cure visit (28 ± 2 days after start of therapy). • To evaluate the pharmacokinetics (PK) of dalbavancin in pediatric patients from birth to 17 years of age (inclusive).	

4.3 Schedule of Activities

Table 4-1 Schedule of Activities

Protocol Activity	**Baseline** Pre-Dose (Day -1 to 1)[a]	Study Day[b]						Premature Discontinuation[d]
		1[b]	48-72 hours	8 ± 1	14 ± 2 (EOT Visit)[c]	28 ± 2 (TOC Visit)[c]	54 ± 7 (Follow-up Visit)[c]	
Informed Consent/Assent	X							
Access IWRS for PID	X							
Medical History and Demographics	X							
Complete Physical Examination	X							
Targeted Examination of Infection Site[e]	X[f]		X[f]	X	X	X	X	X
Vital Signs[g]	X	X	X	X	X	X	X	X
Hematology	X[h]		X[q]		X			X
Serum Chemistry	X[h]		X[q]		X			X
hs-CRP	X		X[q]		X[q]			
Pregnancy testing[i]	X[h]					X		X
Whole blood for pathogen diagnosis[j] (in children ≥ 2 years old **and** ≥ 12 kg)	X							
Estimate CrCL with Schwartz "bedside" equation (3 months to 17 years inclusive)	X							
Urine output (birth to < 3 months only)	X							
Infection site specimen collection[k]	X							
Peripheral blood culture[l]	X							
Audiology[m]	X					X		X
Bowel flora testing (C. diff PCR and VRE culture)[n]	X					X		X
Previous Drug and Non-drug Treatments	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Concomitant Non-drug Adjunctive Therapy	X	X	X	X	X	X	X	X
Randomization		X						
Treatment Administration[o]		[Through at least Day 10]						
Dalbavancin plasma PK sampling[p]		X	X	X	X			X
Investigator Assessment of Clinical Response					X	X	X	X
SSTI-Convenience Questionnaire					X			X
Resource utilization					X	X		X
Record oral dosing (comparator)					X			
Adverse Events	X	X	X	X	X	X	X	X

Abbreviations: ABSSSI: acute bacterial skin and skin structure infections, C. diff: *Clostridium difficile*, CrCL: creatinine clearance, hs-CRP: high sensitivity C-reactive protein, EOT: end of treatment visit, IV: intravenous, IWRS: interactive web randomization system, MRSA: methicillin resistant Staphylococcus aureus, PCR: polymerization chain reaction, PID: Patient Identification [number], PK: pharmacokinetic, SSTI: Skin and Soft Tissue, TOC: test of cure visit, VRE: vancomycin resistant enterococci

[a] The measurement of temperature to satisfy entry criteria may be a body temperature measured by the patient/caregiver or investigator within 24 hours of first dose.

[b] Study "Day" is calendar day beginning with Day 1, the calendar day the first infusion of study medication is started.

[c] The EOT Visit should be targeted for Day 14 ± 2 days, the TOC Visit should be targeted for Day 28 ± 2 days, and the Follow-up Visit should be targeted for Day 54 ± 7 days.

[d] Obtain specimen or measurement at time of premature discontinuation, if patient discontinues earlier than last scheduled assessment for that particular activity.

[e] Done by reviewing presence or absence of symptoms of ABSSSI. In Cohort 5 (birth to < 3 months), a complete physical examination will be performed at all noted timepoints.

[f] Ruler measurements are to be performed at Baseline (within 4 hours prior to first dose of study drug) and at 48-72 hours post randomization (in Cohorts 1 – 4 and ABSSSI patients in Cohort 5 [birth to < 3 months]).

[g] Vital signs include blood pressure, respiratory rate, heart rate, and temperature (oral, rectal or tympanic). Height and weight will be obtained at baseline only.

[h] If not already collected per standard of care, at Baseline, hematology, serum chemistry, and serum or urine pregnancy testing (for post-menarchal females) will also be done locally in order to qualify the patient for the study.

[i] Pregnancy test to be performed on post-menarchal female patients only. Serum or urine test is acceptable. Performed at Baseline and Day 28.

[j] At Baseline, a whole blood sample will be obtained to identify the bacteria that cause ABSSSI (EDTA whole blood, frozen) in children ≥2 years old **and** ≥ 12 kg.

[k] If an exudate/aspirate/pus sample can be obtained per Appendix 3, it should be cultured by the local laboratory, which should also conduct organism identification and antibiotic susceptibility testing. In all patients who are considered treatment failures, direct demonstration of eradication or persistence of the causative organism must be done.

[l] ***A*** blood culture (1 aerobic bottle) must be drawn at Baseline (prior to study drug treatment) not through an existing intravascular line. Blood cultures should be repeated upon knowledge of a positive result, until sterilization is confirmed. If clinically indicated, blood cultures should be collected at time of treatment discontinuation or for determination of treatment failure.

[m] Audiologic testing will be conducted in at least 20 children < 12 years old (in selected centers), of which at least 9 children will be less than 2 years old. Audiologic testing to be conducted on infants (<12 months old) will include: evoked otoacoustic emissions testing, acoustic immittance measures (tympanometry and contra and ipsilateral acoustic reflex thresholds) and (optional) threshold auditory brainstem responses. For the older children, testing will include evoked otoacoustic emissions, acoustic immittance measures (tympanometry and contra ipsilateral acoustic reflex thresholds), and age appropriate behavioral audiologic threshold assessment. Testing will be performed at Baseline and repeated at Day 28 (± 2 days). Testing (as specified in the protocol) performed within 7 days prior to study drug administration can be used as the Baseline assessment. If the audiologic assessment at Day 28 shows an abnormality that exceeds by a clinically significant margin any abnormality observed in the pre-study assessment, follow-up assessments will be performed at 3 months and 6 months post-dose, as needed or until returned to baseline. If necessary, the patient will be referred to an otolaryngologist or other hearing specialist for further testing.

[n] PCR for *Clostridium difficile* (C diff) and culture for vancomycin-resistant enterococci (VRE) on stool specimen or rectal swab will be done only in all patients aged birth to < 2 years.

[o] First dose should be administered within 4 hours after randomization. In the comparator arm, after at least 72 hours of IV oxacillin or flucloxacillin, patients may be switched to oral cefadroxil if criteria for oral therapy are met; if on IV vancomycin, they may be switched to oral clindamycin if MRSA is documented and if criteria for oral therapy are met, as noted in protocol.

[p] Plasma PK samples will be collected on all patients on dalbavancin (single-dose arm and two-dose arm), at 30 minutes and at 2 hours (Day 1), at 48-72 hours (Day 3-4), at 168 ± 24 hours (Day 8 ± 1) before the Day 8 dalbavancin dose, at 312 ± 48 hours (Day 14 ± 2), and at Premature Discontinuation.

[q] For Cohort 5 only (birth to < 3 months): hematology and serum chemistry will also be performed at the 48-72 hours timepoint. hs-CRP will be repeated at both 48 – 72 hours and Day 14 ± 2 days.

5. Statistical Methodology and Study Endpoints

5.1 Statistical Methods Planned in the Protocol and Determination of Sample Size

This SAP will be approved prior to database lock. The SAP expands the statistical section of the protocol and contains a detailed description of methods to analyze data collected in the study. The text portion of the SAP will be included in the CSR report as Appendix 16.1.9. The details of the analysis of PK and health outcome (resource utilization and patient and parent/guardian satisfaction with therapy) data collected as part of this protocol are not the scope of this SAP and will be detailed in separate analysis documents.

5.1.1 Statistical and Analytical Plans

Statistical analyses will be conducted using SAS Version 9.3 or newer.

5.1.1.1 Common Conventions

5.1.1.1.1 Analysis Populations

The analysis populations will consist of patients as defined below:

Table 5-1 Analysis Populations

Population	Definition	Study Treatment
Screened	All screened patients who sign informed consent	—
Intent-to-Treat (ITT)	All randomized patients regardless of whether or not they received study drug.	Randomized assignment
Safety	All patients in the ITT population who received at least 1 dose of study drug.	Actual received[1]
Modified Intent-to-Treat (mITT)	All randomized patients who received at least one dose of study drug and had a diagnosis of ABSSSI (or a suspected or confirmed sepsis for Cohort 5) not known to be caused exclusively by a Gram-negative organism.	Randomized assignment
Clinically Evaluable (CE)	Four CE populations will be defined based on the timing of the outcome assessment, CE-48-72 hours (post randomization), CE-EOT, CE-TOC, and CE- Follow-up visit. Patients who meet all of the following criteria will be considered to be clinically evaluable at the respective visit: • Fulfilled inclusion/exclusion criteria such that the clinical response is not confounded (if a patient is subsequently found to have violated an enrollment criteria, even if not noted at the baseline visit, the patient will not be included in the clinical evaluable population); • For patients randomized to dalbavancin, received at least 1 dose of active study medication. For patients randomized to comparator, received at least 5 days of study drug therapy;	Randomized assignment

Population	Definition	Study Treatment
	• For Cohorts 1-4: received no more than one dose of another systemic antibacterial therapy (with the exception of systemic aztreonam, oral or IV metronidazole or oral vancomycin) with documented activity against the causative organism from study drug initiation until the outcome assessment (visit) for a non-ABSSSI indication. [Note: Patients receiving a new non-study systemic antibacterial treatment (with the exception of aztreonam or metronidazole) for treatment of the ABSSSI from initiation of study drug through the outcome assessment (visit) will be assessed as Evaluable Failures]. Note: Cohort 5 are permitted to receive allowed concomitant antibacterials. • Had an outcome assessment at which a clinical response could be evaluated for the time point specified; • Received appropriate adjunctive antibacterial coverage if the patient had a culture-documented mixed ABSSSI (one or more Gram-positive pathogens with one or more Gram-negative aerobic or anaerobic organisms).	
Microbiological ITT (microITT)	This population will consist of all patients in the ITT population who had at least 1 Gram-positive pathogen isolated at Baseline (refer to Protocol Appendix 2).	Randomized assignment
Microbiologically Evaluable (ME)	This population will consist of patients who meet all of the criteria for the CE population and microITT population. There are 4 ME populations: ME-48-72 hours, ME-EOT, ME-TOC, and ME-Follow-up visit.	Randomized assignment

[1] Patients will be summarized according to the first study treatment received/study treatment received for majority of Treatment Period.

5.1.1.1.2 Study Treatments

The following treatment groups are defined for this study:

- Dalbavancin Single-Dose
- Dalbavancin Two-Dose
- Comparator

5.1.1.1.3 Statistical Methodology

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

Table 5-2 Statistical Methodology

Methodology	Description
Categorical counts	• Number of patients in individual categories ○ Patients with ≥ 1qualifying event counted once per individual category

Categorical descriptives	• Number and percentage of patients in individual categories
	  ○ Patients with ≥ 1qualifying event counted once per individual category
	• Show N1 if percentage denominator ≠ number of patients in the population (standard percentage denominator)
	  ○ N1 = patients with non-missing baseline value

PCS descriptives	• Number and percentage of patients meeting potentially clinically significant (PCS) criteria
	  ○ Patients with ≥ 1qualifying event counted once per PCS category
	• Percentage denominator = number of patients with non-missing baseline and >=1 non-missing postbaseline assessment
	  ○ Unevaluable assessments considered missing

Event descriptives	• Number and percentage of events in individual categories ○ Events counted individually for each instance • Percentage denominator = total number of events
Shift analysis	• Number and percentage of patients in individual baseline and postbaseline categories • Percentage denominator = number of patients in individual baseline categories • N1 = patients with non-missing values at both baseline and the specified postbaseline analysis visit
Continuous descriptives	• N1, mean, standard deviation (SD), median, minimum, maximum • N1 = patients with non-missing value
CFB descriptives	• Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values • N1 = patients with non-missing values at both baseline and the specified postbaseline analysis visit

Responder	• Categorical descriptives for responders and nonresponders
	  ○ Nonresponders include:
	  ▪ Patients who do not meet responder criteria
	  ▪ Patients with no postbaseline values
	• N1 = patients with assessment at the post baseline visit

Concordance analysis	• Categorical descriptives for Variable 2 conditional on the values of Variable 1 • Percentage denominator = number of patients with non-missing values for Variable 1 and Variable 2

CFB = change from baseline.

Raw and derived data listings will be provided, and will be fully defined in the table, figure, and data listing specification document.

5.1.1.1.4 Missing Data

General missing data handling conventions are specified for methodologies in Section 5.1.1.1.3 and summarized as follows:

Table 5-3 Missing Data Handling by Endpoint Type

Parameter type	Timing	Missing Data Handling
Responder	All	• All patients included • Patients with no postbaseline values = nonresponders

5.1.1.2 Demographics

5.1.1.2.1 Analysis Populations

The distribution of patients within the analysis populations will be summarized as follows:

Table 5-4 Analysis Population Summaries

Population	Description	Timing	Methodology
Screened, ITT, Safety, mITT, all CE, microITT, all ME populations	Distribution overall and within countries/regions in total and by treatment group	—	Categorical counts
Screened, ITT, Safety, mITT, all CE, microITT, all ME populations	Distribution within age cohorts and by treatment group	—	Categorical counts

5.1.1.2.2 Patient Disposition

Patient disposition encompasses the distribution of patients who enter, complete, and discontinue each specified analysis period, along with eCRF-reported discontinuation reasons from each respective analysis period. Patient disposition will be summarized as follows:

Table 5-5 Patient Disposition Summaries

Parameter	Description	Timing	Methodology
Screening disposition	Distribution in the Screened Population in total	Screening	Categorical descriptives
Study disposition	Distribution in the ITT Population in total and by treatment group	Baseline period (Baseline visit) Study drug period Treatment period (Day 1 to Day 14) and Follow-up period (Day 15 to Day 54)	Categorical descriptives
Study disposition	Distribution in the ITT Population by age cohort	Treatment period (Day 1 to Day 14) and Follow-up period (Day 15 to Day 54)	Categorical descriptives

5.1.1.2.3 Protocol Deviations

Protocol deviations will be defined in a separate document, including importance classification. Protocol deviations will be summarized as follows:

Table 5-6 Protocol Deviation Summary

Parameter	Description	Timing	Methodology
Important protocol deviations	Distribution in the ITT Population in total and by treatment group	—	Categorical descriptives

5.1.1.2.4 Demographics

Demographics will be summarized in total and by treatment group, as well as by treatment group within each age cohort for the ITT, Safety, mITT, all CE, microITT and all ME populations as follows:

Table 5-7 Demographic Summaries

Parameter	Description	Timing	Methodology
Age	Age (years) relative to informed consent date; for subjects < 3 months, also include gestational age	Informed consent	Continuous descriptives
Age Cohort	• Birth to < 3 months • 3 months to < 2 years old • 2 years to < 6 years old • 6 years to < 12 years old • 12 years to 17 years old	Informed consent	Categorical descriptives

Sex, race, and ethnicity	• eCRF categories
	• Race group
	  ○ White
	  ○ Non-white
		Baseline	Categorical descriptives

5.1.1.2.5 Baseline Characteristics

Baseline characteristics will be summarized in total and by treatment group, as well as by treatment group within each age cohort for the ITT, Safety, mITT, all CE, microITT and all ME populations (if appropriate), as follows:

Table 5-8 Baseline Characteristics Summaries

Parameter	Description	Population	Methodology
Baseline characteristics	• Height (cm) • Weight (kg) • Body mass index (BMI) ○ Weight (kg) / height $(m)^2$ • Creatinine clearance ($mL/min/1.73m^2$) • Temperature (°C)	All	Continuous descriptives

Baseline characteristics	• Creatinine clearance category[1]
	  ○ <30 $mL/min/1.73m^2$
	  ○ $>=30$ $mL/min/1.73m^2$
	• Prior Antibiotic Use,
	  ○ Yes
	  ○ No
	• Audiologic (Individual) test result
	  ○ Normal
	  ○ Abnormal
	• Bowel flora (Individual) test result
	  ○ Negative
	  ○ Positive
		All	Categorical descriptives

Type and Anatomical Site of ABSSSI	• Infection type
	  ○ Cellulitis
	  ○ Major Cutaneous Abscess
	  ○ Surgical Site/Traumatic Wound Infection
	• Does the total affected area involve at least 35 cm^2 of erythema, or total affected area of erythema at least BSA (m^2) x 43 (cm^2/m^2)? (Y/N)
	• Does the infection involve the central face and is it associated with an affected area of at least 15 cm2? (Y/N)
	• Does the infection require surgical incision and drainage? (Y/N)
	• Infection Location
	  ○ All locations from CRF
		All	Categorical descriptives

Infection Measurements	• Lesion Length (cm) • Lesion Width (cm) • Lesion Size (cm^2)	All	Continuous descriptives

Clinical Assessment of Signs and Symptoms	• Erythema
	• Purulent discharge/drainage
	• Swelling/induration
	• Fluctuance
	• Pain/tenderness to palpation
	• Heat/localized warmth
	
	Each signs/symptons care categorized as:
	  ○ Absent
	  ○ Mild
	  ○ Moderate
	  ○ Severe
		All	Categorical descriptives

Parameter	Description	Population	Methodology
Pathogens from the ABSSSI Site or Blood	• With at least one Pathogen from the ABSSSI Site or Blood as defined in protocol Appendix 2 (after manual review by Sponsor)	microITT and all ME	Categorical descriptives
Abnormal clinical and laboratory parameter related to sepsis (Cohort 5 only)	Clinical: • Hypothermia (<36°C) • Fever (>38.5°C) • Bradycardia • Tachycardia • Rhythm instability • Hypotension • Mottled skin • Impaired peripheral perfusion • Petechial rash • New onset or worsening of apnea episode • Tachypnea episodes • Increased oxygen requirements • Requirement for ventilation support • Feeding intolerance • Poor sucking • Abdominal distension • Irritability • Lethargy • Hypotonia Laboratory: • White blood cell count ≤4.0 × 109/L • White blood cell count ≥20.0 × 109/L • Immature to total neutrophil ratio >0.2 • Platelet count ≤100 × 109/L • C-reactive protein (CRP) >15 mg/L • Procalcitonin ≥ 2 ng/mL • Hyperglycemia • Hypoglycemia • Metabolic acidosis	All (Cohort 5 only)	Categorical descriptives
Hospitalization Criteria (Cohort 5 only)	• Cutaneous or subcutaneous abscess • Surgical site or traumatic wound infection • Cellulitis, Erysipelas • Omphalitis • Impetigo and bullous impetigo • Pustular folliculitis • Scarlet fever • Staphylococcal scalded skin syndrome • Streptococcal toxic shock syndrome • Erythematous based-erosion • Other, specify	All (Cohort 5 only)	Categorical descriptives

5.1.1.2.6 Medical History

Medical history, encompassing abnormalities and surgeries reported as occurring before the Screening Visit, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1 or newer. Unique patients who report medical history events will be summarized by MedDRA system organ class (SOC) and preferred term (PT) in total and by treatment group for the Safety Population as follows:

Table 5-9 Medical History Summary

Parameter	Description	Timing	Methodology
Medical history / Physical examination findings	Abnormalities and surgeries occurring before and at the Screening Visit	Screening Period	Categorical descriptives

SOCs will be sorted alphabetically; PTs will be sorted in descending frequency.

5.1.1.2.7 Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary, version MAR2016 or newer. Unique patients who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) 4 class and PT in total and by treatment group for the Safety Population as follows:

Table 5-10 Medication Summaries

Parameter	Description	Timing	Methodology
Prior Antibiotic Medications	Antibiotic Medications taken ≥ 1 time before the study treatment start date, regardless of medication end date	Screening Period	Categorical descriptives
Concomitant Antibiotic Medications	Antibiotic Medications taken ≥ 1 time on or after the study treatment start date, regardless of medication start date	Treatment Period	Categorical descriptives
Prior Nonantibacterial Medications	Non-Antibiotic Medications taken ≥ 1 time before the study treatment start date, regardless of medication end date	Screening Period	Categorical descriptives
Concomitant Nonantibacterial Medications	Non-Antibiotic Medications taken ≥ 1 time on or after the study treatment start date, regardless of medication start date	Treatment Period	Categorical descriptives
Prior Non-drug Adjunctive Therapy	Non drug interventions performed ≥ 1 time before the study treatment start date, regardless of medication end date	Screening Period	Categorical descriptives
Concomitant Non-drug Adjunctive Therapy	Non drug interventions performed ≥ 1 time on or after the study treatment start date, regardless of medication start date	Treatment Period	Categorical descriptives

ATC4 classes will be sorted alphabetically; PTs will be sorted in descending frequency.

5.1.1.3 Efficacy Analyses.

Efficacy analyses will be based on the mITT Population and specified CE, microITT and ME populations.

The following efficacy assessments and terms are defined:

Table 5-11 Efficacy Assessments

Assessment/Term	Time Points	Description
Temperature	Baseline, Day 1, 48-72 hours post randomization, Day 8 (± 1 day), Day 14 (± 2 days), Day 28 (± 2 days), and Day 54 (± 7 days)	As a physical sign consistent with systemic inflammation, either a core, oral, rectal or tympanic (ear) temperature
High-sensitivity C-reactive protein (hs-CRP), WBC count and manual differential	Baseline, 48-72 hours post randomization, and/or EOT	Laboratory measurements as markers of systemic infection; hs-CRP at baseline; WBC count at baseline and EOT. For Cohort 5 only: WBC count at 48-72 hours post randomization and hs-CRP at 48-72 hours post randomization and EOT
Infection site assessment	Baseline (within four hours prior to the first dose of study drug), 48-72 hours post randomization, Day 8 (± 1 day), Day 14 (± 2 days), Day 28 (± 2 days), and Day 54 (± 7 days)	For Cohorts 1-4 and ABSSSI patients in Cohort 5: Includes the following: purulence/drainage, erythema, heat/localized warmth, pain/tenderness to palpation, fluctuance and swelling/induration. Ruler measurements of the area of erythema will be obtained at Baseline (within four hours prior to the first dose of study drug), and at 48-72 hours post randomization in Cohorts 1 – 4 and ABSSSI patients in Cohort 5..
Clinical response	48-72 hours post randomization	For cohort 1-4: Defined as ≥ 20% reduction in lesion size compared to baseline, measured in patients who did not receive rescue therapy and are alive. In Cohort 5 (birth to < 3 months), clinical response in patients with ABSSSI at 48-72 hours post-randomization is defined as cessation of increase in lesion size and decreased erythema or tenderness compared to baseline with no appearance of new lesions. In patients diagnosed with sepsis in Cohort 5, clinical response at 48-72 hours postrandomization is defined as improvement of at least one abnormal clinical and laboratory parameter related to sepsis.
Clinical response	EOT visit (14 ± 2 days)	Categorized as Cure, Improvement, Failure, or Unknown by investigator and by sponsor (refer to Section 6.4.1)
Clinical response	TOC visit (28 ± 2 days) and follow-up visit (54 ± 7 days)	Categorized as Cure, Failure or Unknown by investigator and by sponsor (refer to Section 6.4.1)
Microbiological response	48-72 hours post randomization, EOT, TOC, and last follow-up visit	The response will be categorized as: • Eradication • Presumed eradication • Persistence • Presumed persistence • Indeterminate Refer to Section 6.4.2 for definitions

Baseline assessments for applicable efficacy endpoints defined as the latest assessment before/on the first dose of study drug.

Pharmacokinetic blood sampling and concentrations will be listed for the Safety Population.

5.1.1.3.1 Analysis of Efficacy Endpoints

Efficacy endpoints will be analyzed by treatment as follows:

Table 5-12 Efficacy Endpoint Analyses

Endpoint	Description	Timing	Population	Summary	Methodology
Clinical response	Categories: • Clinical responder • Clinical non-responder	48-72 hours post randomization	mITT, CE-48-72 hours	Overall and by Age Cohort	Responder
Clinical response by investigator and by sponsor	Categories: • Cure • Improvement • Failure • Unknown • Missing	EOT visit (14 ± 2 days)	mITT, CE-EOT, microITT, ME-EOT	Overall and by Age Cohort	Responder
Clinical response by investigator and by sponsor	Categories: • Cure • Failure • Unknown • Missing	TOC visit (28 ± 2 days) and follow-up visit (54 ± 7 days)	mITT, CE-TOC, CE-follow-up	Overall and by Age Cohort	Responder
Clinical response by baseline pathogen, by investigator and by sponsor (as applicable)	Categories depend on timing Refer to categories above	48-72 hours post randomization, EOT, TOC, and last follow-up visit	microITT, applicable ME	By baseline pathogen for overall	Responder
Relapse/recurrence[1]	Categories[2] • Continued success • Relapse/recurrence	Follow-up visit (54 ± 7 days)	CE-follow-up for cured at TOC	Overall and by Age Cohort	Responder
Concordance of clinical response[1]	Categories: • Responder - Cure/Improvement • Responder - Failure/Unknown • Non-Responder - Cure/Improvement • Non-responder - Failure/Unknown	48-72 hours post randomization, EOT	mITT	Overall and by Age Cohort	Concordance analysis
Microbiological response	• Eradication • Presumed eradication • Persistence • Presumed persistence • Indeterminate	48-72 hours post randomization, EOT, TOC, and last Follow-up visit	microITT, all applicable ME	Overall and by age cohort and by Baseline Pathogen for overall	Responder

Endpoint	Description	Timing	Population	Summary	Methodology
Temperature	• Absolute values, and change from baseline	Baseline and all post-baseline visits	ITT, mITT, CE, microITT and ME populations	Overall and by age cohort	CFB descriptives
High-sensitivity C-reactive protein (hs-CRP), WBC count and manual differential	• Absolute values • percentage of patients with … increased WBCs >12,000 cells/mm3 or bands ≥ 10% • percentage of patients with an elevated high sensitivity C-reactive protein (defined as above the ULN)	Baseline, 48-72 hours post randomization and/or EOT	ITT, mITT, CE, microITT and ME populations	Overall and by age cohort	CFB descriptives
ABSSSI lesion measurements	• Absolute values, change from baseline, and percentage change from baseline (For percent change from baseline, the following categories were used: 0 - < 10%, 10% - < 20%, 20 - < 30%, 30% - < 40%, 40% - < 50%, 50% - < 60%, 60% - < 70%, 70% - < 80%, 80% - < 90%, ≥ 90%.)	48-72 hours post randomization	ITT, mITT	Overall and by age cohort	CFB descriptives
Clinical Assessment of Signs and Symptoms	Categories: • Absent • Mild • Moderate • Severe for each of the local sign: • Erythema • Purulent drainage/discharge • Swelling/induration • Fluctuance • Tenderness to palpation • Heat/localized warmth	All post-baseline visits	ITT, mITT	Overall and by age cohort	Shift analysis

Endpoint	Description	Timing	Population	Summary	Methodology
Complete resolution of all local signs	• Complete resolution (Complete resolution of local signs will be defined as absence of drainage/discharge, erythema, fluctuance, heat/localized warmth, tenderness to palpation and swelling/induration .)	All post-baseline visits	ITT, mITT	---	Categorical descriptives
All cause mortality (Cohort 5 only)	• All-cause mortality	TOC	Cohort 5 only	Overall (Cohort 5 only)	

[1] Based on clinical response by sponsor.
[2] Refer to Section 6.4.3 for definitions.

5.1.1.4 Safety Analyses

Safety analyses will be based on the Safety Population. Patients who receive the wrong regimen of study drug for their entire course of treatment will be analyzed in the group based on the regimen received.

Baseline assessments for applicable safety endpoints defined as follows:

Table 5-13 Safety Endpoint Baseline Definitions

Parameter	Description	Timing
• Audiologic Testing • Bowel Flora Testing • Clinical laboratory evaluations • Vital signs	eCRF- or (standardized) vendor-provided assessments	Latest non-missing assessment on/before treatment start date

5.1.1.4.1 Study Treatment Exposure and Compliance

Study treatment exposure and compliance will be summarized by treatment group, both overall and within each age cohort, in the Safety, ITT, mITT, CE-EOT, CE-Follow up visit, microITT, ME-EOT and ME-Follow up visit Populations. Study treatment exposure and compliance will be listed for the Safety Population.

Table 5-14 Study Treatment Summaries

Parameter	Description	Timing	Methodology
Study treatment exposure	• Total Days on Therapy (Both IV and Oral) • Total Days on Therapy (IV only) Days = Date of the last dose of specified study drug - Date of the first dose of specified study drug + 1 day	Treatment Period	Continuous descriptives
Categorical study treatment exposure	• Number of doses, for the Dalbavancin Single-Dose or Two-Dose treatment groups only: o 1 Dose o 2 Dose • Number of Patients Who Received IV Vancomycin • Number of Patients Who Received IV Oxacillin • Number of Patients Who Received IV Flucloxacillin • Total Days on Therapy (Both IV and Oral) o No dose o <1 o 1 - 3 o 4 - 5 o 6 - 7 o 8 - 9 o 10 - 14 o >14 • Total Days on Therapy (IV only) o No dose o <1 o 1 - 3 o 4 - 5 o 6 - 7 o 8 - 9 o 10 - 14 o >14 • Number of Patients Who Received Oral Clindamycin • Number of Patients Who Received Oral Cefadroxil • Number of Patients Who Received other oral antibiotic • Days on Oral Therapy o <1 o 1 - 3	Treatment Period	Categorical descriptives

Parameter	Description	Timing	Methodology
	○ 4 - 5 ○ 6 - 7 ○ 8 - 9 ○ >=10 • Number of Patients Who Received Metronidazole • Number of Patients Who Received Aztreonam • Number of Patients Who Received Oral Vancomycin • Number of Patients Who Received Metronidazole, Aztreonam, and/or Oral Vancomycin • Days on Metronidazole, Aztreonam, and/or Oral Vancomycin, n/N2 (%) ○ <1 ○ >=1 - 3 ○ 4 - 5 ○ 6 - 7 ○ 8 - 9 ○ 10 - 14 ○ >14		
Study treatment exposure for comparator systemic antibiotics	• Initial Vancomycin Dose ○ <=10 mg/kg ○ >10-15 mg/kg ○ >15-20 mg/kg ○ > 20 mg/kg • Initial Oxacillin Dose ○ < 30 kg ○ 30 mg/kg ○ > 30 mg/kg • Initial Flucloxacillin Dose ○ < 50 mg/kg ○ 50 mg/kg ○ > 50 mg/kg • Patients on IV oxacillin or flucloxacillin switched to oral cefadroxil • Patients on IV vancomycin switched to clindamycin • Patients on IV vancomycin switched to IV oxacillin or flucloxacillin • Patients on IV vancomycin switched to other oral antibiotic • Patients on IV oxacillin or flucloxacillin switched to IV vancomycin	Treatment Period	Categorical descriptives

Parameter	Description	Timing	Methodology
Study Treatment Compliance	• Summary by visit interval and overall Compliance rate = The number of doses actually received / The expected number of doses to be received x 100	Treatment Period	Continuous descriptives
Categorical Study Treatment Compliance	• Summary by visit interval and overall o < 80% o >= 80% - <100% o > =100 % - <=120% o > 120%	Treatment Period	Categorical descriptives

5.1.1.4.2 Audiologic Testing and Impact of Dalbavancin on Bowel Flora

The following safety assessments and terms are defined:

Table 5-15 Assessments for Audiologic and Bowel Flora Testings

Assessment/Term	Time Points	Description
Audiologic Testing	Baseline and TOC visit	Audiologic testing will be conducted in at least 20 children < 12 years old (in selected centers), of which at least 9 children will be < 2 years old. Audiologic testing will be performed at Baseline and repeated at Day 28 (± 2 days). Testing (as specified in the protocol) performed within 7 days prior to study drug administration can be used as the Baseline assessment. There are 5 testings performed: • Distortion Product Otoacoustic Emission • Auditory Brainstem Response Test • Acoustic Immittance Test Results • Behavioral Audiometric Evaluation • Bone Conduction Test
Bowel Flora Testing	Baseline and TOC visit	The impact of dalbavancin on bowel flora, to be evaluated in all patients from birth to < 2 years, by performing PCR for Clostridium difficile (C diff) and culture for vancomycin-resistant enterococci (VRE) on a stool specimen or rectal swab. The testing of bowel flora in this age group will be done in all three study arms. The bowel flora test at TOC visit will be categorized as the following, for each of the tests: • Positive • Negative

The following endpoints will be summarized in total and by treatment group, as well as by treatment group within each age cohort for Safety Population:

Table 5-16 Analyses for Audiologic and Bowel Flora Testings

Endpoint	Description	Time Point	Methodology
Distortion Product Otoacoustic Emission Shift	Shift from Baseline based on interpretation of results in categories of: • Normal • Abnormal • Missing	TOC	Shift analysis
Distortion Product Otoacoustic Emission Results	Individual test component results: What ear, frequency range, amplitude, signal to noise ratio Per CRF	Baseline and TOC	Categorical descriptives/ Continuous descriptives
Auditory Brainstem Response Shift	Shift from Baseline based on interpretation of results in categories of: • Normal • Abnormal • Missing	TOC	Shift analysis
Auditory Brainstem Response Test Results	Individual test component results: What ear, frequency, Air Conduction Minimum Response Level, Bone Conduction Minimum Response Level Per CRF	Baseline and TOC	Categorical descriptives/ Continuous descriptives
Acoustic Immittance Shift	Shift from Baseline based on interpretation of results in categories of: • Normal • Abnormal • Missing	TOC	Shift analysis
Acoustic Immittance Test Results	Individual test component results: What ear, ear canal volume, peak, Ipsilateral Acoustic Reflex, Contralateral Acoustic Reflex Per CRF	Baseline and TOC	Categorical descriptives/ Continuous descriptives
Behavioral Audiometric Shift	Shift from Baseline based on interpretation of results in categories of: • Normal • Abnormal • Missing	TOC	Shift analysis
Behavioral Audiometric Evaluation Resuts	Individual test component results: Sounds booth, type of procedure, what ear, frequency, Minimum Response Level, Confidence level in response Per CRF	Baseline and TOC	Categorical descriptives/ Continuous descriptives
Bone Conduction Shift	Shift from Baseline based on interpretation of results in categories of: • Normal • Abnormal • Missing	TOC	Shift analysis

Endpoint	Description	Time Point	Methodology
Bone Conduction Test Results	Individual test component results: what ear, frequency, Minimum Response Level, Confidence level in response Per CRF	Baseline/TOC	Categorical descriptives/ Continuous descriptives
Bowel Flora Shift: PCR for *Clostridium difficile*	Shift from Baseline in categories of: • Positive • Negative • Missing	TOC	Shift analysis
Bowel Flora Shift: culture for vancomycin-resistant enterococci (VRE)	Shift from Baseline in categories of: • Positive • Negative • Missing	TOC	Shift analysis
Bowel Flora Testing Result: PCR for *Clostridium difficile*	• Positive • Negative	Baseline and TOC	Categorical descriptives
Bowel Flora Testing Result: culture for vancomycin-resistant enterococci (VRE)	• Positive • Negative	Baseline and TOC	Categorical descriptives

5.1.1.4.3 Adverse Events

The following adverse event (AE) terms are defined:

Table 5-17 AE Terms

Term	Description
Treatment-emergent	An AE will be considered a treatment-emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first dose of study drug. Per case report form instructions, a new AE record will be created for any AE that worsens; therefore TEAEs can be identified as those AEs with recorded onset date (and time, if known) on or after the date (and time) of the first dose of study intervention

AEs, encompassing abnormalities and surgeries reported as occurring after the Screening Visit, will be coded using MedDRA version 19.1 or newer. Unique patients reporting AEs in the following AE categories will be summarized by treatment group and in total, as well as by treatment group within each age cohort for the Safety Population as follows:

Table 5-18 AE Summaries

Parameter	Description	Timing	Methodology
Overall summary	Overall summary only for the following categories: • AEs • Treatment-emergent AEs (TEAEs) • Treatment-related TEAEs • Treatment-emergent Serious AEs (SAEs) • Treatment-related Treatment-emergent SAEs • AEs leading to study treatment discontinuation • AEs leading to study discontinuation • Treatment-emergent SAEs leading to death[1]	After the Screening Visit	Categorical descriptives
Common TEAEs	Summary by PT • Includes TEAEs occurring in ≥ 2% of patients in any treatment group	During or after the first dose of study drug through Follow-up visit	Categorical descriptives
TEAEs by Severity	Overall summary and by SOC, PT, and Severity(Mild/Moderate/Severe) • Patients categorized overall and within each SOC and PT for the most severe occurrence	During or after the first dose of study drug through Follow-up visit	Categorical descriptives
TEAEs by Relationship	Overall summary and by SOC, PT, and Relationship(Related/Not related) • Patients categorized overall and within each SOC and PT for the most related occurrence	During or after the first dose of study drug through Follow-up visit	Categorical descriptives
Treatment-emergent SAEs[1]	Overall summary and by PT	During or after the first dose of study drug through Follow-up visit	Categorical descriptives
Treatment-emergent SAEs leading to death[1]	Overall summary and by PT	During or after first dose of study drug	Categorical descriptives
AEs associated with premature discontinuation of study drug[1]	Overall summary and by PT	During or after the first dose of study drug through Follow-up visit	Categorical descriptives
AEs associated with withdrawal from the study[1]	Overall summary and by PT	During or after the first dose of study drug through Follow-up visit	Categorical descriptives

[1] Patients who report ≥ 1 AE in the AE category and all AEs for those patients will be listed.
SOCs will be sorted alphabetically; PTs will be sorted in descending frequency.
All deaths will be listed, if any.

5.1.1.4.4 Clinical Laboratory Assessments

Clinical laboratory assessments will be summarized by treatment group and in total, as well as by treatment group within each age cohort for the Safety Population as follows:

Table 5-19 Clinical Laboratory Summaries

Endpoint	Description	Timing	Methodology
Potentially clinically significant (PCS) values[1]	Summary by laboratory category, parameter, and PCS criteria • Patients with baseline PCS values excluded from analysis • Parameters and PCS criteria specified in Section 6.5.2.1	All post-baseline	PCS descriptives
Descriptives	Summary by laboratory category and parameter in SI units and analysis visit • Parameters specified in Section 6.5.2.2	All baseline and applicable post-baseline visits.	CFB descriptives

[1] Patients who report ≥ 1 postbaseline PCS value for those patients will be listed.
[2] Analysis visits defined in Section 6.2.2.

For the same visit, central laboratory results will be used for analysis. Local laboratory results will be used only if central laboratory results are missing.

5.1.1.4.4.1 Potential Hy's Law

Potential Hy's Law criteria will be summarized by treatment group for the Safety Population as follows:

Table 5-20 Potential Hy's Law Summaries

Endpoint	Description	Timing	Methodology
Potential Hy's Law within 24-hour window	Postbaseline assessment of the following laboratory parameters based on blood draws collected within a 24-hour period: • ALT or AST ≥ 3 × ULN and • TBL ≥ 2 × ULN and • ALP < 2 × ULN	Treatment Period + up to final visit	Categorical descriptives

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin.
ALP = alkaline phosphatase; ULN = upper limit of normal.

5.1.1.4.5 Vital Signs

Vital signs will be summarized by treatment group and in total, as well as by treatment group within each age cohort for the Safety Population as follows:

Table 5-21 Vital Signs Summaries

Endpoint	Description	Timing	Methodology
Potentially clinically significant (PCS) values[1]	Summary by laboratory category, parameter, and PCS criteria • Patients with baseline PCS values excluded from analysis • Parameters and PCS criteria specified in Section 6.5.3.1	All post-baseline	PCS descriptives
Descriptives	Summary by parameter and analysis visit Parameters specified in Section 6.5.3.2	All baseline and applicable post-baseline visits.	CFB descriptives

[1] Patients who report ≥ 1 postbaseline PCS value for those patients will be listed.
[2] Analysis visits defined in Section 6.2.2.

5.1.1.5 Subgroup Analyses

Analyses above are presented by age cohort as specified.

5.1.1.6 Interim Analyses

There is no interim analysis planned for this study.

5.1.2 Determination of Sample Size

The study is designed to determine the safety and descriptive efficacy of dalbavancin for the treatment of ABSSSI known or suspected to be caused by susceptible Gram-positive organisms, including MRSA. Since the study is primarily a safety study, the sample size was not calculated based on a power calculation for a hypothesis test.

The study will enroll approximately 188 patients from birth (inclusive) to 17 years old (such that 188 patients will be included in the Safety Population). Patients 3 months and older will be randomized to receive dalbavancin or comparator, in a 3:3:1 randomization scheme: 76 patients will be randomized to dalbavancin (single-dose IV), 76 patients will be randomized to dalbavancin (2 doses once weekly IV therapy), and 26 patients will be randomized to comparator (IV vancomycin or IV oxacillin or flucloxacillin). The randomization scheme will not include the youngest age cohort (birth to < 3 months of age), as all 10 patients in this cohort will receive the single-dose regimen of dalbavancin, bringing the total number of patients enrolled in the study to approximately 188 patients. No patient in Cohort 5 (birth to < 3 months) will be randomized to the comparator arm.

The enrollment target for Cohort 5 includes at least 5 patients ≤ 28 days (including pre-term neonates).

There will be 5 age cohorts:

- Cohort 1 --12 years to 17 years old, inclusive,
- Cohort 2 -- 6 years to <12 years old,
- Cohort 3 -- 2 years to < 6 years old,
- Cohort 4 -- 3 months to < 2 years old, and
- Cohort 5 – birth to < 3 months of age (including pre-term neonates with gestational age ≥ 32 weeks).

With the exception of Cohort 5, patients will be randomized 3:3:1 to each of the three treatment groups. In Cohorts 3 and 4 (enrolled patients aged 2 years to < 6 years old and 3 months to < 2 years old, respectively), there will be approximately 15 patients in each dalbavancin arm, and 5 patients in each comparator arm. In Cohorts 1 and 2 (enrolling patients 12 years to 17 years old, inclusive and 6 years to < 12 years old, respectively), there will be approximately 23 patients in each dalbavancin arm, and 8 patients in each comparator arm.

5.2 Changes in the Conduct of the Study or Planned Analyses

There were no changes in study conduct or planned analyses from what was described in the protocol and detailed in the SAP.

5.2.1 Changes in the Conduct of the Study

Not applicable.

5.2.2 Changes to Analyses

Not applicable.

6. Data Handling and Analysis Conventions

6.1 Study Treatment Conventions

6.1.1 Analysis Days

Treatment and Off-treatment days are defined as follows:

Table 6-1 Analysis Day Definitions

Term	Description
Treatment Day	Relative to treatment start date If analysis date ≥ treatment start date: • Day = analysis date – treatment start date + 1 o Day 1 = treatment start date If analysis date < treatment start date: • Day = analysis date – treatment start date o Day -1 = day before treatment start date o There is no Day 0

6.1.2 Missing/Incomplete Treatment End Date

If the investigator is unable to provide the treatment end date, treatment end date will be imputed to the last available dosing record date.

6.2 Analysis Visit Windows

6.2.1 Efficacy

The analysis visit windows for efficacy endpoints are defined as follows:

Table 6-2 Efficacy Analysis Visit Definitions

Analysis Phase	Analysis Visit (Derived)	Study Visit (eCRF)	Window
Pretreatment	Baseline	Baseline	Pre-Dose (Day -1 to 1), within 24 hours prior to first dose
Post-Treatment	48-72 hours[1]	48-72 hours	36-79 hours[2]
	EOT	Day 14	± 2 days Treatment Day [12, 16]
	TOC	Day 28	± 2 days Treatment Day [26, 30]
	Follow-up Visit	Day 54	± 7 days Treatment Day [47, 61] Latest non-missing assessment for all follow-up visits

[1] post randomization except for Cohort 5 (birth to < 3 months). Because in Cohort 5 only the single-dose regimen of dalbavancin (22.5 mg/kg) is assigned, randomization is not meaningful for Cohort 5. The 48-72 hours analysis visit window for Cohor 5 will be calculated based on the first dose datetime rather than the randomization datetime..
[2] If time is missing, the window is calculated by Day 3 (±1) Day.

6.2.2 Safety

The analysis visit windows for all safety endpoints, including laboratory and vital sign assessements, are defined as follows:

Table 6-3 Safety Analysis Visit Definitions

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Pretreatment	Baseline	Baseline	Pre-Dose (Day -1 to 1), within 24 hours prior to first dose
Post-Treatment	Day 1	Day 1	Post-dose (Day 1)
	48-72 hours[1]	48-72 hours	48-72 hours
	Day 8	Day 8	± 1 days Treatment Day [7, 9]
	EOT	Day 14	± 2 days Treatment Day [12, 16]
	TOC	Day 28	± 2 days Treatment Day [26, 30]
	Follow-up Visit	Day 54	± 7 days Treatment Day [47, 61] Latest non-missing assessment for all follow-up visits

[1] post randomization except for Cohort 5 (birth to < 3 months). Because in Cohort 5 only the single-dose regimen of dalbavancin (22.5 mg/kg) is assigned, randomization is not meaningful for Cohort 5. The 48-72 hours analysis visit window for Cohor 5 will be calculated based on the first dose datetime rather than the randomization datetime..

The following general conventions for repeated or unscheduled assessments will apply unless otherwise specified:

- The latest non-missing assessment within any analysis window will be flagged as the analysis value for any summaries by analysis visit
- All postbaseline assessments will be considered for PCS categorization
- All assessments will be included in respective listings

Audiology testing performed within 7 days prior to study drug administration can be used as the Baseline assessment.

6.3 Missing/Incomplete Date Conventions

Dates may be imputed with year, month, and day values under certain scenarios:

Table 6-4 Imputation Scenarios

Scenario	Complete			Imputable
	Year	Month	Day	
1	Yes	Yes	Yes	Complete
2	Yes	Yes	—	Yes
3	Yes	—	Yes	Yes
4	Yes	—	—	Yes
5	—	Yes	Yes	No[1]
6	—	Yes	—	No[1]
7	—	—	Yes	No[1]
8	—	—	—	Yes

[1] Not allowed per database design.

Dates will be imputed initially toward a specified target date for imputable scenarios 2, 4, and 8, and adjusted against the latest reasonable dates. The initial imputed date is determined by the following algorithm:

Table 6-5 Initial Imputed Date Algorithm

Available Year (YYYY)	Available Month (MM)			
	Missing	< Target Month	= Target Month	> Target Month
Missing	Target Date	—		
< Target Year	YYYY-12-31	YYYY-MM-LD		
= Target Year	Target Date	YYYY-MM-LD	Target Date	YYYY-MM-01
> Target Year	YYYY-01-01	YYYY-MM-01		

YYYY = available start date year; MM = available start date month; LD = last day of the month.

6.3.1 Missing/Incomplete AE Start Date

AE start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date
- Complete end date

6.3.2 Missing/Incomplete Medication Start Date

Medication start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date –1
- Complete end date

6.3.3 Missing/Incomplete AE/Medication End Date

AE and medication end dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment end date + 30
- Death date

6.4 Efficacy Endpoint Conventions

6.4.1 Clinical Response at EOT, TOC and Follow-up Visits

Clinical response at EOT, TOC, and follow-up visits will be based primarily on the global clinical assessment of the patient made by the investigator at that evaluation time-point.

Clinical response at the End of Treatment (EOT) visit (14 ± 2 days) is defined as Cure, Improvement, Failure, or Unknown.

Clinical response at the TOC visit (28 ± 2 days), and at the follow-up visit (54 ± 7 days) is defined as Cure, Failure or Unknown.

- Cure: Resolution of the clinical signs and symptoms of infection, when compared to baseline. No additional antibacterial treatment is required for disease under study
- Improvement: Reduction in severity of two or more, but not all, clinical signs and symptoms of infection, when compared with baseline (Cohorts 1-4, and ABSSSI patients in Cohort 5). In sepsis patients in Cohort 5 (birth to < 3 months), improvement is defined as reduction in severity of at least one abnormal clinical and laboratory parameter related to sepsis (see Inclusion Criteria for Cohort 5), when compared with baseline. For Cohorts 1-4 only, no additional antibacterial treatment is required for disease under study. This outcome category will only be used at the EOT evaluation. For Cohort 5, no rescue medication is required after at least 48 hours of start of study treatment.
- Failure: Persistence or progression of baseline clinical signs and symptoms of infection after at least 2 days (48 hours) of treatment or development of new clinical findings consistent with active infection
- Unknown: Extenuating circumstances preclude classification to one of the above
- Missing: Study data are not available for evaluation of efficacy for any reason

When classifying the patient's clinical response using the criteria listed above, "no additional antibacterial treatment is required for the disease under study" refers to: no additional treatment with an antibacterial agent with activity against the patient's isolate is required for the disease under study.

The occurrence of any of the following conditions will result in reassignment by sponsor as a failure:

- Patients previously assessed as a clinical failure: the outcome will always be clinical failure at subsequent time-points

- For Cohorts 1 – 4 (3 months to 17 years of age, inclusive): Patients who were given a concomitant antibiotic with activity against the patient's isolate for the disease under study prior to the evaluation time-points will be classified as a failure. For Cohort 5 (birth to < 3 months): Patients who are given rescue therapy (additional antibiotic therapy initiated after at least 48 hours of start of study treatment) will be classified as a failure.
- If a patient undergoes an unplanned surgical procedure (e.g., incision and drainage of abscess, major debridement, amputation) for non-improving or worsening infection after 3 days (72 hours) of study drug treatment, the clinical response should be considered a failure

6.4.2 Microbiological Response

Microbiological responses are defined as:

- Eradication: Source specimen demonstrates absence of the original baseline pathogen
- Presumed eradication: Source specimen was not available to culture and the subject was assessed as a clinical responder (48-72 hours post randomization), cure of improvement (EOT visit), cure (TOC and follow-up visit).
- Persistence: Source specimen demonstrates continued presence of the original baseline pathogen
- Presumed persistence: Source specimen was not available to culture and the subject was assessed as a clinical non-responder (48-72 hours post randomization), failure (EOT, TOC and follow-up visit)
- Indeterminate: Source specimen was not available to culture and the subject's clinical response was assessed as unknown or missing (EOT, TOC and follow-up visit)

6.4.3 Clinical Relapse

Clinical relapses for those patients who were cure at TOC visit are defined as:

Continued success

- Continuing favorable response (i.e, still cure at follow-up visit)

Relapse/Recurrence

- Relapse/recurrence of ABSSSI (i.e., failure at follow-up visit)

6.5 Safety Endpoint Conventions

6.5.1 Adverse Events

6.5.1.1 Missing Intensity or Relationship

If the investigator is unable to provide the actual values, the following imputations will be applied:

Table 6-6 Missing AE Intensity and Relationship Imputation Algorithms

Missing Value	Imputation	Timing
Intensity	Mild	Pretreatment Period
	Severe	Treatment Period
Relationship	—	Pretreatment Period
	Related	Treatment Period

6.5.2 Clinical Laboratory Assessments

6.5.2.1 Potentially Clinically Significant Criteria

Laboratory assessments values meeting the following criteria will be categorized as PCS. Note that for the PCS low flags, both the lower limit and percentage decrease criteria must be met, and for PCS high flags, both the upper limit and percentage increase criteria must be met.

Table 6-7 Clinical Laboratory PCS Criteria

Category	Parameter	Lower Limit	Upper Limit	Percent decrease from baseline	Percent increase from baseline
Chemistry	Albumin	< 0.6 × LLN	N/A	> 60%	N/A
	Amylase	N/A	> 3.0 × ULN	N/A	> 300%
	Alanine aminotransferase (ALT)	N/A	> 3.0 × ULN	N/A	>300%
	Alkaline phosphatase	< 0.5 x LLN	> 3.0 × ULN	>80%	>300%
	Aspartate aminotransferase (AST)	N/A	> 3.0 × ULN	N/A	>300%
	Bicarbonate (HCO3)	< 0.7 × LLN	> 1.3 × ULN	>50%	>30%
	Bilirubin, direct (conjugated)	N/A	> 2.5 × ULN	N/A	>150%
	Bilirubin, total	N/A	> 2.5 × ULN	N/A	>300%
	Blood urea nitrogen	N/A	> 3 × ULN	N/A	>300%
	Chloride	< 0.8 × LLN	>1.2 x ULN	>20%	>20%
	Creatinine	N/A	> 2.0 × ULN	N/A	>100%
	Gamma Glutamyl Transferase (GGT)	N/A	> 3.0 × ULN	N/A	>300%
	Glucose, random	< 0.6 × LLN	> 4.0 × ULN	>40%	>200%
	Lactate Dehydrogenase	<0.4 x LLN	> 4.0 × ULN	>60%	>300%
	Potassium	< 0.8 × LLN	> 1.2 × ULN	>15%	>20%
	Protein, total	< 0.6 × LLN	N/A	>60%	N/A
	Sodium	< 0.85 × LLN	> 1.1 × ULN	>10%	>10%
Hematology	Hematocrit	< 0.6 × LLN	> 1.3 × ULN	>25%	>30%
	Hemoglobin	< 0.6 × LLN	> 1.3 × ULN	>25%	>30%
	Red blood cell count	< 0.8 × LLN	> 1.3 × ULN	>20%	>30%
	White blood cell count	< 0.5 × LLN	> 2.0 × ULN	>60%	>100%
	Eosinophils, absolute cell count	N/A	> 4.0 × ULN	N/A	>400%
	Lymphocytes, absolute cell count	< 0.2 × LLN	> 2.2 × ULN	>70%	>100%
	Neutrophils, absolute cell count	< 0.5 × LLN	> 2.2 × ULN	>70%	>100%
	Platelet count	< 0.4 × LLN	> 2.0 × ULN	>40%	>100%

LLN: lower limit of normal; ULN: upper limit of normal; N/A: not applicable.

6.5.2.2 Continuous Descriptives Table Parameters

The following laboratory parameters will be summarized:

Table 6-8 Clinical Descriptive Table Parameters

Category	Parameters			
Hematology	Platelet count	***WBC count with Differential:***		
	RBC count	Neutrophils		
	Hemoglobin	Lymphocytes		
	Hematocrit	Monocytes		
		Eosinophils		
		Basophils		
Chemistry	BUN	Potassium	AST (SGOT)	Total bilirubin
	Creatinine	Sodium	ALT (SGPT)	Total protein
	Glucose (random)	Chloride	Alkaline phosphatase	Direct billirubin
	Gamma-glutamyl Transpeptidase (GGT)	Albumin	Lactate Dehydrogenase (LDH)	Amylase
	Bicarbonate	High-sensitivity C-reactive protein (hs-CRP)		

6.5.2.3 Character Values

Character values (eg, < 5, negative) will be reviewed prior to database lock and converted to numeric for analysis as appropriate. These conversions will be documented in the ADaM specifications.

6.5.3 Vital Signs

6.5.3.1 Potentially Clinically Significant Criteria

Vital sign values meeting *both* the actual value and change from baseline PCS criteria will be categorized as PCS:

Table 6-9 Vital Sign PCS Criteria

Parameter	Unit	PCS Category	PCS Criteria				
			Actual Value				Change from Baseline
			3 months to < 2 years old	2 years to < 6 years old	6 years to < 12 years old	12 years to 17 years old	
Systolic BP	mmHg	High	> 110	> 110	> 120	> 135	Increase ≥ 30
		Low	< 70	< 80	< 80	< 100	Decrease ≥ 30
Diastolic BP	mmHg	High	> 60	> 70	> 80	> 85	Increase ≥ 20
		Low	< 55	< 60	< 60	< 60	Decrease ≥ 20
Pulse rate	bpm	High	> 140	> 130	> 110	> 105	—
		Low	< 80	< 65	< 60	< 55	—

BP = blood pressure; bpm = beats per minute; Change from Baseline applies to all age cohorts.

6.5.3.2 Continuous Descriptives Table Parameters

The following vital sign parameters will be summarized:

Table 6-10 Vital Sign Descriptive Table Parameters

Parameters		
Systolic BP	Respiratory rate	Height[1]
Diastolic BP	Temperature	Weight[1]
Pulse rate		BMI[1]

BP = blood pressure.
[1]Baseline only.

6.6 Imputed Value Listing Conventions

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in endpoint derivation. In instances where imputed values will be presented, imputed values will be flagged. Actual rules will be fully defined in the table, figure, and data listing specification document.

7. References

Not applicable.

8. History of Change

Amendment 1:

Date	Section(s)	Description
1/17/2020	5.1.1.2.5	Modified unit for Creatinine clearance.
1/17/2020	5.1.1.4.4	Clarified to use central or local laboratory results.
1/17/2020	6.2.1	Revised and add footnote to clarity efficacy window.
1/17/2020	6.3	Revised imputation scenario.
1/17/2020	6.3.2	Revised imputation algorithm.
1/17/2020	6.5.2.1	Updated PCS criteria table.
3/2/2020	6.2.1, 6.2.2	Revised and added footnote on analysis visit window of 48-72 hours for Cohort 5 (birth to < 3 months).

Amendment 2:

Date	Section(s)	Description
10/26/2020	4	Specified all analyses were run for the U.S. CSR and will be rerun for EU CSR.