Basilea Pharmaceutica International Ltd.

Protocol BPR-CS-009

A randomized, double-blind, multi-center study to establish the efficacy and safety of ceftobiprole medocaril compared to daptomycin in the treatment of *Staphylococcus aureus* bacteremia, including infective endocarditis

17 June 2022

Statistical Analysis Plan

Version 2.0

Prepared by:

[redacted] **on Behalf of**
Basilea Pharmaceutica International Ltd.
Grenzacherstrasse 487
CH-4058 Basel/Switzerland

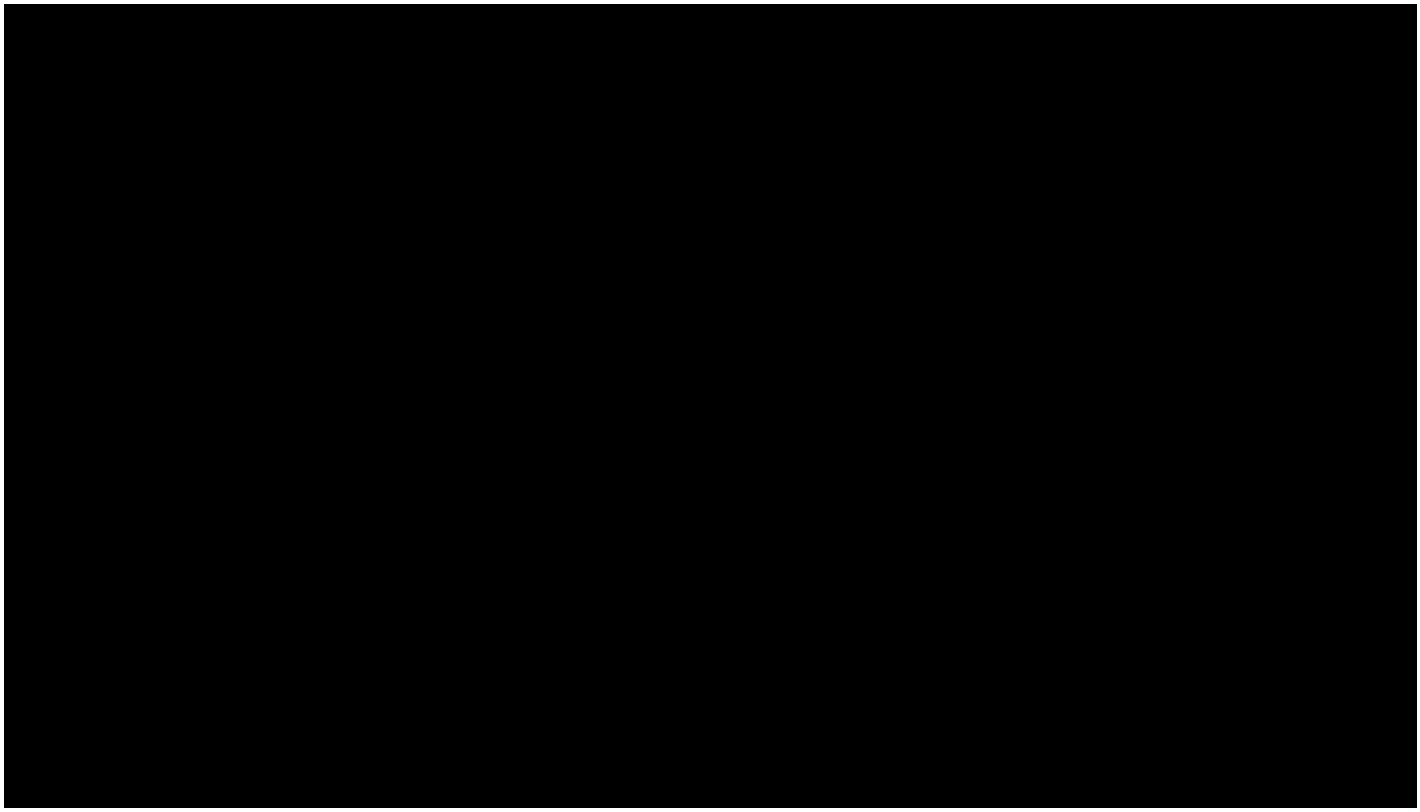

TABLE OF CONTENTS

LIST OF TABLES

List of Abbreviations	
ABSSSI	Acute Bacterial Skin and Skin Structure Infection
ACM	All-Cause Mortality
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CE	Clinically Evaluable
CI	Confidence Interval
CL_{CR}	Creatinine Clearance
CLSI	Clinical and Laboratory Standards Institute
CMH	Cochran–Mantel–Haenszel
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRP	C-reactive Protein
CV	Coefficient of Variation
DAIDS	Division of AIDS
DMID	Division of Microbiology and Infectious Diseases
DRC	Data Review Committee
DRM	Data Review Meeting
DSMB	Data and Safety Monitoring Board
DILI	Drug Induced Liver Injury
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
EOT	End-Of-Treatment
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	(United States) Food and Drug Administration
GGT	Gamma-Glutamyl Transferase
h	Hour(s)
HCT	Hematocrit
HGB	Hemoglobin
HR	Hazard Ratio
ICH	International Council for Harmonisation
IE	Infective Endocarditis
INR	International Normalized Ratio
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
K-M	Kaplan-Meier
LDH	Lactate Dehydrogenase
LIE	Left-Sided Infective Endocarditis
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration

mITT	Modified Intent-to-Treat
MLST	Multilocus Strain Typing
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
PD	Protocol deviation
PK	Pharmacokinetic(s)
PT	Preferred Term
PTE	Post-Treatment Evaluation
PVL	Panton-Valentine Leucocidin
RBC	Red Blood Cell
RIE	Right-Sided Infective Endocarditis
SAB	*Staphylococcus aureus* Bacteremia
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography
ULN	Upper Limit of Normal
WHO DDE	World Health Organization Drug Dictionary Enhanced
WBC	White Blood Cell

1. Introduction

This document outlines the statistical methods to be implemented in the analysis of data collected within the scope of Basilea Pharmaceutica International Ltd., Protocol BPR-CS-009 (A randomized, double-blind, multi-center study to establish the efficacy and safety of ceftobiprole medocaril compared to daptomycin in the treatment of *Staphylococcus aureus* bacteremia, including infective endocarditis).

The purpose of this Statistical Analysis Plan (SAP) is to define the planned statistical methods consistent with the study objectives. This plan should be read in conjunction with the study protocol version 9.0 (27 February 2020) and the case report forms (CRFs) version 13.0 (26 October 2021). All analyses will be conducted using SAS® Version 9.4 or higher.

2. Objectives

2.1. Primary objective

To demonstrate the non-inferiority of ceftobiprole to daptomycin for overall success as assessed by an independent Data Review Committee (DRC) in the treatment of *S. aureus* bacteremia (SAB), including infective endocarditis (IE), at the post-treatment evaluation (PTE) visit[1] in the modified intent-to-treat (mITT) population.

2.2. Secondary objectives

- To compare ceftobiprole with daptomycin with respect to:
  1. All-cause mortality (ACM) through Day 70 (PTE visit) and Day 28 in the ITT and mITT populations.
  2. Microbiological eradication rates (negative blood culture for *S. aureus*) at Day 4, Day 8, and the end-of-treatment (EOT) and PTE visits in the mITT and clinically evaluable (CE) populations.
  3. Overall success rates in the ITT, mITT, and CE populations:
     a) at the EOT and PTE (ITT and CE populations only) visits,
     b) at the EOT and PTE visits, for IE vs non-IE SAB,
     c) at the EOT and PTE visits, by renal-function status.
  4. Development of new metastatic foci, or other complications of SAB, after Day 7 in the mITT and CE populations.
  5. Time to *S. aureus* bloodstream clearance in the mITT and CE populations.
  6. Safety and tolerability (Safety population).
- To assess the pharmacokinetics (PK) of ceftobiprole (PK population).

[1] The PTE visit will be performed 70 days (±5 days) after randomization.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a randomized, double-blind, double-dummy, active-controlled, parallel-group, multi-center study in adult hospitalized patients with SAB, including IE, which is conducted in two parts.

The minimum treatment duration of ceftobiprole and daptomycin in both parts of the study is 21 days.

Part 1: Study treatment was restricted to a maximum of 28 days (N=80 patients who received study medication for 21–28 days, subject to a decision to proceed earlier to Part 2).

Part 2: Following a protocol pre-defined Data and Safety Monitoring Board (DSMB) interim safety assessment after treatment of 80 patients (approximately 40 patients per treatment group) who received study medication for 21–28 days, a decision was made to extend the maximum treatment duration to 42 days, and the protocol was amended accordingly.

Table 1 Summary of Treatment and Follow-Up Schedule

Study phase			
1	**2**	**3**	
Pre-treatment	**Active-treatment**	**Post-treatment**	
Screening assessments	**Randomization and study-drug treatment**	**End-of-treatment visit (EOT)**	**Post-treatment evaluation visit (PTE)**
Up to 72 h prior to randomization	Day 1 up to Day 42	Within 72 h after the last treatment administration	Day 70 (±5 days) post-randomization

The study comprises three phases (see Table 1):

1. Screening assessments of up to 72 h prior to randomization (with the possibility of utilizing existing transthoracic [TTE] and transesophageal [TEE] echocardiography assessments that demonstrated definite right-sided infective endocarditis (RIE) within 10 days of randomization).
2. Randomization and subsequent active treatment with intravenous study drug (ceftobiprole or daptomycin).
3. Post-treatment, comprising an EOT visit (within 72 h of last study-drug administration), Day 35 (±3 days), Day 42 (±3 days), and a PTE visit on Day 70 (±5 days) post-randomization.
   Note: Day 35 and Day 42 may be active treatment visits for patients in Part 2 if treatment for longer than 28 days is required. Day 35 and Day 42 are post-treatment visits

for all patients in Part 1, and for patients in Part 2 who are treated for longer than 28 days but have completed treatment by the Day 35 or Day 42 visits.

After randomization and during active treatment, patients will receive ceftobiprole medocaril powder for solution for infusion (administered as 2-h intravenous infusion) or daptomycin lyophilized powder for solution for infusion (administered as 0.5-h intravenous infusion).

3.2. Study Endpoints

3.2.1. Primary Endpoint

The study is designed to determine whether ceftobiprole is non-inferior to daptomycin for the primary endpoint of overall success as assessed by the DRC at the PTE visit.

Overall success is defined as all of the following criteria being met:

1. Patient alive at Day 70 (±5 days) post-randomization.
2. No new metastatic foci or complications of the SAB infection.
3. Resolution or improvement of SAB-related clinical signs and symptoms.
4. Two negative blood cultures for *S. aureus* (without any subsequent positive blood culture for *S. aureus*):
    - at least one while the patient is on active study treatment; AND
    - confirmed by at least one subsequent negative blood culture for *S. aureus*
        - either in the period between 7 days after the EOT visit and the PTE visit
        - or at the PTE visit.

Treatment failure is defined as any of the following:

1. Premature discontinuation of study treatment due to DRC-assessed lack of efficacy or for adverse events (AEs) that represent manifestation of disease progression or relapse, at any time between first dose of study drug and the PTE visit.
2. Development of new metastatic or other complications related to SAB (see Section 5.4.5.3.2 of the Protocol) between Day 8 and the PTE visit. Development of new metastatic or other complications of SAB prior to Day 8 will be assessed by the DRC on a case-by-case basis to assess whether these constitute a delayed manifestation of the baseline disease or new complications.
3. SAB relapse/reinfection based on evidence from a blood culture positive for *S. aureus* (after documented clearance of *S. aureus* from the bloodstream and clinical improvement) between the EOT and PTE visits.
4. Receipt of systemic non-study antibacterial treatment, other than those permitted under the protocol, for the treatment of SAB. This includes patients who are prematurely discontinued from study therapy due to an AE, but who require continuation of antibacterial treatment for SAB.

5. Treatment of infections other than SAB with systemic non-study antibacterial treatment which is potentially effective against *S. aureus* (see Appendix 5 of the Protocol), and which is considered by the DRC to have a relevant impact on the primary endpoint in accordance with guidelines provided in Appendix 6 of the Protocol.
6. Death for any reason between first administration of study drug and the PTE visit.
7. Indeterminate outcome, defined as any data needed to determine whether the outcome is success or failure missing at the PTE visit, including but not limited to:
   a) missing PTE visit, or missing key data to evaluate the primary endpoint
   b) lost-to-follow-up, or patients who withdrew consent prior to the PTE visit
   c) patients not meeting the criteria for Success or Failure, or patients not meeting all criteria for overall success
8. Requirement for systemic antibacterial treatment for SAB beyond EOT.

As specified in point 7 above, patients with missing data relevant for the assessment of the primary endpoint, or who are lost to follow-up, will be considered by the DRC as having indeterminate outcome (treatment failure) and will be analyzed accordingly for the primary analysis.

The primary endpoint is to be assessed in the modified intent-to-treat (mITT) population.

3.2.2. Secondary Endpoints

1. ACM will be assessed at Day 70 (PTE visit) in the mITT population.

   ACM will also be assessed at Day 28 in the mITT population, and at Day 28 and Day 70 in the ITT population.
2. Microbiological eradication will be assessed by DRC at Day 70 (PTE visit) in the mITT population.

   Microbiological eradication will also be assessed by DRC at Day 70 (PTE visit) in the CE population, and at Day 4, Day 8, and the EOT visit in the mITT and CE populations.

   Eradication: No growth of the baseline *S. aureus* pathogen(s) from blood, secondary to an adequate clinical response, based on a negative blood culture while the patient is on active study treatment, which is confirmed by at least one subsequent negative blood culture for *S. aureus* at least 24 h after the first negative blood-culture, without any subsequent *S. aureus* positive blood culture, either in the period between 7 days after EOT and the PTE visit, or at the PTE visit.

   Failure: Persistence, relapse/reinfection of *S. aureus* infection, defined as one or more of:

   - Ongoing *S. aureus* positive blood cultures leading to discontinuation of the study drug
   - Subsequent isolation (relapse/reinfection) of *S. aureus* from a blood culture after clearance of *S. aureus* bacteremia and clinical improvement

- Absence of at least two *S. aureus* negative blood cultures (at least one negative blood culture on active study treatment, and at least one post-treatment) to confirm eradication

Relapse/reinfection between EOT and PTE that is reported to the Investigator from a healthcare provider not involved in the study (e.g., from another hospital), needs to be thoroughly documented and will be reviewed by the Investigator and the DRC for determination.

3. The overall success rate (as described in Section 3.2.1) will be assessed in the ITT, mITT, and CE populations:
   a) at the EOT and PTE (ITT and CE populations only) visits,
   b) at the EOT and PTE visits, for RIE vs non-IE SAB (see Section 4.4.5),
   c) at the EOT and PTE visits, by renal-function status (see Section 4.4.5).
4. Development of new metastatic foci or other complications of SAB after Day 7 will be assessed in the mITT and CE populations. Complications include newly diagnosed IE or complicated SAB with metastatic foci or other complications of *S. aureus* infection, including metastatic foci in the vertebral column (vertebral abscess, osteomyelitis, discitis or epidural abscess), cerebral abscess/infarction, splenic abscess/infarction, renal abscess/infarction, psoas abscess or other deep-tissue abscess, other metastatic infection of native tissue, septic arthritis (or bacterial joint infection/empyema), septic or suppurative thrombophlebitis, and septic pulmonary emboli/infarction.
5. Time to *S. aureus* bloodstream clearance is defined as the elapsed time (days) from randomization to bloodstream clearance. Bloodstream clearance is defined as the occurrence of two consecutive study days with blood-culture-negative assessments for S. aureus; bloodstream clearance in patients with intermittent positive on treatment blood cultures will start after the last positive blood culture. Patients with S. aureus relapse or reinfection as per DRC assessment will not be considered as bloodstream clearance. Time to bloodstream clearance will be assessed in the mITT and CE populations.
6. Safety and tolerability of ceftobiprole will be assessed in the Safety population by incidence, type, severity, and relationship to study medication of AEs; and changes in laboratory tests (hematology, blood chemistry including haptoglobin, urinalysis, and Coombs test).
7. Pharmacokinetics of ceftobiprole in the PK population.

   Plasma levels of ceftobiprole and the β-lactam ring open product BAL1029:

   <u>Sparse PK sampling (all patients)</u>

   - Day 3: predose, 2 h (end of infusion), 4 to 6 h
   - Day 12: predose, 2 h (end of infusion), 4 to 6 h

   <u>Rich PK sampling (selected sites, N=40 patients)</u>

   - Day 3: predose, 2 h (end of infusion), 3 h, 4 h, 6 h
   - Day 12: predose, 2 h (end of infusion), 4 to 6 h

3.2.3. Additional Endpoints

The following endpoints (in addition to those described in protocol) will be used to further explore the available data and provide more comparisons between ceftobiprole and daptomycin.

- Mortality due to SAB as assessed by DRC at Day 28 and Day 70 (PTE visit) (mITT and ITT populations)
- Investigator-assessed overall success evaluated at EOT and PTE (mITT and CE populations)

  Note: The level of clinical success is rated by the Investigator as cured, improved, stable, worsened, and failure. Overall success is defined as a clinical success rated as cured or improved. Other clinical outcomes will be considered as failure.
- Concordance between Investigator and DRC-assessed overall success (mITT and CE populations).
- Microbiological eradication rate (as per secondary endpoint) in patients with an overall outcome of failure at EOT and PTE visits per DRC assessment (primary endpoint) (mITT and CE populations).
- Time to (any pathogen) bloodstream clearance is defined as the elapsed time (days) from randomization to bloodstream clearance. Bloodstream clearance is defined as the occurrence of two consecutive study days with blood-culture-negative assessments, with the first day with negative blood culture assessment being used for calculating the time to bloodstream clearance; bloodstream clearance in patients with intermittent positive on treatment blood cultures will start after the last positive blood culture. Patients with subsequent positive blood culture will not be considered as bloodstream clearance. Time to bloodstream clearance will be assessed in the mITT and CE populations.
- Distribution at baseline and post-baseline of patients (mITT and CE populations) with
  - blood *S. aureus*,
  - blood other than *S. aureus* (Gram-positive/Gram-negative) pathogens,
  - non-blood *S. aureus*,
  - non-blood other than *S. aureus* (Gram-positive/Gram-negative) pathogens.
- Distribution of patients with blood *S. aureus* by virulence markers (Panton-Valentine Leucocidin [PVL] status, *mecA* status, oxacillin susceptibility) at baseline (mITT and CE populations). Other genotypic markers (e.g., SCCmec, *spa,* multilocus strain typing [MLST], and clonal complex typing) will be summarized when available.
- Distribution of ceftobiprole, daptomycin, and aztreonam minimum inhibitory concentration (MIC) (mITT and CE populations) for each pathogen. For this analysis, the highest MIC of each pathogen will be used if there are multiple isolates of the same pathogen.
- Shift in ceftobiprole, daptomycin, and aztreonam MIC results from baseline to PTE by specimen source (blood or non-blood) and pathogen (any) (mITT and CE populations).

- Shift in ceftobiprole, daptomycin, and aztreonam MIC results from baseline to maximum MIC value post-baseline by specimen source (blood or non-blood) and pathogen (any) (mITT and CE populations).
- Health economic outcome measures (mITT and CE populations).

3.3. Treatments

After randomization and during active treatment, patients will receive either ceftobiprole as 2-h intravenous infusions (Table 2), or daptomycin as 0.5-h intravenous infusions (Table 3).

Aztreonam may be used in the daptomycin group for coverage of Gram-negative infections (i.e., for polymicrobial bloodstream infections or for Gram-negative non-bloodstream infections). Patients randomized to the ceftobiprole group who are considered to require coverage against Gram-negative infections will receive dummy treatment with placebo so that blinding is maintained during the active treatment phase.

The target treatment duration is 21 to 42 days of study drug, with the treatment duration within this range as per the Investigator's discretion.

Exceptional cases of patients who are considered after randomization to require longer than 42 days of treatment will be discontinued from the study, with treatment allocation remaining blinded. These patients are to be switched to open-label non-study treatment according to institutional practice and considered failures in the ITT and mITT analyses irrespective of treatment group.

Ceftobiprole medocaril powder for solution for infusion will be administered as a 2-h intravenous infusion according to the schedule in Table 2.

Table 2 Ceftobiprole Administration

Study day	Normal renal function to mild renal impairment ($CL_{CR} \geq 50$ mL/min)	Renal impairment (non-dialysis)	Intermittent hemodialysis or peritoneal dialysis
Day 1 to Day 8	500 mg q6h	**CL_{CR}** 30– < 50 mL/min : 500 mg q8h CL_{CR} <30 mL/min : 250 mg q8h	250 mg q24h
Day 9 onwards	500 mg q8h	CL_{CR} 30–< 50 mL/min : 500 mg q12h CL_{CR} < 30 mL/min : 250 mg q12h	250 mg q24h

CL_{CR}=Creatinine clearance based on the Cockcroft-Gault formula.

Daptomycin lyophilized powder for solution for infusion will be administered as a 0.5-h intravenous infusion according to the schedule in Table 3.

Table 3 Daptomycin Administration

	Normal renal function to moderate renal impairment ($CL_{CR} \geq 30$ mL/min)	Renal impairment (non-dialysis) ($CL_{CR} < 30$ mL/min)	Intermittent hemodialysis or peritoneal dialysis
Daptomycin (0.5-h infusion)	6 mg/kg q24h	6 mg/kg q48h	6 mg/kg q48h

CL_{CR}=Creatinine clearance based on the Cockcroft-Gault formula.

In accordance with institutional standards, an increase in the dose of daptomycin administered (up to 10 mg/kg) may be implemented.

To maintain the blinding of study treatments, patients in the ceftobiprole group will receive dummy infusions with placebo (physiological saline, 0.9% NaCl) matching daptomycin, and patients in the daptomycin group will receive dummy infusions with placebo (physiological saline, 0.9% NaCl) matching ceftobiprole.

3.4. Dose Adjustment/Modifications

Study drug treatment must be initiated within the 6 h after randomization. On each treatment day, study-drug administration should occur within ±1 h for ≤ q6h dose regimens, and ±2 h for > q6h dose regimens, of the scheduled time point.

3.4.1. Ceftobiprole

- For patients with normal to mildly-impaired renal function (i.e., $CL_{CR} \geq 50$ mL/min), ceftobiprole 500 mg is to be administered as a 2-h intravenous infusion every 6 h, from study Day 1 up to and including study Day 8. From study Day 9 until the end of treatment, ceftobiprole 500 mg is to be administered as a 2-h intravenous infusion every 8 h.
- For patients with renal impairment (i.e., $CL_{CR} < 50$ mL/min) who do not require dialysis, the following dose adjustments will be made (see Table 2):
  - CL_{CR} 30 – < 50 mL/min: ceftobiprole 500 mg is to be administered as a 2-h intravenous infusion every 8 h from study Day 1 up to and including study Day 8. From study Day 9 until the end of treatment, ceftobiprole 500 mg is to be administered as a 2-h intravenous infusion every 12 h.
  - $CL_{CR} < 30$ mL/min: ceftobiprole 250 mg is to be administered as a 2-h intravenous infusion every 8 h from study Day 1 up to and including study Day 8. From study Day 9 until the end of treatment, ceftobiprole 250 mg is to be administered as a 2-h intravenous infusion every 12 h.
- For patients with renal impairment who require hemodialysis or peritoneal dialysis, ceftobiprole 250 mg is to be administered as a 2-h intravenous infusion every 24 h, from study Day 1 up to the end of treatment. On the days of hemodialysis, ceftobiprole will be administered after the hemodialysis session has been completed.

3.4.2. Daptomycin

- For patients with normal to moderately-impaired renal function (i.e., $CL_{CR} \geq 30$ mL/min), daptomycin 6 mg/kg is to be administered as a 0.5-h intravenous infusion every 24 h, from study Day 1 until the end of treatment (see Table 3).
- For patients with renal impairment (i.e., $CL_{CR} < 30$ mL/min) who do not require dialysis, daptomycin 6 mg/kg is to be administered as a 0.5-h intravenous infusion every 48 h, from study Day 1 until the end of treatment (see Table 3).
- For patients with renal impairment who require hemodialysis or peritoneal dialysis, daptomycin 6 mg/kg is to be administered as a 0.5-h intravenous infusion every 48 h, from study Day 1 until the end of treatment (see Table 3).

4. General Statistical Considerations

Continuous data will be described using descriptive statistics (i.e., n, mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be described using the patient count and percentage in each category. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported up to a maximum of 3 decimal places. Mean and median will be displayed to one level of precision greater than the data collected up to a maximum of 3 decimal places. Standard deviation and standard error (SE) will be displayed to two levels of precision greater than the data collected up to a maximum of 3 decimal places.

When count data are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of patients in that treatment within the population of interest, unless otherwise specified.

All comparisons will be for ceftobiprole versus daptomycin. For between-group comparisons, a two-sided 95% CI for the difference in outcome rates between the two treatment groups will be derived, unless otherwise specified. A two-sided test will be used at a Type I error rate of 0.05 for comparison between the ceftobiprole group and the daptomycin group. No adjustment for Type I error will be made for multiple comparisons.

P-values will be rounded to four decimal places. If a p-value is less than 0.0001 it will be reported as “<0.0001.” If a p-value is greater than 0.9999 it will be reported as “>0.9999”.

Data will be displayed in all listings sorted by treatment group.

4.1. Sample Size

The sample size estimate is based on:

- A point estimate for overall success of 40% in each treatment group in the mITT population
- One-sided alpha level of 0.025
- Power of > 80%
- Non-inferiority margin of 15% for the between-group difference in the primary endpoint

With these assumptions, enrollment of 175 patients per treatment group (total of 350 patients) is required in the mITT population. Assuming that approximately 90% of patients in the ITT population will have confirmed SAB and will therefore be included in the mITT population, 195 patients per group (total of 390 patients) will need to be randomized and receive study treatment.

A sample size of 350 patients in the mITT population (175 per group) provides at least 80% power to reject the null hypothesis (H_0) against the alternative hypothesis (H_A) at the one-sided alpha level of 0.025 as follows, using a two-group large-sample normal approximation test of proportions:

H_0: $P_{daptomycin}$ minus $P_{ceftobiprole} \geq 0.15$ versus

H_A: $P_{daptomycin}$ minus $P_{ceftobiprole} < 0.15$

A justification of the non-inferiority margin of 15% is provided in Appendix 8 of the study protocol. The assumption of an overall success rate of 40% in each treatment group in the mITT population is based on the respective outcomes in patients with complicated bacteremia from a previous Phase 3 study (Fowler 2006), in which overall success across treatment groups in patients with complicated SAB was 40% (49/121). Using a conservative approach in the sample size calculation, a sample size of 350 patients (175 patients per group) in the mITT population would still provide 80% power for the assessment of the primary endpoint if the overall success rate is 50% instead of 40% (see Appendix 8 Table E3 of the study protocol).

The assumption that approximately 90% of patients in the ITT population will have confirmed SAB is based on the result from a previous Phase 3 study (Fowler 2006) in SAB, in which 96% of patients in the ITT population (235 out of 246 patients) were in the mITT population.

4.2. Randomization, Stratification, and Blinding

Patients will be randomly assigned in a blinded manner using the centralized Interactive Web Response System (IWRS) according to pre-generated randomization schedules. Eligible patients will be randomized in a 1:1 ratio to receive ceftobiprole or daptomycin. The investigator/designee will contact the IWRS to obtain the study treatment assignment and will dispense blinded treatment accordingly.

Randomization will be stratified via block randomization by:

- Study site
- Dialysis status
- Prior antibacterial treatment use (i.e., use of any systemic antibacterial treatment potentially effective against *S. aureus* within 7 days of randomization)

The unblinded site pharmacist/designee will provide blinded and properly-labeled study medication to investigational staff. At the site, only the unblinded pharmacist/designee will have access to treatment codes via the IWRS. Investigators, other site staff, sponsor and contract research organization employees involved in the conduct of the study will remain blinded to the treatment codes until the database has been locked for final analysis. Refer to the Blinding Plan for further details.

Individual treatment codes for each randomized patient will be available to investigators from the IWRS. The treatment code should only be broken in medical emergencies. It is advisable to contact the medical monitor prior to breaking the blind. The investigator will record the reason for unblinding in the patient's records/source documents.

4.3. Analysis Populations

4.3.1. Intent-to-Treat (ITT) Population

The ITT population consists of all randomized patients. All patients in the ITT population will be analyzed according to the treatment they were randomized, not according to what they received.

4.3.2. Modified Intent-to-Treat (mITT) Population

The mITT population consists of the subset of patients in the ITT population who have received any amount/dose of study medication, and who have a blood culture positive for *S. aureus* at baseline based on a central microbiology laboratory assessment. Note that patients who are missing a central microbiological assessment may be included in the mITT population if there is documented unequivocal evidence of a baseline blood culture positive for *S. aureus* at the local laboratory. The mITT population will be used for the primary efficacy analysis as well as key secondary efficacy analyses.

4.3.3. Clinically Evaluable (CE) Population

The CE population consists of the subset of patients in the mITT population who have complied with important aspects of the study:

- No major protocol deviations, as per PD review process document version 5.0 or above.
- No treatment with potentially effective (anti-staphylococcal) systemic antibacterial treatment (see Appendix 14.2) for more than 48 hours within the 7 days prior to randomization, in patients classified as non-persistent SAB per DRC assessment. This will be based on medical review of reported antibiotic treatments, including susceptibility information from the central microbiology laboratory.

- No uncomplicated SAB per investigator assessment,
- No LIE as a baseline condition for patients in cohort 1 per investigator assessment,
- No indeterminate outcome for the primary endpoint at PTE as per DRC, unless the indeterminate outcome is due to a safety reason.

Major protocol deviations and patients excluded from CE population will be identified prior to the database lock and study unblinding. The CE population will be used for secondary efficacy analyses.

4.3.4. Safety Population

The Safety population consists of all randomized patients who received at least one dose of study drug. Patients in the safety population will be analyzed according to the first study drug received.

4.3.5. Pharmacokinetic (PK) Population

The PK population will include all patients who received at least one dose of ceftobiprole and have at least one plasma concentration measurement obtained by the appropriate methodology.

4.4. Other Important Considerations

4.4.1. Definition of Baseline

Unless otherwise specified, baseline will be defined as the last non-missing assessment prior to the first study drug administration. Both scheduled and unscheduled visits and assessments will be used in determining baseline.

For microbiological analysis, the identification of baseline pathogen(s) is based on all isolates collected within 80 hours prior to randomization date and time, up to first dose date and time.

4.4.2. Definition of Infecting Organism (i.e., Pathogen), Monomicrobial vs Polymicrobial Infections, MIC Value, and Virulence Factors

S. aureus (MSSA, MRSA) is the target organism for this bacteremia study. It is expected to be identified (at least from blood) for all enrolled patients, and it will be considered as infecting regardless of the infection site (blood or other specimen type).

The identification of other organisms as infecting (i.e., pathogen) or non-infecting is based on investigator assessment as reported in the appropriate section of the CRF.

When multiple blood samples are taken on a specific study day and are not all sent for central microbiology testing, only the results from the central microbiology lab on that study day will be considered for the identification of organisms.

Infections will be classified as monomicrobial or polymicrobial as follows:

- A monomicrobial infection is an infection with *S. aureus* (MRSA and/or MSSA and/or Methicillin Susceptibility Unknown) in blood without any other non-*S. aureus* pathogen from any source.
- A polymicrobial infection is an infection with *S. aureus* from blood plus any other non-*S. aureus* pathogen, whatever the source is (blood or non-blood).

  Polymicrobial infections will be further classified according to the source of the sample:
  - Bloodstream polymicrobial infection: an infection with *S. aureus* isolated from blood plus any other non-*S. aureus* pathogen also isolated from blood, regardless of presence or absence of pathogen from non-blood source.
  - Non-bloodstream polymicrobial infection: an infection with *S. aureus* isolated from blood plus any pathogen isolated from non-blood source, and without any pathogen other than *S. aureus* isolated from blood.

Table 4 Classification of Monomicrobial vs Polymicrobial Infections

			Blood Non-*S. aureus*	
			Present	**Absent**
Non-blood	***S. aureus***	**Present**	Bloodstream polymicrobial	Monomicrobial
		Absent	Bloodstream polymicrobial	Monomicrobial
	Non-*S. aureus*	**Present**	Bloodstream polymicrobial	Non-blood polymicrobial
		Absent	Bloodstream polymicrobial	Monomicrobial

For the purpose of the MIC distribution analysis, in case of MIC results from multiple isolates of the same species, the highest MIC value will be retained for that pathogen. Separate MIC distribution analysis will be presented for blood and non-blood isolates.

For the *S. aureus* PVL status, *mecA* status, oxacillin susceptibility and other genotypic markers data from all isolates will be considered.

4.4.3. Study Day Calculation and Visit Windows

Visit windowing approaches will not be used for this study. Visit based summaries will include scheduled assessments only. If more than the specified number of measurements has been taken in a scheduled visit, the latest recorded values will be used in visit summaries, unless otherwise stated. All scheduled and unscheduled post-baseline assessments will be used for derivation of minimum and maximum post-baseline values. If more than one assessment has the same maximum value, then the record with earliest occurrence will be selected as the maximum assessment. If more than one assessment has the same minimum value, then the record with earliest occurrence will be selected as the minimum assessment.

For microbiology, unscheduled visits reconcilable with a scheduled visit will be considered as assessed at the scheduled visit (e.g., unscheduled Visit 3 will be considered as Visit 3 since Visit 3 is a scheduled visit per protocol).

The following conventions will be used to calculate analysis study day:

- Day 1 is the day of first study drug administration. Day −1 is the day before Day 1.
  No Day 0 is defined for this study.
- Prior to Day 1, the algorithm is:
  Study Day = visit/examination date – date of first study drug administration.
- For Day 1 and subsequent days, the algorithm is:
  Study Day = visit/examination date – date of first study drug administration + 1.

Summary data such as adverse events and concomitant medications will not be reported by visit. Tables which report abnormalities (e.g., clinically notable abnormalities, laboratory shift tables) will include all assessments.

4.4.4. Missing and Partial Data

Patients with missing data relevant for an assessment will be considered non-responders for the response analysis of that assessment.

For partial dates, the algorithms for imputation will vary depending upon the parameter; the details can be found in Appendix 14.1.

4.4.5. Pre-specified Subgroups

Subgroup analyses will be performed for the primary and secondary efficacy endpoints where applicable.
Subgroup analyses will include the following factors:

- Age (years) (18–34, 35–64, 65–74, ≥75)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Geographic Region (Europe, North America, Latin America, Other Regions)
  Note: In case of limited information (<10 patients per region) to properly assess a Region group, pre-defined Region groups may be further pooled.
- Baseline blood *S. aureus* (MRSA, MSSA), overall and by Panton-Valentine Leucocidin (PVL) status (Positive, Negative, Unknown)
- Baseline blood MRSA, overall and by *mecA* status, oxacillin susceptibility and other genotypic markers when available
- Bloodstream infection type (monomicrobial, polymicrobial [any, bloodstream, non-bloodstream]) (see Section 4.4.2)

- Study Drug(s) (ceftobiprole, daptomycin, aztreonam) MIC for pathogens at baseline, including pathogens other than *S. aureus* isolated from blood and pathogens from sources other than blood, overall, by bloodstream infection type, and geographical region.
- Baseline SAB Category per Investigator assessment (except for persistent SAB which will be assessed per DRC because the evaluation of prior appropriate anti-staphylococcal antibiotic treatment requires the review of central microbiology/susceptibility results), overall and by baseline blood *S. aureus* (i.e., MRSA, MSSA and Methicillin Susceptibility Unknown). The different subgroups are specified in Section 6.2.2.
- Baseline SAB Category per DRC assessment (primary endpoint only). The different subgroups are specified in Section 6.2.2.
- Known Predisposing Risk Factors for SAB/Endocarditis (e.g., History of Injection Drug Use, Hemodialysis Dependence)
- Type of Device Used (Intravascular, Extravascular)
- Baseline Fever Status (Fever [> 38°C / 100.4°F oral, > 38.5°C / 101.3°F tympanic, > 37.5°C / 99.5°F axillary, or > 39°C / 102.2°F rectal], No Fever [Formulae applicable to 'Fever' inverted, i.e., using ≤ in place of >])
- Prior Antibacterial Treatment (Yes, No)
  Note: Patients with prior antibacterial treatment are patients treated with potentially effective systemic antibacterial treatment within the 7 days prior to randomization (see Appendix 14.2 for example of potentially effective systemic antibacterial treatment).
- Prior Antibacterial Treatment (Yes, No), excluding DRC-assessed persistent SAB (primary endpoint only)
- Prior Antibacterial Treatment (Yes, No), excluding DRC-assessed persistent SAB, and considering susceptibility information from the central microbiology laboratory to define effective antibacterial treatment (primary endpoint only). See Appendix 14.3 for the algorithm to define susceptibility of MSSA/MRSA against the respective antibiotic treatments.
- Baseline Creatinine Clearance (mL/min) (Chronic Dialysis, < 30, 30 – < 50, 50–80, >80)
  Note: Patients on chronic dialysis are those undergoing chronic dialysis as per Investigator's assessments on the 'Categories of Complicated SAB' CRF page. Patients on chronic dialysis with any creatinine clearance entered fall only under the Chronic Dialysis category. The other numerical categories apply for patients not on chronic dialysis.
- Concomitant Antibacterial Treatment Potentially Effective against *S. aureus* (Yes, No)
- Concomitant Antibacterial Treatment for Gram-Negative Coverage (Yes, No)

4.4.6. Duration (e.g., for Adverse Events)

If date and time are collected, then duration is calculated as event end date and time minus event onset date and time. Duration will be displayed as days and fraction of days or as hours and fractions of hours depending on which appears most appropriate. Unit is days or hours.

If only date is collected, then duration is calculated as event end date minus event onset date + 1. Unit is days.

4.4.7. Coding Dictionaries

Adverse events, medical history and prior and concomitant medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or later.

Previous and concomitant treatments will be coded with the World Health Organization Drug Dictionary Enhanced (WHO DDE) dated 01MAR2021 or later (format B3).

5. Subject Disposition

5.1. Disposition

A summary of the analysis sets includes the number and percentage of patients for the following categories: patients in the ITT population, patients randomized but never dosed, patients in the Safety population, patients in the mITT population, patients in the CE population, and patients in the PK population**.** All percentages will be based on the number of patients in ITT population. Patients who failed screening and the reasons for screen failure will only be listed for all enrolled patients.

A summary of the patients excluded from mITT/CE populations and the reasons for exclusion will be presented. This summary will include the number and percentage of patients for the following categories: patients excluded from the mITT population and reasons, and patients excluded from the CE population and reasons. Percentages for exclusion reasons will be based on the number of patients excluded from the specific analysis set being summarized. Patients could be excluded from an analysis set for more than one reason.

Patient disposition will be summarized for ITT and mITT, and CE populations overall and by baseline blood *S. aureus*. A disposition of patients includes the number and percentage of patients for the following categories: patients who completed the study, patients who did not complete the study with reasons, patients who completed the study treatment, patients who discontinued study treatment early with reasons for discontinuation, patients who completed the EOT visit, patients did not complete the EOT visit with overall reasons, patients who completed the PTE visit, patients who did not complete the PTE visit with overall reasons. All percentages will be based on the number of patients from the respective analysis population.

A table and plot of time to discontinuation of study drug will be provided using Kaplan-Meier (K-M). Time to discontinuation is defined as the time from date and time of

randomization to date and time of study drug discontinuation. Patients who completed study treatment will be censored at the last point of known study drug administration. If the patient is not given study drug, then the time to discontinuation will be 0. Analysis will be conducted based on ITT, mITT and CE populations overall and by baseline blood *S. aureus*.

Patient disposition data will also be presented in a listing.

A summary of enrollment will be provided for each geographical region, country, and site for ITT Population.

5.2. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The protocol deviations will be categorized as significant and non-significant deviations. The significant deviations will be further classified as major and minor. The final list of protocol deviations will be documented prior to unblinding the study data, and patients with major protocol deviations will be identified as part of the data review meeting (DRM) process, prior to database lock.

Major protocol deviations will be presented in a summary table by protocol deviation category and treatment for ITT and mITT populations. All the significant deviations will be presented in a listing.

5.3. COVID-19 and Related Events

The number and percentages of patients with COVID-19 (either as medical history and/or adverse events) will be tabulated. The number and percentages of patients with COVID-19 related events as defined in Section 8.1.3 will also be provided. Patients with COVID-19 events will be presented in a listing.

6. Demographics and Baseline Characteristics

The following demographics and baseline characteristics data will be presented in tables using descriptive statistics for ITT, mITT and CE populations overall and by baseline blood pathogen. The demographic and baseline characteristics consist of:

- Age (integrated from IWRS)
- Age Category (years) (< 18, 18–34, 35–64, 65–74, ≥ 75)
- Gender (integrated from IWRS) (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Geographic Region (Europe, North America, Latin America, Other Regions)
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline Body Mass Index (BMI) (kg/m^2)

- Prior Antibiotic Medication (Prior Treatment, No Prior Treatment) according to the definitions and note for Prior Antibacterial Treatment subgroups in Section 4.4.5
- Concomitant Antibacterial Medication (Aztreonam, Metronidazole)
- Baseline Creatinine Clearance (mL/min) (Chronic dialysis, Not on Chronic Dialysis [<30, 30 – <50, 50–80, >80]); see note for Baseline Creatinine Clearance subgroups in Section 4.4.5
- Baseline Fever Status (Fever [> 38 °C / 100.4 °F oral, > 38.5 °C / 101.3 °F tympanic, > 37.5 °C / 99.5 °F axillary, or >39 °C / 102.2 °F rectal], No Fever [Formulae applicable to 'Fever' inverted, i.e., using ≤ in place of >])
- Baseline WBC Count [Abnormal (WBC < 4.0×10^9/L or WBC > 10.0×10^9/L), Normal (4.0×10^9/L ≤ WBC ≤ 10.0×10^9/L)]
- Baseline Systolic Blood Pressure (mmHg) (< 90, ≥ 90)
- Baseline Pulse Rate (bpm) (> 90, ≤ 90)

Demographics and baseline characteristics data will be listed for ITT and mITT and CE population will be flagged corresponding to each patient.

Baseline microbiological characteristics will be presented in separate tables displaying the number of patients with pathogen(s) identified at baseline, overall and by bloodstream infection type (monomicrobial, polymicrobial [any, bloodstream, non-bloodstream]) and geographical regions, for mITT and CE populations. Note that pathogens will be identified by the central or local microbiology laboratory. Identification and susceptibility test results from the central microbiology laboratory will be used in the analyses. Local laboratory identification results will only be used if no central laboratory data are available.

Baseline characteristics data will be listed.

6.1. Female Reproductive System

Female reproductive system at screening will be listed for female patients for the ITT population and will consist of fertility status, number of months if post-menopausal, and method of birth control.

6.2. Medical/Surgical History

6.2.1. General Medical/Surgical History

The number and percentage of patients with any medical history other than SAB history will be summarized overall and for each system organ class (SOC) and preferred term (PT) for ITT, mITT and CE analysis populations. Percentages will be calculated based on number of patients from the respective analysis population.

Patient medical/surgical history data including specific details will be presented in a listing for ITT population.

6.2.2. Disease-Specific History

Number and percentage of patients with following disease specific history will be summarized for the ITT, mITT and CE populations:

- The number and percentage of patients with predisposing risk factors for SAB/Endocarditis will be summarized. Status of each predisposing risk factor (ongoing or not) at the start of dosing will be summarized only if applicable.
- Details of intravascular catheter or prosthetic device used (type, location, ongoing, infection status, source of SAB)

Details of SAB-specific medical history, planned surgeries, intravascular implant and removal dates, SAB category confirmation, and signs and symptoms will also be listed.

The number and percentage of the following six categories of *S. aureus* bacteremia SAB (by Investigator, except for persistent SAB that will be assessed by DRC) will be summarized by treatment group at baseline, by bloodstream infection type for ITT, mITT and CE populations. Investigator assessments performed up to 7 days after randomization (i.e., aiming to confirm the diagnosis of complicated SAB) will be considered. Patients with no SAB will be summarized separately. Category numbers #1, #2 and #4 from below will not be available for post baseline sections.

1. Uncomplicated SAB
2. Any complicated SAB
3. Chronic intermittent dialysis (Yes/No)
   If Yes, Type of dialysis: Hemodialysis and Peritoneal Dialysis
   If Hemodialysis, main type of vascular access: Graft (synthetic conduit), Tunneled Catheter, Fistula (natural vessel only), Temporary catheter, Other
4. Persistent SAB (Yes/No)
5. Other forms of complicated SAB (Yes/No)
   ABSSSI
   Metastatic Infection of Native Tissue (Yes/No)
   If Yes,
   Intra-Abdominal Abscess
   Hepatic Abscess
   Psoas Abscess
   Pancreatic/Omental Abscess
   Other Intra-abdominal Abscess (including Renal Abscess)
   Thoracic Abscess
   Pleura Empyema/Lung Abscess
   Mediastinitis
   Septic Arthritis
   Septic or Suppurative Thrombophlebitis
   Septic Pulmonary Emboli/Infarction

Other Metastatic Infection of Native Tissue
Osteomyelitis
Epidural or Cerebral Abscess
Other

Note: terms reported under 'Other Metastatic Infection of Native Tissue' or 'Other' field on the 'Categories of Complicated SAB' CRF page will be subject to medical review and analyzed according to the above categories.

6. Definite native-valve Right-sided IE (Yes/No) and/or Left-sided IE (Yes/No)

The percentages for these six SAB categories (uncomplicated, any complicated, chronic intermittent dialysis, persistent SAB, other forms of complicated SAB, definite native-valve right-sided and/or left-sided IE) will be based upon the number of patients from the respective analysis population.

Categories of complicated SAB according to DRC assessment will be summarized similarly:

1. Uncomplicated SAB
2. Any complicated SAB
3. Chronic intermittent Hemodialysis and Peritoneal Dialysis (Yes/No)
4. Persistent SAB (Yes/No)
5. Other forms of complicated SAB with underlying or metastatic foci (Yes/No)

   ABSSSI
   Septic Arthritis
   Septic or Suppurative Thrombophlebitis
   Septic Pulmonary Emboli/Infarction
   Visceral Soft Tissue Abscesses (including abdominal abscesses, thoracic abscesses and deep neck space infections)
   Osteomyelitis
   Epidural or Cerebral Abscess
   Other
6. Definite native-valve Right-sided IE (Yes/No) and/or Left-sided IE (Yes/No)

Note: terms reported under 'Other' field on the 'Categories of Complicated SAB' DRC page will be subject to medical review and analyzed according to the above categories.

Categories of SAB will be listed by patient and visit for ITT population including the additional information available under each categories (i.e., type of dialysis, other complications or other specify etc.), date of SAB category confirmation, diagnostic method (biopsy/aspirate, CT, culture, MRI, etc.).

6.3. Modified Duke's Criteria

Modified Duke's Criteria (listed in Appendix 1 of Protocol) are assessed at Screening. In patients without definite Infective Endocarditis (IE), Modified Duke's Criteria will be assessed at every scheduled visit from Day 2 until PTE visit. Modified Duke's Criteria will be assessed in all patients (including those with definite IE) at Screening, EOT and PTE.

A shift table from baseline to maximum post baseline will be presented for Investigator assessed Modified Duke's Criteria for the Diagnosis of Infective (Right/Left Sided) Endocarditis. Categories are "Definite", "Possible" and "Rejected" where "Definite" is considered as maximum and "Rejected" is considered as lowest in maximum post baseline category. This shift table will be presented for ITT, mITT and CE populations.

All Modified Duke's Criteria information on ITT patients will be included in a by-patient listing.

6.4. Inclusion and Exclusion Criteria

The details of Inclusion and Exclusion criteria are listed in Section 4.2 and 4.3 of the protocol. All inclusion/exclusion information on ITT patients will be included in a by-patient listing. For patients who did not satisfy these criteria, the criteria numbers will be listed with the deviation.

7. Treatments and Medications

7.1. Prior and Concomitant Medications/Non-Drug Procedures

7.1.1. Prior and Concomitant Medications

All medications taken other than the study medications during the study (including 30 days prior to Screening) must be documented on the appropriate section of the CRF.
Prior non-antibiotic medications are defined as medications with a stop date prior to the first dose date. Concomitant non-antibiotic medications are defined as medications that are ongoing on the first dose date, or with a start date missing or occurring on or after the first dose date. The number and percentage of patients who receive prior and concomitant non-antibiotic medication will be summarized separately by drug class and PT.

Prior antibiotic medications are defined as medications with a stop date and time prior to the first dose date and time. Concomitant antibiotic medications are defined as medications that are ongoing on the first dose date and time, or with a start date and time missing or occurring on or after the first dose date and time. The number and percentage of patients who receive prior and concomitant antibiotic medication will be summarized separately by ATC level 2, ATC level 4 and PT.

At each level of summarization, a patient is counted once if he/she reports one or more medications at that level. All prior medications and concomitant medications (including systemic antibacterial treatments as defined in study protocol Appendix 5) will be summarized for the ITT population.

The imputation algorithm for partial and missing concomitant medication dates is provided in Appendix 14.1.

All prior and concomitant medications will be presented in a listing.

7.1.2. Prior and Concomitant Non-Drug Procedures

Prior non-drug procedures are defined as procedures with a stop date occurring within 30 days prior to the first dose date. Concomitant non-drug procedures are defined as procedures that are ongoing on the first dose date, or with a start date missing or occurring on or after the first dose date. The number and percentage of patients who receive prior and concomitant non-drug procedures will be summarized separately. All prior and concomitant non-drug procedures will be summarized for the ITT population.

All prior and concomitant non-drug procedures will be presented in a listing.

7.2. Study Treatments

7.2.1. Extent of Exposure

Duration of exposure is defined as the total number of days a patient is exposed to any study drug and will be presented as the total number of days from the first dose date and time (Day 1) to the last dose date and time (date of last known study drug administration minus the date and time of first dose + 1) as recorded on the Study Completion/Termination page on the CRF. If the last dose date and time on the Study Completion/Termination page is missing, or if a patient is lost to follow-up, then the last infusion end date and time recorded on the Exposure page on the CRF will be used. Duration of exposure to Aztreonam will be calculated separately using the same approach.

The duration of exposure to study drug and to Aztreonam by treatment will be summarized using descriptive statistics. The duration of exposure will then be classified into one of the following categories: 1–< 7, 7–14, 15–< 21, 21–28, 29–< 35, 35–42, > 42 days and 1–14, 15–28, 29–42, > 42 days. Number and percentage of patients will be presented in each duration category. Also, study day of start of aztreonam defined as the total number of days from the first study drug dose date and time to the first aztreonam dose date and time will also be summarized.

Because study drug dose adjustment may occur during the study, the exposure to study drug will also be characterized by cumulative dose, which is defined as the sum of all doses (mg) administered to a patient. In addition, for daptomycin the average dose expressed in mg/kg and defined as the mean of daptomycin doses taken by each subject will be classified into one of the following categories: < 6, 6–< 8, 8–< 10, and ≥ 10. Also, the total number of actual doses is defined as the number of occasions the dose is administered. Total cumulative dose and the total number of actual doses per study drug (including Aztreonam) will be summarized for Day 1 to Day 8 and Day 9 onwards periods.

All these summaries will be presented regardless of and by baseline renal function (Dialysis, CL_{CR}< 30 mL/min, CL_{CR} 30–< 50 mL/min, CL_{CR} ≥ 50 mL/min). For Aztreonam, additional summaries will be provided for patients with concomitant Gram-negative pathogen.

The overall compliance by treatment will be summarized by descriptive statistics. For each patient, the compliance will be calculated as the total number of actual doses divided by the total number of planned doses, across the overall treatment period. The compliance will then be classified into one of the following categories: < 80%, 80 – 120 % and > 120 % and will be presented as the number and percentage of patients in each category. Percentages will be computed from the number of patients in the Safety population.

All summaries will be based on the Safety population.

7.2.2. Treatment Administration and Modifications

Patients with missed dose, dose interruption, reason for interruption, infusion completion status, infusion performed place will only be listed for Safety population.

8. Efficacy Analysis

8.1. Primary Efficacy Analysis

8.1.1. Main Analysis

The main primary analysis will be based on the mITT population.
The number and percentage of patients with overall success (i.e. responders) versus overall failure (i.e., non-responders) determined by the independent DRC at the PTE visit (Day 70±5 days post-randomization) will be presented in each treatment group along with the reasons for failure.

The observed difference in percentage of responders at PTE (ceftobiprole group minus the daptomycin group) will be determined and a two-sided 95% confidence interval (CI) for the observed difference will be computed, with adjustment for actual stratum (dialysis status and prior antibacterial treatment use). Cochran-Mantel-Haenszel (CMH) weights will be used for the stratum weight in the calculation of the CI.

Note: Patients' dialysis status (Chronic dialysis, Not on chronic dialysis) is based on the Investigator's assessments on the 'Categories of Complicated SAB' CRF page. Patients on chronic dialysis are those assessed as undergoing chronic dialysis.

Patients with prior antibacterial treatment are patients with treatment with potentially effective systemic antibacterial treatment (see Appendix 14.2) within the 7 days prior to randomization.

It is anticipated that the consideration of the study site strata as a covariate will cause convergence issue of the model; therefore, study site will not be considered in the modelling.

The non-inferiority hypothesis test is a one-sided hypothesis test performed at the 2.5% level of significance. If the lower limit of the two-sided 95% CI for the difference in overall success rate in the mITT population is greater than -15%, the non-inferiority of ceftobiprole to daptomycin therapy will be concluded.

Test hypotheses:

$H_0: \pi_1 - \pi_2 \leq -0.15$

$H_A: \pi_1 - \pi_2 > -0.15$

Where,

π_1 = Proportion of patients with overall success for ceftobiprole group

π_2 = Proportion of patients with overall success for daptomycin group

The primary efficacy analysis will be based on the difference in the overall success rates between the two treatment groups at PTE visit. The risk ratio and odds ratio will also be estimated.

If non-inferiority is declared at the one-sided significance level of 0.025, then the difference will be tested for superiority.

Test hypotheses for superiority:

$H_0: \pi_1 - \pi_2 \leq 0$

$H_A: \pi_1 - \pi_2 > 0$

Where,

π_1 = Proportion of patients with overall success for ceftobiprole group

π_2 = Proportion of patients with overall success for daptomycin group

Superiority will be declared if the lower limit of the two-sided 95% CI exceeds 0 (or equivalently p-value less than 0.05 using CMH test).

8.1.2. Supplementary Analyses

To supplement the primary efficacy analysis results, the following analyses will be performed for the primary outcome in mITT population:

- The subgroup listed in Section 4.4.5 will be used to conduct subgroup analysis for the primary efficacy outcome in the mITT population.
- In addition to tabulating the subgroup analyses, a forest plot showing the weighted treatment differences with associated 95% CI and p-values, computed using CMH weights statistics controlling for actual stratum (dialysis status, and prior antibacterial treatment use), will be produced for mITT population.

- A forest plot by geographical region, country and site showing the treatment differences with associated 95% CIs (computed using unstratified Wald statistics) and p-values (computed using Chi-square test) will be produced.
- An unadjusted analysis, i.e., the 95% CI will not be adjusted for actual stratum (dialysis status and prior antibacterial treatment use).

8.1.3. Sensitivity Analysis

Should there be an imbalance of more than 50% between the two treatment groups in the percentage of indeterminate outcome as per DRC assessment, then further sensitivity analyses will be performed. A first sensitivity analysis will be performed to exclude those patients with indeterminate outcome as per DRC and this assumes missing at random (MAR). Additional analyses will explore the robustness of the conclusion of the non-inferiority of ceftobiprole to further missingness not at random (MNAR) assumptions. In particular, various proportions of the patients with missing data (10%, 20%, 30%, and 40%) in the daptomycin group will be considered successes, while only half of the respective proportions of patients in the ceftobiprole group will be considered successes (5%, 10%, 15%, and 20%), and the analysis of non-inferiority repeated for each of the assumed proportions.

The COVID-19 pandemic poses risks to the safety of subjects enrolled in, and to the availability and interpretability of data from this clinical study. It is expected that there will be a relatively small proportion of patients with COVID-19 related events, and therefore, the objective of this sensitivity analysis is to explore the robustness of the primary analysis (Section 8.1.1) conclusions when patients who had COVID-19 related events are excluded from the primary analysis.

COVID-19 related events are defined as follows:

COVID-19 death:	Death due to COVID-19 disease prior to the PTE visit
COVID-19 related AE:	COVID-19 related AE leading to premature study discontinuation
COVID-19 medications:	Use of antibiotic/antibacterial medications because of COVID-19 (e.g., treatment of secondary bacterial pneumonia) prior to the PTE visit that might interfere with evaluation of efficacy

The number and percentage of patients with COVID-19 related events will be tabulated. The primary analysis (Section 8.1.1) will be then conducted for the subset of patients not incurring any COVID-19 related event. Additional sensitivity analyses may be conducted as needed (e.g., through multiple imputation modelling).

8.2. Secondary Efficacy Analysis

8.2.1. DRC-Assessed Overall Success Rate Analysis

The statistical analysis described in Section 8.1.1 and 8.1.2 will be repeated for the overall success rate as assessed by DRC at the

- PTE visit for CE and then ITT populations.
- EOT visit for ITT, mITT and CE populations

8.2.2. All-Cause Mortality

The observed difference in percentage of ACM at study day 28 and at end of study (ceftobiprole group minus the daptomycin group) in the ITT and mITT populations will be determined and a two-sided 95% CI for the observed difference will be computed, with adjustment for actual stratum (dialysis status and prior antibacterial treatment use). Cochran-Mantel-Haenszel weights will be used for the stratum weight in the calculation of the CI. The risk ratio and odds ratio will also be estimated.

Time to death is defined as the actual elapse time from date of randomization to date of death. Patients without death records (alive at completion of study or alive at time of early discontinuation or lost to follow-up) will be censored at the last point they were known to be alive.

The survival time between the two treatment groups will be compared using K-M estimates. Greenwood formula will be used for CIs of K-M estimates. The median of the observed survival time, the 25^{th} and 75^{th} percentiles along with 95% CI will be provided.

An unstratified log rank test will be performed to assess the difference between treatment groups which will include all available mortality data. Survival rates (Event-Free Probability Estimates) at study Day 28 and study Day 70 in the ITT and mITT populations will be estimated using K-M estimate. Associated two-sided 95% CI will be calculated using Greenwood formula. Hazard ratio (HR) for ACM and associated 95% CI will also be provided using Cox proportional-hazard model with treatment and actual stratum (dialysis status and prior antibacterial treatment use) as covariates.

A K-M plot of survival time will also be provided.

The subgroup listed in Section 4.4.5 will be used to conduct subgroup analysis in the mITT populations.

8.2.3. Microbiological Response

8.2.3.1. Microbiological Eradication

The observed difference in percentage of microbiological eradication in the mITT population at PTE (ceftobiprole group minus the daptomycin group) will be determined and a two-sided 95% CI for the observed difference will be computed, with adjustment for actual strata (dialysis status and prior antibacterial treatment use). Cochran-Mantel-Haenszel weights will be used for the stratum weight in the calculation of the CI. The risk ratio and odds ratio will also be estimated.

Microbiological eradication will also be assessed at PTE in the CE population, and at Day 4, Day 8, and the EOT visit in the mITT and CE populations.

The subgroups listed in Section 4.4.5 will be used to conduct subgroup analysis in the mITT populations. As an additional subgroup analysis, microbiological eradication rate in patients with an overall outcome of failure at EOT and PTE visits per DRC assessment will be analyzed in mITT population.

8.2.3.2. Time to *S. aureus* Bloodstream Clearance

A K-M analysis on the difference in *S. aureus* clearance will be performed in the mITT and CE populations. Greenwood formula will be used for CIs of K-M estimates. The median of the observed survival time, the 25th and 75th percentiles along with 95% CI will be provided.

An unstratified log rank test will be performed to assess the difference between treatment groups. HR for *S. aureus* clearance and associated 95% CI will also be provided using Cox proportional-hazard model with treatment and actual stratum (dialysis status and prior antibacterial treatment use) as covariates.

Time to *S. aureus* bloodstream clearance is defined as the elapsed time (in days) from date of randomization to bloodstream clearance. Bloodstream clearance is defined as the occurrence of two consecutive study days with blood-culture-negative assessments for *S. aureus*, with the first day with negative blood culture being used for calculating the time to bloodstream clearance; bloodstream clearance in patients with intermittent positive on treatment blood cultures will start after the last positive blood culture. Patients with S. aureus relapse or reinfection as per DRC assessment will not be considered as bloodstream clearance. Patients without *S. aureus* bloodstream clearance or no blood culture post-randomization will be censored at their last study visit.

A Kaplan-Meier plot of time to bloodstream clearance will also be provided.

In addition, subgroup analysis will be conducted in the mITT and CE populations, as well as in the subset of patients with overall success per DRC assessment at PTE visit, by baseline blood *S. aureus*, geographical region, and both subgroups combined.

8.2.4. Development of New Metastatic Foci or Other Complications of SAB after Day 7 (DRC Assessment)

The numbers and percentages of patients who develop new metastatic foci or other complications of SAB after Day 7 will be determined in each treatment group in the mITT and CE populations.

The observed difference in percentage of development of new metastatic foci or other complications of SAB after Day 7 (ceftobiprole group minus the daptomycin group) will be determined and a two-sided 95% CI for the observed difference will be computed, with adjustment for actual stratum (dialysis status and prior antibacterial treatment use). Cochran-Mantel-Haenszel weights will be used for the stratum weight in the calculation of the CI. The associated risk ratio and odds ratio will also be provided.

The subgroups listed in Section 4.4.5 will be used to conduct subgroup analysis in the mITT populations.

8.3. Additional Efficacy Analysis

8.3.1. Mortality due to SAB

Mortality due to SAB as assessed by DRC at Day 28 and Day 70 (PTE visit) (mITT and ITT populations) will be analyzed using a similar approach to that described for secondary analysis in Section 8.2.2.

8.3.2. Investigator-Assessed Overall Success

Investigator assessed overall success evaluated at EOT and PTE visits (mITT and CE populations) will be analyzed using a similar approach to that described for primary analysis in Section 8.1.1.

8.3.3. Concordance between DRC and Investigator-Assessed Overall Success

To study the concordance between DRC and Investigator-assessed overall success, the observed agreement relative to each rating category individually will be computed using the two indices, positive agreement (PA) and negative agreement (NA), calculated as follows:

$$PA = \frac{2a}{2a + b + c} \qquad NA = \frac{2d}{2d + b + c}$$

with the values a, b, c and d here denote the observed frequencies for each possible combination of ratings by DRC and investigator, i.e.,

		Investigator
DRC	Success	Non-Success
Success	a	b
Non-Success	c	d

For instance, PA estimates the conditional probability, given that DRC makes a positive rating, the investigator will also do so.

The Wald method will be used to estimate confidence limits of the proportions as follows:

$$CL = p - SE \times z_{crit}$$
$$CU = p + SE \times z_{crit}$$

where SE is SE(p) estimated described below. CL and CU are the lower and upper confidence limits, and z_{crit} is the z-value associated with a confidence range with coverage probability crit. For a 95% confidence range, $z_{crit} = 1.96$.

$$SE(PA) = \text{sqrt}\left[4a (c + b) (a + c + b) \right] / (2a + b + c)^2$$
$$SE(NA) = \text{sqrt}\left[4d (c + b) (d + c + b) \right] / (2d + b + c)^2$$

The observed frequencies for each possible combination of ratings by DRC and Investigator at PTE will be tabulated for the mITT population, along with the estimated PA and NA with associated 95% CI.

8.3.4. Time to any Bloodstream Clearance

A similar K-M analysis as described in Section 8.2.3.2 will be conducted for the time (days) to bloodstream clearance of any pathogen in the mITT and CE populations. Time to (any pathogen) bloodstream clearance is defined as the elapsed time (days) from randomization to bloodstream clearance. Bloodstream clearance is defined as the occurrence of two consecutive study days with blood-culture-negative assessments, with the first day with negative blood culture assessment being used for calculating the time to bloodstream clearance; bloodstream clearance in patients with intermittent positive on treatment blood cultures will start after the last positive blood culture. Patients with subsequent positive blood culture will not be considered as bloodstream clearance. Patients without bloodstream clearance or no blood culture post-randomization will be censored at their last study visit.

8.3.5. Microbiology

Distribution of patients at baseline and post-baseline with blood *S. aureus*, other blood (Gram-positive [i.e., other than *S. aureus*]/Gram-negative) pathogens, non-blood *S. aureus*, other non-blood (Gram-positive [i.e., other than *S. aureus*]/Gram-negative) pathogens will be provided for the mITT and CE populations, overall and by geographical region.

The number of patients with blood *S. aureus* by virulence markers (PVL status, *mecA* status, oxacillin susceptibility and other genotypic markers) at baseline will also be provided for the mITT and CE populations, overall and by geographical region.

Distribution of ceftobiprole, daptomycin, and aztreonam MIC, including MIC50, MIC90 and MIC range, for blood *S. aureus*, MRSA and MSSA, will be tabulated for the mITT and CE populations. Note that MIC50 is defined as the MIC value which inhibits 50% of pathogens isolated, MIC90 as the MIC value which inhibits 90% of pathogens isolated, and MIC range as the minimum and maximum MIC values measured for pathogens isolated at baseline.

Shift in ceftobiprole, daptomycin and aztreonam MIC results from baseline to PTE and the shift in ceftobiprole, daptomycin and aztreonam MIC results from baseline to the maximum value post-baseline by baseline infecting organisms (i.e., pathogens) will be presented in a shift table overall, by geographical region for each specimen source (blood, non-blood) separately in the mITT and CE populations.

In addition to listing all recorded microbiological data, a separate listing of patients identified as having Relapse/reinfection will be provided.

8.3.6. Health Economic Outcome Measures

Information on health economics outcome measures from baseline to the PTE visit will be collected at the PTE visit to perform summarization for total length of stay in hospital, length

of stay per treatment location within the hospital, type of encounter and reason for healthcare encounter, and incidence of re-hospitalization due to adverse events.

All the Health economic outcome measures will be summarized by treatment group in the mITT and CE populations.

A listing will also be presented for health economic outcome measures.

9. Safety Analysis

All analysis of safety will be conducted using the Safety population.

9.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A serious (SAE) is any AE that meets one or more of the following criteria:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is classified as an important medical event or a medically significant event

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient, or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

All AEs are defined as treatment-emergent AEs (TEAEs), i.e. occurring from the start of first dosing up to and including the scheduled PTE visit, and will be considered for the analysis purpose. Any event occurring prior to the first dosing will be recorded as medical history. For calculating inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix 14.1.

AEs will be classified by System Organ Class (SOC) and PT according to MedDRA (Version 24.0 or higher).

An overview summary of number and percentage of patients for any TEAE, study drug related TEAEs, serious TEAEs, study drug related serious TEAEs, TEAEs leading to treatment discontinuation, study drug related TEAEs leading to treatment discontinuation, TEAEs leading to death, study drug related TEAEs leading to death, TEAEs of special interest and study drug related TEAEs of special interest will be provided by treatment group and in total. Percentages will be calculated using number of patients in the Safety set.

9.1.1. Incidence of Adverse Events

The incidence of AEs table will include only one occurrence of a PT per patient. If a patient reports the same PT multiple times, then that PT will only be incremented by one since patient counts will be presented. As with the PT, if a patient reports multiple AEs within the same SOC, then that SOC will only be incremented by one since patient counts will be presented.

For tables showing incidence by SOC and PT, SOC will be sorted in alphabetical order. Within each SOC, PTs will be sorted in descending order of frequency on total of all treatment groups.

The incidence of all AEs and SAEs will be presented by SOC and PT and separately by PT only. SAEs will also be tabulated only for patients with COVID-19 events (see Section 5.3).

Dot and interval plot showing the largest difference in the proportion of AEs between the two treatment groups will be created. The plot will include risk differences and their corresponding 95% Confidence Intervals (CIs). All AEs will be sorted by descending difference in proportion.

All AEs and SAEs will be presented in a separate listing including, but not limited to, verbatim term, PT, SOC and relationship to study drug.

9.1.2. Relationship of Adverse Events to Study Drug

The relationships will be collected as the possibility that study drug caused the event. The possible relationships are “Not Related”, “Unlikely”, “Possible”, and “Probable”. A treatment-related AE is an AE with any relationship to study drug other than “Not Related” or “Unlikely”.

A summary of treatment-related AEs and SAEs will also be presented in a table by SOC and PT. A summary of AEs and SAEs by relationship to study drug will also be presented.

In the AE relationship table, if a patient reports multiple occurrences of the same AE, only the most closely related occurrence will be presented. AEs that are missing relationship will be presented in the summary table as “Unknown” but will be presented in the data listing with a missing relationship.

9.1.3. Severity of Adverse Event

A summary of AEs and SAEs by severity will be presented in a table. AEs will be classified by severity (mild, moderate and severe). In the AE severity table, if a patient reported multiple occurrences of the same AE, only the most severe will be presented. AEs that are missing severity will be presented on tables as “Unknown” but will be presented in the data listing with a missing severity.

9.1.4. Adverse Events Leading to Treatment Discontinuation

Summary tables of AEs leading to study drug discontinuation by SOC and PT by treatment arm will be provided. A treatment-related AEs leading to study drug discontinuation will be listed by patient.

9.1.5. Outcome of Adverse Event

AEs will be classified by outcome (Recovered or Resolved, Recovered or Resolved with Sequelae, Recovering or Resolving, Not Recovered or Not Resolved, Death Related to Adverse Event and Unknown). The outcomes will be listed by patients.

9.1.6. Adverse Events of Special Interest

AEs of special interest (AESIs) (Convulsions, Rhabdomyolysis/Myopathy, Hypersensitivity, Pseudomembranous Colitis, Peripheral Neuropathy, Eosinophilic Pneumonia) are summarized based on the narrow Standardized MedDRA Query (SMQ) by SOC, PT and Severity in a manner similar to that described in Section 9.1.3.

AEs of convulsions are summarized based on the narrow Standardized MedDRA Query (SMQ) by PT and the periods whereas period 1 is ≤ 28 days of treatment and period 2 is > 28 days of treatment. Percentage will be based on the number of patients in safety population under each treatment period.

9.2. Deaths

The AEs where the answer to "Outcome" is "Death Related to Adverse Event" will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1. At each level of summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated using number of patients in the Safety set. SOC will be sorted in alphabetical order. Within each SOC, total AEs of preferred terms will be sorted in descending order of frequency on total of all treatment groups.

All patient deaths during this study will be collected and presented in a listing. The information that is presented includes days on study and AE with an outcome of "Death Related to Adverse Event".

Survival status including date of contact and type of contact of all patients in ITT population will be listed separately.

9.3. Clinical Laboratory Evaluations

Local safety laboratory parameters to be used to assess patient eligibility at Screening include hematology, blood chemistry, coagulation, blood glucose, and urinalysis. Local Creatinine Clearance data will be listed and summarized. All other local laboratory data will be listed only.

Central laboratory safety parameters carried out in accordance with the schedule of assessments in Section 5.1 of the protocol, will be used for analysis in the study. All summaries will be based on the standard international (SI) units provided by the central lab.

Implausible central laboratory results will be flagged by the central laboratory; these results will not be tabulated but will be listed.

Summary tables for central laboratory safety parameters including actual values and change from baseline values will be presented for clinical laboratory tests with numeric values by visit.

Central laboratory data will also be summarized using shift tables where appropriate. Each patient's continuous laboratory safety parameter values will be flagged as "low", "normal", or "high" relative to the normal ranges of the central laboratory. Each patient's categorical laboratory safety parameter values will be flagged as "abnormal" or "normal". These categorical data will be summarized in shift tables comparing the minimum post-baseline value, maximum post-baseline value and all other relevant post-baseline visits with those at the baseline visit.

Laboratory results will be graded using the modified Division of AIDS (DAIDS) for Adverse Events Version 2.1 (see Appendix 14.5). In case, if any laboratory parameter is not present in the grading criteria of DAIDS then Division of Microbiology and Infectious diseases (DMID) dated Nov 2007 grading scale will be used. These categorical data will be summarized in shift tables.

Laboratory data collected at unscheduled visits will be included in listings and will contribute to tables of shifts from baseline and in tables showing changes from baseline to highest value and lowest value. Unscheduled lab results will not be windowed for the purposes of assigning a nominal visit. However, they will be included in calculations of highest/lowest values in selected laboratory parameters.

Original laboratory values and their respective reference ranges will be reported to the same number of decimal places as provided by the laboratory.

If any laboratory value falls above or below the upper or lower level of quantification, the following rule will be applied for summary statistics: values reported as < XX or ≤ XX will be analyzed as XX/2; values reported as > XX or ≥XX will be analyzed as XX (e.g., <0.2 will become 0.1, >0.2 will become 0.2). Reported values will be listed.

Differentials will be displayed in the laboratory output as absolute values. If the laboratory can provide only percentage values, these will be converted into absolute for reporting.

9.3.1. Hematology

The laboratory tests listed in the Appendix 14.3 will be included in hematology summary tables.

All hematology data by patient will be presented in a listing including normal ranges and indicating if value is out of range.

9.3.2. Blood Chemistry

The laboratory tests listed in the Appendix 14.3 will be included in clinical chemistry summary tables.

All chemistry data by patient will be presented in a listing including normal ranges and indicating if value is out of range.

The incidence of patients with abnormalities in ALT or AST will be summarized overall (highest post-baseline value) for each treatment group for the following categories:

- ≤ 3 × ULN
- > 3 to ≤ 5 × ULN
- > 5 to ≤ 8 × ULN
- > 8 to ≤ 10 × ULN
- > 10 × ULN

Also, the incidence of patients with abnormalities in ALT or AST associated to abnormalities in total bilirubin will also be summarized overall (highest post-baseline value) for each treatment group for the following categories:

- ALT or AST ≤ 3 ULN and BILI ≤ 2 ULN
- ALT or AST > 3 ULN and BILI ≤ 2 ULN
- ALT or AST ≤ 3 ULN and BILI > 2 ULN
- ALT or AST > 3 ULN and BILI > 2 ULN

Patients with at least one post-baseline ALT or AST that is ≥ 3 × ULN will be listed showing all LFTs (ALT, AST, bilirubin (direct & indirect), alkaline phosphatase, and GGT) observed across all visits.

Evaluation of drug-induced serious hepatotoxicity (eDISH) plots of maximum ALT/AST values versus maximum Bilirubin will be presented for assessment of potential Drug Induced Liver Injury (DILI).

9.3.3. Urine (dipstick Analysis)

The following local laboratory tests will be collected at screening for urine (dipstick analysis): blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, bilirubin, and urobilinogen. Urine (dipstick analysis) results at screening will be listed only.

9.3.4. Coagulation

The laboratory tests listed in the Appendix 14.3 will be included in the coagulation summary tables.

All coagulation data by patient will be presented in a listing including normal ranges and indicating if value is out of range.

9.3.5. Reticulocytes, haptoglobin and Coombs test

Reticulocytes, haptoglobin and Coombs test will be assessed by central laboratory according to the schedule shown in Section 5.1 of the protocol. Reticulocytes, haptoglobin and Coombs test values will be summarized and will be presented in a listing.

9.3.6. Creatinine clearance

Creatinine clearance (CL_{CR}) test will be assessed by local laboratory data.

Box plots will be provided to display the distribution of the CL_{CR} level reported by sites at each visit. In addition, line plots of means and SEs will be created to display the actual value, change from baseline and percent change from baseline over the entire study period.

The CL_{CR} level reported by sites will be summarized and will be presented in a listing.

9.3.7. Pregnancy Test

Pregnancy testing is to be performed for women of childbearing potential; at Screening a serum pregnancy test is to be obtained; at the EOT and PTE visit it is at the discretion of the Investigator whether a serum or urine pregnancy test is obtained, and patient to local regulations. The Investigator may conduct additional (serum or urine) pregnancy tests to confirm the absence of pregnancy at any time during the study. If a pregnancy test result is positive, study drug must be discontinued, and the patient followed for safety, and assessment of the pregnancy outcome.

Pregnancy test data will be presented in a listing.

9.4. Vital Signs Measurements

Vital signs include weight, respiratory rate, radial pulse rate, systolic blood pressure and diastolic blood pressure and are to be taken once at each study visit at a time point when temperature assessment is performed. Body temperature is to be measured every 8 h for the first 96 h after start of treatment, and every 8 h thereafter, until a 24 h period is achieved during which no measurement is greater than 38 °C / 100.4 °F oral, 38.5 °C / 101.3 °F tympanic, 37.5° C / 99.5 °F axillary, or 39 °C / 102.2 °F rectal. Temperature measurements will then be taken once on each scheduled study visit. The same method of measuring temperature should be chosen within a site for all patients during course of the study. Pulse rate and blood pressure must be obtained in the same position throughout a visit, i.e. either sitting or supine as appropriate, after the patient has been at rest for at least 5 min. The patient's height assessment is only at the Screening visit.

Summary tables of observed values and changes from baseline as well as minimum and maximum post-baseline values will be presented for vital sign data, including weight (kg), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (°C), pulse rate (bpm), and respiration (breaths/minute), by treatment group at each visit on a given timepoint in the safety population. Change from baseline will only be calculated for patients having non-missing baseline and post-baseline measurements. The change from baseline in temperature will be calculated only if the baseline and post-baseline measurements are done by same method.

All vital signs data by patient will be presented in a listing.

Box plots will be provided to display the distribution of vital signs results at each visit. In addition, line plots of means and standard errors (SEs) will be created to display the change from baseline over the entire study period.

The following values should be used as default Marked Reference Ranges:

- Diastolic Blood Pressure: < 60 or > 100 mmHg.
- Systolic Blood Pressure: < 80 or > 180 mmHg.
- Pulse rate: < 40 or > 120 beats/min.
- Temperature: < 36 °C / 96.8 °F.
- Temperature: > 38 °C / 100.4 °F oral.
- Temperature: > 38.5 °C / 101.3 °F tympanic.
- Temperature: > 37.5 °C / 99.5 °F axillary.
- Temperature: > 39 °C / 102.2 °F rectal.

Each patient's continuous vital signs results values will be flagged as "low", "normal", or "high" relative to the marked reference ranges. These categorical data will be summarized in shift tables comparing the changes in marked reference ranges from baseline to each scheduled post-baseline visit. Changes in marked reference ranges from baseline to the minimum and maximum post-baseline values will also be provided.

9.5. Physical Examination

A complete physical examination will be performed at screening visit. Complete physical examination includes general appearance, skin, neck inclusive thyroids, eyes, nose, throat, cardiovascular system, thorax/lungs, abdomen, lymph nodes, extremities, nervous system, and mental status. Thereafter, a brief physical examination, focused on any change from baseline, will be performed from Day 2, up to PTE visit.

A table will summarize physical examination results by treatment group and overall, by visit, for the Safety population. Each visit captures the status of a body system and any finding associated with the body system as normal, abnormal, or not done. Physical examination results for all patients will be presented in a listing.

9.6. Electrocardiogram

All patients will have a standard 12-lead electrocardiogram (ECG) performed at Screening and EOT visit.

Summary tables of observed values, changes from baseline and worst post-baseline value will be presented for electrocardiogram data, including PR Interval (msec), QRS Duration (msec), RR Interval (msec), QT Interval (msec), QTcB Interval (msec), QTcF Interval (msec), Mean Heart Rate (beats/min) by treatment group and overall at each scheduled visit for patients in the Safety set. Implausible ECG results will be flagged based on sponsor medical review; these results will not be tabulated but will be listed.

A shift table from baseline to post-baseline ECG interpretations by visit will be displayed for the Safety set. Interpretation results include Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant, and Not Done.

All ECG results and interpretation will be presented in a listing by treatment group, patient and visit using Safety set.

9.7. Transthoracic and Transesophageal Echocardiography

All transthoracic (TTE) and transesophageal (TEE) echocardiogram data will be presented in a listing by treatment group, patient and visit using the Safety set.

10. Pharmacokinetics

Plasma concentration data will be analyzed at each time point specified in the schedule of assessments and will be presented as individual concentrations in a listing and summarized with descriptive statistics (mean, standard deviation [SD], coefficient of variation [CV%], min, median and max).

Non-compartmental PK analysis and a population PK model will be developed and reported as a separate study not performed by PPD.

11. Interim analysis

As animal studies have indicated the potential of an increased risk of convulsions with prolonged ceftobiprole therapy (> 4 weeks treatment duration), an initial cohort of patients was enrolled for a maximum treatment duration of 28 days (Cohort 1, Part 1 of study). An interim safety analysis was performed by an independent DSMB after 80 patients (approximately 40 patients per treatment group) had completed 21–28 days of treatment and safety follow-up.

Based on this analysis the treatment duration was extended up to 42 days (Part 2), after discussion with the United States Food and Drug Administration (FDA). Decision rules for the DSMB interim safety assessment of Cohort 1 are provided in Appendix 7 of Protocol.

No further interim analyses are planned.

12. Changes in the Planned Analysis

- The protocol suggested that there would be a distinction based on genotyping between microbiological relapse and reinfection; the genotyping data will only be listed, and further post database lock analyses of reinfection versus relapse would be performed if warranted.
- The sensitivity analyses specified in the protocol regarding the impact of missing data for the primary endpoint will only be conducted if there is an imbalance of more than 50% between the two treatment groups in the percentage of indeterminate outcome as per DRC assessment.
- This study is conducted primarily in region Europe with limited patients included from the other geographical regions (North America, Latin America, Other Regions). Therefore, it is not appropriate to include geographical region as a covariate in the statistical analyses.

- Bloodstream clearance definition has been modified to consider all blood samples within a day; using this approach ensures that if multiple blood cultures have been obtained on a specific day, clearance can only be assigned for that day if there is no positive blood culture on that day.
- The window for identification of baseline pathogen(s) has been extended from 72 hours prior to randomization date and time to 80 hours prior to randomization date and time, up to first dose date and time.
- It was clarified in the SAP that investigator's assessment (except for persistent SAB) would be used for the summary of categories of complicated SAB, and for subgroup analyses that are based on categories of complicated SAB. An additional analysis of the primary endpoint will be performed using categories of SAB per DRC.
- Additional endpoints (Section 3.2.3) have been added to explore the data available and support the knowledge obtained from the endpoints included in the Basilea BPR-CS-009 study.
- In Appendix 14.2 below, the list of potentially effective antibiotics as per Appendix 5 from the study protocol has been updated by adding or removing several antibiotics for analysis purposes. Specifically penicillin G, penicillin V/benzyl-penicillin, amoxicillin, ampicillin, mezlocillin, piperacillin and ticarcillin have been removed because most *S. aureus* are penicillinase/betalactamase producers and are resistant to these antibiotics. In addition it was specified that only intravenous but not oral fosfomycin is considered potentially effective against *S. aureus*, because oral fosfomycin at approved dosing regimens does not achieve sufficient plasma levels to provide coverage against *S. aureus.* Finally oral administration of vancomycin and teicoplanin were removed as these do not achieve sufficient plasma levels to provide coverage against *S. aureus.* Cefalotin, ceftobiprole, cloxacillin and lomefloxacin were added to the list of potentially effective antibiotics.

13. References

1. International Conference on Harmonization (ICH) Harmonized Tripartite Guideline – Statistical Principles for Clinical Trials, E9 (http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/statistical-principles-for-clinical-trials.html).
2. Fowler VG, Jr., Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med. 2006; 355:653–65.
3. Wilson, E.B., Hilferty, M.M. 1931. The distribution of chi-squared. Proceedings of the National Academy of Sciences, Washington, 17, 684–688.
4. PharmaSUG 2013 - Paper SP03. Combining Analysis Results from Multiply Imputed Categorical Data. Bohdana Ratitch, Quintiles, Montreal, Quebec, Canada Ilya Lipkovich, Quintiles, NC, U.S. Michael O'Kelly, Quintiles, Dublin, Ireland.
5. Raw Agreement Indices (john-uebersax.com).

14. Appendices

14.1. Imputation Algorithm for Partial and Missing Dates and Time

Prior and Concomitant Medications/ Prior and Concomitant Non-Drug Procedures

Impute partial/missing start date with earliest possible date, and end date with latest possible date.

If start date of medication is completely missing in which the day, month, and year are all unknown, then the start date will not be imputed.

For the partial start date of medication,

- If the year is present and the month and day are missing, set month and day to January 1st.
- If the year and month are present and the day is missing and year and month are equal to year and month of first dose, set day to the first dose day.
- If the year and month are present and the day is missing and year and month are not equal to year and month of first dose, set to 1st day of month.

If the end date of medication is completely missing, in which the day, month, and year are all unknown, then the end date will not be imputed.

For the partial end date of medication,

- If the year is present and the month and day are missing, set month and day to December 31st.
- If the year and month are present and the day is missing, set day to last day of the month.

Medications with both missing start and end date after imputation will be considered as concomitant medication.

Adverse Event

If onset date is completely missing, onset date is set to date of first dose.

If (year is present and month and day are missing):

- If year = year of first dose, then set month and day to month and day of first dose.
- If year < year of first dose, then set month and day to December 31st.
- If year > year of first dose, then set month and day to January 1st.

If month and year are present and day is missing:

- If year = year of first dose and
  - If month = month of first dose then set day to day of first dose
  - If month < month of first dose then set day to last day of month
  - If month > month of first dose then set day to first day of month
- If year < year of first dose then set day to last day of month
- If year > year of first dose then set day to first day of month

If the end date is completely missing, in which the day, month, and year are all unknown, then the end date will not be imputed.

For the partial end date,

- If the year is present and the month and day are missing, set month and day to December 31st.
- If the year and month are present and the day is missing, set day to last day of the month.

14.2. Systemic Antibacterial Treatments Considered to be Potentially effective against *S. aureus*

Amoxicillin/Clavulanic acid	Doxycycline
Ampicillin/Sulbactam	Ertapenem
Azithromycin	Erythromycin
Cefaclor	Flucloxacillin
Cefadroxil	Fosfomycin (except oral administration)
Cefamandole	Gemifloxacin
Cefalotin	Imipenem/cilastatin
Cefazolin	Levofloxacine
Cefdinir	Linezolid
Cefditoren pivoxil	Lomefloxacin
Cefepime	Loracarbef
Cefixime	Meropenem
Cefoperazone	Meropenem/vaborbactam
Cefotaxime	Minocycline
Cefotetan	Moxifloxacin
Cefoxitin	Nafcillin
Cefpodoxime proxetil	Ofloxacin
Cefprozil	Omadacycline
Ceftaroline fosamil	Oritavancin
Ceftazidime	Oxacillin
Ceftazidime/avibactam	Piperacillin/tazobactam
Ceftibuten	Quinupristin/dalfopristin
Ceftizoxime	Rifampin
Ceftobiprole	Teicoplanin (except oral administration)
Ceftolozane/tazobactam	Tedizolid
Cefuroxime	Telavancin
Cephalexin	Telithromycin
Ceftriaxone	Tetracycline
Chloramphenicol	Ticarcillin/clavulanate
Ciprofloxacin	Tigecycline
Clarithromycin	Trimethoprim
Clindamycin	Trimethoprim-sulfamethoxazole
Cloxacillin	Vancomycin (except oral administration)
Dalbavancin	
Daptomycin	
Delafloxacin	
Dicloxacillin	
Doripenem	

14.3. Algorithm to define susceptibility of MSSA/MRSA against the respective antibiotic treatment

The table below provides a mapping of specific antibiotic treatments potentially effective against S. *aureus* using the central microbiology results to identify their MRSA/MSSA susceptibility. If the susceptibility testing was not performed for a specific antibiotic by the central microbiology laboratory, a convention is provided for MSSA and MRSA susceptibilities, respectively.

Antibiotic Name	Central Microbiology Antibiotic Name	MSSA Convention	MRSA Convention
amoxicillin/clavulanic acid		Susceptible	Not susceptible
ampicillin/sulbactam		Susceptible	Not susceptible
azithromycin	erythromycin		
cefazolin		Susceptible	Not susceptible
cefepime		Susceptible	Not susceptible
cefixime		Susceptible	Not susceptible
cefoperazon		Susceptible	Not susceptible
cefotetan		Susceptible	Not susceptible
ceftazidime		Susceptible	Not susceptible
ceftriaxone		Susceptible	Not susceptible
cefuroxime		Susceptible	Not susceptible
cephalexin		Susceptible	Not susceptible
ciprofloxacin	levofloxacin		
clindamycin	clindamycin		
cloxacillin	oxacillin		
daptomycin	daptomycin		
doxycycline		Susceptible	Susceptible
ertapenem		Susceptible	Not susceptible
imipenem-cilastatin		Susceptible	Not susceptible
levofloxacin	levofloxacin		
linezolid	linezolid		
meropenem		Susceptible	Not susceptible
moxifloxacin	levofloxacin		
oxacillin	oxacillin		
piperacillin-tazobactam		Susceptible	Not susceptible
trimethoprim-sulfazoxazole	trimethoprim sulfa		
vancomycin	vancomycin		

14.4. List of Clinical Central Laboratory Tests

Hematology	Blood Chemistry	Coagulation
Hemoglobin (HGB) (g/dL)	Albumin (g/L)	Prothrombin Time (PT) (sec)
Hematocrit (HCT) (L/L)	Total Protein (g/L)	International Normalized Ratio (INR)
Red Blood Cell (RBC) Count (10^12/L)	Alkaline Phosphatase (AP) (U/L)	Activated Partial Thromboplastin Time (aPTT) (sec)
White Blood Cell (WBC) Count (10^9/L)	Alanine Aminotransferase (ALT) (U/L)	Fibrinogen (mg/dL)
Platelets (10^9/L)	Aspartate Aminotransferase (AST) (U/L)	
Absolute Basophils (10^9/L)	Creatine phosphokinase (U/L)	
Absolute Eosinophils (10^9/L)	Gamma Glutamyl Transferase (GGT) (U/L)	
Absolute Lymphocytes (10^9/L)	Lactate Dehydrogenase (LDH) (U/L)	
Absolute Monocytes (10^9/L)	Direct Bilirubin (umol/L)	
Absolute Neutrophils (10^9/L)	Total Bilirubin (umol/L)	
	Potassium (mmol/L)	
	Sodium (mmol/L)	
	Chloride (mmol/L)	
	Creatinine (umol/L)	
	Blood Urea Nitrogen (mmol/L)	
	Uric Acid (umol/L)	
	Glucose (mmol/L)	
	C Reactive Protein (CRP) (mg/L)	
	Procalcitonin (µg/L)	

14.5. Toxicity Grade for Central Laboratory Data

Laboratory Test	Direction	Grade 1	Grade 2	Grade 3	Grade 4	Scale
Hematology						
Hemoglobin (Male)	Lower	10.0 – 10.9 g/dL	9.0 – <10.0 g/dL	7.0 – <9.0 g/dL	<7.0 g/dL	DAIDS
Hemoglobin (Female)	Lower	9.5 – 10.4 g/dL	8.5 – <9.5 g/dL	6.5 – <8.5 g/dL	<6.5 g/dL	DAIDS
Leukocytes	Lower	2.000 – 2.499 × 10^9 /L	1.500 – 1.999 × 10^9 /L	1.000 – 1.499 × 10^9 /L	<1.000 × 10^9 /L	DAIDS
Platelets	Lower	100 – <125 × 10^9 /L	50 – <100 × 10^9 /L	25 – <50 × 10^9 /L	<25 × 10^9 /L	DAIDS
Lymphocytes	Lower	0.600 – <0.650 × 10^9 /L	0.500 – <0.600 × 10^9 /L	0.350 – <0.500 × 10^9 /L	<0.350 × 10^9 /L	DAIDS
Neutrophils	Lower	0.800 – 1.000 × 10^9 /L	0.600 – 0.799 × 10^9 /L	0.400 – 0.599 × 10^9 /L	<0.400 × 10^9 /L	DAIDS
Biochemistry						
Albumin	Lower	30 g/L – <LLN	20 – <30 g/L	<20 g/L		DAIDS
Alkaline Phosphatase	Upper	1.25 – <2.5 × ULN	2.5 – <5.0 × ULN	5.0 – <10.0 × ULN	≥10.0 × ULN	DAIDS
ALT	Upper	1.25 – <2.5 × ULN	2.5 – <5.0 × ULN	5.0 – <10.0 × ULN	≥10.0 × ULN	DAIDS
AST	Upper	1.25 – <2.5 × ULN	2.5 – <5.0 × ULN	5.0 – <10.0 × ULN	≥10.0 × ULN	DAIDS
Total Bilirubin	Upper	1.1 – <1.6 × ULN	1.6 – <2.6 × ULN	2.6 – <5.0 × ULN	≥5.0 × ULN	DAIDS
Creatinine	Upper	1.1 – 1.3 × ULN	>1.3 – 1.8 × ULN	>1.8 – <3.5 × ULN	≥3.5 × ULN	DAIDS
Creatinine Clearance	Lower		<90 – 60 mL/min	<60 – 30 mL/min	<30 mL/min	DAIDS
Creatine Kinase	Upper	3 – <6 × ULN	6 – <10 × ULN	10 – <20 × ULN	≥20 × ULN	DAIDS
GGT	Upper	1.1 – <2.0 × ULN	2.0 – <3.0 × ULN	3.0 – 8.0 × ULN	>8.0 × ULN	DMID
Glucose	Lower	3.05 – <3.55 mmol/L	2.22 – <3.05 mmol/L	1.67 – <2.22 mmol/L	<1.67 mmol/L	DAIDS
Glucose (Non-fasting)	Upper	6.44 – <8.89 mmol/L	8.89 – <13.89 mmol/L	13.89 – <27.75 mmol/L	≥27.75 mmol/L	DAIDS
Glucose (Fasting)	Upper	6.11–<6.95 mmol/L	6.95 – <13.89 mmol/L	13.89 – <27.75 mmol/L	≥27.75 mmol/L	DAIDS
Potassium	Upper	5.6 – <6.0 mmol/L	6.0 – <6.5 mmol/L	6.5 – <7.0 mmol/L	≥7.0 mmol/L	DAIDS
Potassium	Lower	3.0 – <3.4 mmol/L	2.5 – <3.0 mmol/L	2.0 – <2.5 mmol/L	<2.0 mmol/L	DAIDS
Sodium	Upper	146 – <150 mmol/L	150 – <154 mmol/L	154 – <160 mmol/L	≥160 mmol/L	DAIDS
Sodium	Lower	130 – <135 mmol/L	125 – <130 mmol/L	121 – <125 mmol/L	≤120 mmol/L	DAIDS
Uric Acid	Upper	0.45 – <0.59 mmol/L	0.59 – <0.71 mmol/L	0.71 – <0.89 mmol/L	≥0.89 mmol/L	DAIDS
Blood Urea Nitrogen	Upper	1.25 – ≤2.5 × ULN	2.6 – ≤5 × ULN	5.1 – ≤10 × ULN	>10 × ULN	DMID
Coagulation						
APTT	Upper	1.1 – <1.66 × ULN	1.66 – <2.33 × ULN	2.33 – <3.00 × ULN	≥3.00 × ULN	DAIDS
Prothrombin INR	Upper	1.1 – <1.5 × ULN	1.5 – <2.0 × ULN	2.0 – <3.0 × ULN	≥3.00 × ULN	DAIDS
Prothrombin Time	Upper	1.1 – <1.25 × ULN	1.25 – <1.50 × ULN	1.50 – <3.00 × ULN	≥3.00 × ULN	DAIDS
Fibrinogen	Lower	0.75 – <1.00 × LLN or 100 – <200 mg/dL	≥0.50 – <0.75 × LLN or 75 – <100 mg/dL	0.25 – <0.50 × LLN or 50 – <75 mg/dL	<0.25 × LLN or <50 mg/dL	DAIDS

ALAT= Alanine Aminotransferase; ASAT=; GGT=Gamma Glutamyl Transferase; APTT=Activated Partial Thromboplastin Time; INR=Intl. Normalized Ratio.
Results are graded using modified Division of AIDS (DAIDS) for Adverse Events Version 2.1. In case, if any laboratory parameter not present in grading criteria of DAIDS then Division of Microbiology and Infectious diseases (DMID) dated Nov 2007 grading scale is used.