Basilea Pharmaceutica International Ltd.

Protocol BPR-CS-008

A randomized, double-blind, multicenter study to establish the safety and efficacy of ceftobiprole medocaril compared with vancomycin plus aztreonam in the treatment of acute bacterial skin and skin structure infections

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Statistical Analysis Plan

Version 3.0

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TABLE OF CONTENTS

List of Abbreviations	
ABSSSI	Acute Bacterial Skin and Skin Structure Infection
ACM	All-Cause Mortality
AE	Adverse Event
AIC	Akaike's Information Criterion
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AP	Alkaline Phosphatase
AR(1)	Auto-Regressive
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
CE	Clinically Evaluable
CSH	Heterogeneous Compound Symmetry
CI	Confidence Interval
CLCR	Creatinine Clearance
CLSI	Clinical and Laboratory Standards Institute
CMH	Cochran-Mantel-Haenszel
CS	Compound Symmetry
CV	Coefficient of Variation
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOT	End-Of-Treatment
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	United States Food and Drug Administration
GGT	Gamma-Glutamyl Transferase
h	Hour(s)
ICH	International Conference on Harmonization
ITT	Intent-To-Treat
IWRS	Interactive Web Response System
K-M	Kaplan-Meier
LFT	Liver Function Test
LFU	Last Follow-Up (visit)
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
mITT	Microbiological Intent-To-Treat
MMRM	Mixed-Model Repeated Measures
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Preferred term

QD	Once Daily
QW	Once Weekly
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
T > MIC	Time Drug Concentration is above the MIC
US	United States
VTT	Vancomycin Trough Testing
WHO	World Health Organization
WBC	White Blood Cell

1. Introduction

BPR-CS-008 is a phase 3 randomized, double-blind, active-controlled, parallel-group, multicenter study in adult hospitalized patients with ABSSSIs to establish the safety and efficacy of ceftobiprole medocaril compared with vancomycin plus aztreonam in the treatment of acute bacterial skin and skin structure infections.

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of clinical data collected in the study. This plan should be read in conjunction with the Final Study Protocol Version 6.0 (Amendment 2.0) – 11 July 2018, and the electronic case report forms (eCRFs) Version 9.0 – 09 May 2019. All analyses will be conducted using SAS® Version 9.3 or higher.

2. Objectives

2.1. Primary objective

To demonstrate the non-inferiority of ceftobiprole to vancomycin plus aztreonam in patients with ABSSSIs with respect to early clinical response based on percentage reduction in lesion size at 48–72 h after first treatment in the ITT population.

2.2. Secondary objectives

2.2.1. Main secondary objective

To demonstrate the non-inferiority of ceftobiprole to vancomycin plus aztreonam in patients with ABSSSIs, with respect to investigator-assessed clinical success at the test-of-cure (TOC) visit 15–22 days after randomization, in the co-primary ITT and Clinically Evaluable (CE) populations.

Note: The primary and the main secondary objectives will be region-specific. The above primary and main secondary objectives are for submission to the United States Food and Drug Administration (US FDA); in the European Union (EU), the above main secondary objective will be the primary objective, and the primary objective listed above will be the main secondary objective. This SAP will be used for submission to the FDA and the European Medicines Agency (EMA).

2.2.2. Other secondary objectives

To compare ceftobiprole with vancomycin plus aztreonam with respect to:

- Early clinical response based on percentage reduction in lesion size at 48–72 h after first treatment (CE population).
- Clinical response based on percentage reduction in lesion size at the end-of-treatment (EOT) and TOC visits (ITT and CE populations).

- Sustained reduction in lesion size at the EOT and TOC visits (ITT and CE populations).
- Investigator-assessed clinical success evaluated at 48–72 h after first treatment and the EOT visit, and sustained clinical success at the last follow-up (LFU) visit (ITT and CE populations).
- All-cause mortality through Day 28 (ITT and CE populations).
- Microbiological response at Day 3, Day 5, and the EOT, TOC and LFU visits (mITT and ME populations).
- Change in patient-reported pain from baseline at all visits except the Day 28 visit (ITT and CE populations).
- Health economic outcome measures (ITT and CE populations).
- Safety: incidence, type, severity and relationship to study medication of adverse events and changes in laboratory tests (hematology and blood chemistry, including haptoglobin, urinalysis, Coombs test) (Safety population).
- To assess the pharmacokinetics (PK) of ceftobiprole (PK population).

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a randomized, double-blind, active-controlled, parallel-group, multicenter study in adult hospitalized patients to establish the safety and efficacy of ceftobiprole medocaril compared with vancomycin plus aztreonam in the treatment of ABSSSIs. Randomization will be stratified by study site and type of ABSSSI (with major cutaneous abscess comprising ≤30% of the ITT population).

Approximately 674 patients will be randomized in a 1:1 ratio to ceftobiprole or the comparator regimen. It is anticipated that the study will be performed at approximately 80 centers in North America and Europe.

Table 1 Summary of treatment and follow-up schedule

Study phase					
1	2	3			
Pre-treatment	Active treatment	Post-treatment			
Screening	Randomization and study-drug treatment	End of treatment (EOT)	Test-of-cure (TOC)	Survival status	Last follow-up (LFU)
Day −1 baseline	From Day 1 at least 5 days, up to 10 days*	Within 24 h after last treatment	15–22 days after randomization	Day 28 (±2 days)	28–35 days after last treatment

*Study treatment may be extended up to 14 days if required in the investigator's opinion and approved by the sponsor's medical monitor.

The study comprises three phases:

1. Pre-treatment: Screening and baseline, duration up to 24 h.
2. Active treatment: Randomization to at least 5 days and up to 10 days, of study drug administration with IV ceftobiprole, or IV vancomycin plus aztreonam. Study treatment may be extended up to 14 days if in the investigator's opinion this is required, and the extension is approved by the sponsor's medical monitor.
3. Post-treatment:
   - an EOT visit within 24 h after last treatment
   - a TOC visit 15–22 days after randomization
   - an LFU visit 28–35 days after last treatment

The total duration of the study for each patient is approximately 5–7 weeks.

In addition, at 28 days after randomization, survival status (Alive; Dead; Lost to Follow-up) is to be verified for evaluation of all-cause mortality (ACM). Survival status (by telephone or visit) must be obtained at Day 28 (±2 days).

3.2. Study Endpoints

3.2.1. Primary Endpoint

The study is designed to determine whether ceftobiprole is non-inferior to vancomycin plus aztreonam for the primary endpoint of early clinical response based on percentage reduction from baseline in lesion size at 48–72 h after first study-drug administration.

Early clinical response 48–72 h after start of treatment based on the patient meeting all of the following criteria:

1. ≥20% reduction from baseline in the area (length × width of erythema, edema, or induration) of the primary lesion. Derived surface area as calculated in the eCRF will be used for the analysis.
2. Survival for ≥72 h from the time of administration of the first dose of study drug.
3. No use of concomitant systemic antibacterial treatments, or topical antibacterial administration on the primary lesion before or on the latest lesion measurement done within 48–72 h after the first dose of study drug.
4. No additional unplanned surgical procedure for the ABSSSI after start of therapy and before or on the latest lesion measurement done within 48–72 h after the first dose of study drug (other than debridement at bedside or local bedside wound care), with the exception of cellulitis where there is a conversion into an abscess within 48 h of study treatment initiation, or, for post-surgery patients, when an extension of the original incision is indicated.

Patients with missing data relevant for the assessment of the primary endpoint will be considered as non-responders for the primary analysis.

Actual elapsed time (rather than calendar day) will be used to measure the time from first dose of study drug to the 48–72 h early-response assessment. In case assessment time is missing, time will be imputed to 12:00.

The primary endpoint is to be assessed in the ITT population.

Standardized measurement of the lesion area (i.e., erythema, edema, or induration, whichever is largest) is to be performed with a flexible plastic ruler or tape measure, by multiplying the longest length of the lesion by the widest width perpendicular to that length.

In addition, a measurement of the maximum width of erythema or edema/induration from the edge of the wound (surgical or traumatic) or abscess will be recorded. If abscess, the measurement should be taken from the end of the fluctuance before drainage or from the edge of the drainage site after drainage.

Measurements are to be performed at Screening (within the 6 h prior to first dose of study drug); twice on Days 2, 3, and 4; and once on Day 8, EOT, and the TOC and LFU visits.

On days when two measurements are obtained, the measurements are to be taken at least 8 h apart.

A digital photograph (primary ABSSSI lesion) will be obtained at Screening, at the early clinical response assessment (48–72 h after first treatment), and at the EOT and TOC visits, for each patient, and will be used for documentation purposes and as source data. Digital photography will not be used for the measurement of the ABSSSI lesion size area;

the determination of the ABSSSI lesion size area will be solely based on the ruler measurements.

This will be the main secondary endpoint for EMA submission.

3.2.2. Main Secondary Endpoint

Investigator-assessed clinical success at the TOC visit 15–22 days after randomization. The TOC visit should be performed at least 5 days after EOT.

Clinical success will be assessed by the investigator using a four-point scale relative to the baseline assessment: cured, improved, stable, or worsened. In case of worsened (e.g., bacteremia, osteomyelitis, amputation), signs and symptoms need to be documented as AEs.

Clinical success is defined as complete (cured) or nearly complete (improved) resolution of baseline signs and symptoms of the primary infection, such that no further antibacterial treatment is needed.

A patient meeting this definition cannot be classified as a clinical success if any of the following criteria are met:

1. Death from any cause prior to TOC.
2. Additional antibacterial therapy received for treatment of the primary lesion prior to TOC.
3. Initiation of non-study antibacterial treatment of another infection, unless the antibacterial agent lacks efficacy in the treatment of ABSSSI prior to TOC.
4. Requirement for an unplanned surgical procedure for the ABSSSI after start of therapy and prior to TOC, (other than debridement at bedside or local bedside wound care), with the exception of cellulitis where there is a conversion into an abscess within 48 h of study treatment initiation, or, for post-surgery patients, when an extension of the original incision is indicated.
5. Indeterminate assessment at TOC for any reason, including but not limited to:
    a. missing TOC visit
    b. lost to follow-up
    c. patient withdrew consent
    d. missing data in relation to signs and symptoms of the ABSSSI
    e. discontinuation from the study due to the need for hemodialysis

The main secondary endpoint is to be assessed in the ITT and CE populations.

This will be the primary endpoint for EMA submission.

3.2.3. Other Secondary Endpoints

1. Early clinical response based on percentage reduction in lesion size at 48–72 h after first treatment in the CE population, using the same definition for response as for the primary endpoint.
2. Clinical response (see Section 3.2.1) defined as ≥80% decrease in lesion area at the EOT visit, and ≥90% decrease in lesion area at the TOC visit (ITT and CE populations), with improvement of local signs of the infection, i.e., achieving clinical success (as discussed in Section 3.2.2) at the respective visit.
3. Sustained reduction in lesion size at the EOT and TOC visits (ITT and CE populations).

   Sustained reduction in lesion size is defined as ≥ 20% decrease in lesion area 48–72 h after start of treatment (primary endpoint) that is sustained at the EOT and TOC visits. Reduction in lesion size is sustained at a specific time point if criteria 2, 3 and 4 detailed in Section 3.2.1 are also satisfied for that specific time point.
4. Investigator-assessed clinical success evaluated at 48–72 h after first treatment and the EOT visit, and sustained clinical success at the LFU visit (ITT and CE populations).

   Clinical success at the 48–72 h after first treatment and EOT visit are defined by the same criteria as for the main secondary endpoint, with an indeterminate assessment to include a missing visit at the 48–72 h after first treatment and EOT visit.

   Clinical success at LFU visit is defined by the same criteria as for the main secondary endpoint, with an indeterminate assessment to include a missing LFU visit.

   Sustained clinical success requires that all criteria listed for the main secondary endpoint are met at TOC and LFU visits.
5. ACM at Day 28 (ITT and CE populations)
   Assessment of survival status at Day 28
6. Microbiological response as assessed by the investigator at Day 3, Day 5, and the EOT, TOC and LFU visits (mITT and ME populations).

   Eradication: No growth of the baseline pathogen(s) based on post-therapy cultures obtained from the primary infection site at the respective time points.

   Presumed eradication: No post-therapy culture due to lack of culturable material, accompanied by investigator-assessed clinical success.

   Persistence: Evidence of continued growth of the baseline pathogen.

   Presumed persistence: No post-therapy culture due to lack of culturable material, accompanied by the absence of investigator-assessed clinical success.

   Superinfection: Emergence of a new pathogen(s) at the primary site of infection, accompanied by the absence of an investigator-assessed clinical success.

   Relapse or recurrence: Pre-therapy pathogen isolated between the EOT and TOC visits, or between the TOC and LFU visits, after a pathogen response of ‘eradication’ or ‘presumed eradication’ at the EOT or TOC visits.

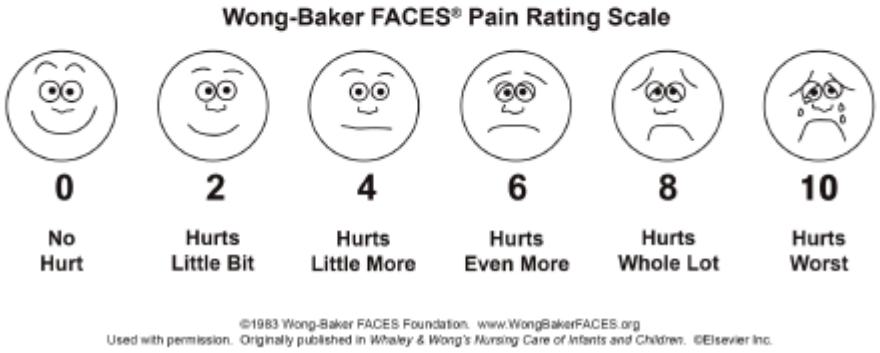
Non-evaluable: No pathogen isolated at baseline (either no sample obtained for culture or culture had no growth at baseline).

7. Change from baseline in patient-reported pain (ITT and CE populations)
   Time points: all visits, (with exception of Day 28)
   Patient-reported pain, assessed at baseline and throughout the study, using a visual analogue scale (VAS) with a 100 mm line, on which the 0 point indicates 'no pain' and the 100 mm point indicates 'worst pain ever', and a Wong-Baker FACES® Pain Rating Scale.

Visual analog scale

0 mm	100 mm
no pain	worst pain ever

Wong-Baker FACES® Pain Rating Scale



8. Health economic outcome measures (ITT and CE populations)
   Time point: From start of study medication until the LFU visit
   Resource requirements and health economic data will be derived from study-specific data, or collected ancillary to study conduct, to perform health economics analyses. These analyses will aim to enable economic comparisons of ceftobiprole with vancomycin and aztreonam.
9. Safety (Safety Population)
   Time point: First dose of study drug until LFU
   Adverse events, laboratory tests (including hematology, blood chemistry, and haptoglobin), Coomb's test, vital signs, physical examination, and concomitant medications.
10. Pharmacokinetics (PK Population)
    Time points: Day 4
    Plasma levels of ceftobiprole.
    Sparse PK sampling

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

Rich PK sampling

- Day 4: predose, 2 h (end of infusion), 3 h, 4 h, 6 h and 8 h

3.3. Treatments

After randomization and during active treatment, patients will receive ceftobiprole and placebo or vancomycin and aztreonam according to the schedule outlined in Table 2. The two intravenous treatment regimens to be administered are:

- Ceftobiprole 500 mg q8h (with dose adjustment for renal impairment).
- Vancomycin 1000 mg (or 15 mg/kg) q12h plus aztreonam 1000 mg q12h (both with dose adjustment for renal impairment). Vancomycin dose adjustments for obese and hypermetabolic patients are according to local standards of care.

Table 2 Study-drug administration

Time (h)	Study drug	Dose (mg)	Volume (mL)	Infusion time (h)	Study drug	Dose (mg)	Volume (mL)	Infusion time (h)
0	Ceftobiprole	500	250	2	Vancomycin	1000*	250	2
	Placebo	NA	100	0.5	Aztreonam**	1000	100	0.5
8	Ceftobiprole	500	250	2	Placebo	NA	250	2
12	Placebo	NA	250	2	Vancomycin	1000*	250	2
	Placebo	NA	100	0.5	Aztreonam	1000	100	0.5
16	Ceftobiprole	500	250	2	Placebo	NA	250	2

* Or 15 mg/kg vancomycin: the decision to use vancomycin at a fixed or weight-based dose is to be made by the investigator on the basis of the site's standard of care, and needs to be communicated prior to randomization to the unblinded pharmacist or delegate. If VTT is performed, the vancomycin dose may be adjusted according to trough levels.

** The requirement for aztreonam therapy will be reassessed at the 72-h study visit.

NA, not applicable.

On each treatment day, study-drug administration should be no more than ± 2 h from the scheduled time point.

3.4. Dose Adjustment/Modifications

The vancomycin dose may be adjusted by the unblinded pharmacist or delegate in accordance with the local standard of care.

The total daily volume of study-drug infusions is 1200 mL for study participants with CL_{CR} ≥70 mL/min, 950 mL for patients with CL_{CR} of 50 – <70 mL/min, 700 mL for patients with CL_{CR} of 30 to <50 mL/min and 450 mL for patients with CL_{CR} of <30 mL/min (see Table 3).

Table 3 Dosing and dose adjustment for ceftobiprole and vancomycin/aztreonam based on CL_{CR}

	Ceftobiprole treatment group				Vancomycin plus aztreonam treatment group			
Time (h)	Study drug	Dose (mg)	Volume (mL)	Infusion time (h)	Study drug	Dose (mg)	Volume (mL)	Infusion time (h)
				CL_{CR} > 100 mL/min				
0	Ceftobiprole	500	250	2	Vancomycin	1000*	250	2
	Placebo	NA	100	0.5	Aztreonam	1000	100	0.5
8	Ceftobiprole	500	250	2	Placebo	NA	250	2
12	Placebo	NA	250	2	Vancomycin	1000*	250	2
	Placebo	NA	100	0.5	Aztreonam	1000	100	0.5
16	Ceftobiprole	500	250	2	Placebo	NA	250	2
				CL_{CR} 70 to 100 mL/min				
0	Ceftobiprole	500	250	2	Vancomycin	750#	250	2
	Placebo	NA	100	0.5	Aztreonam	1000	100	0.5
8	Ceftobiprole	500	250	2	Placebo	NA	250	2
12	Placebo	NA	250	2	Vancomycin	750#	250	2
	Placebo	NA	100	0.5	Aztreonam	1000	100	0.5
16	Ceftobiprole	500	250	2	Placebo	NA	250	2
				CL_{CR} 50 to < 70 mL/min				
0	Ceftobiprole	500	250	2	Vancomycin	1000#	250	2
	Placebo	NA	100	0.5	Aztreonam	1000	100	0.5
8	Ceftobiprole	500	250	2	Placebo	NA	250	2
12	Placebo	NA	100	0.5	Aztreonam	1000	100	0.5
16	Ceftobiprole	500	250	2	Placebo	NA	250	2
				CL_{CR} 30 to < 50 mL/min				
0	Ceftobiprole	500	250	2	Vancomycin	1000#	250	2
	Placebo	NA	100	0.5	Aztreonam	1000	100	0.5
12	Placebo	NA	100	0.5	Aztreonam	1000	100	0.5
	Ceftobiprole	500	250	2	Placebo	NA	250	2
				CL_{CR} < 30 mL/min				
0	Ceftobiprole	250	125	2	Vancomycin	500#	125	2
	Placebo	NA	100	0.5	Aztreonam	1000†	100	0.5
12	Placebo	NA	100	0.5	Aztreonam	500†	100	0.5
	Ceftobiprole	250	125	2	Placebo	NA	125	2

* Or 15 mg/kg vancomycin: The decision to use vancomycin at a fixed or weight-based dose is to be made by the investigator on the basis of the site's standard of care, and needs to be communicated prior to randomization to the unblinded pharmacist or delegate. If VTT is performed, the vancomycin dose may be adjusted according to trough levels.
# Or 15 × CL_{CR} (as determined by Cockcroft-Gault formula) as a total daily dose distributed q12h: The decision to use vancomycin at a fixed or CL_{CR}-based dose is to be made by the investigator on the basis of the site's standard of care, and needs to be communicated prior to randomization to the unblinded pharmacist or delegate. If VTT is performed, the vancomycin dose may be adjusted according to trough levels.
† After an initial dose of 1000 mg, all subsequent maintenance doses of aztreonam should be halved (i.e. 500 mg).

3.4.1. Ceftobiprole

Ceftobiprole 500 mg is to be administered every 8 h as a 2-h IV infusion.

- For patients with mild renal impairment (i.e., CL_{CR} 50 – 80 mL/min), no dosage adjustment is necessary.
- For patients with moderate renal impairment (CL_{CR} 30 – <50 mL/min), the recommended dose of ceftobiprole is 500 mg q12h, as a 2-h IV infusion.
- For patients with severe renal impairment (CL_{CR} <30 mL/min), the recommended dose of ceftobiprole is 250 mg q12h, as a 2-h IV infusion.

A patient who develops the need for hemodialysis must be discontinued from the study before hemodialysis commences.

3.4.2. Vancomycin

The IV vancomycin dose for adults with a CL_{CR} >100 mL/min is either fixed 1000 mg, or weight-based at 15 mg/kg every 12 h, administered as a 2-h IV infusion. The dosage regimen to be used for vancomycin at the study site must be agreed by the investigator and unblinded pharmacist (or delegate) prior to randomization.

If dose adjustments are made based on CL_{CR} values, the following recommendations apply:

- CL_{CR} 70–100 mL/min: vancomycin 750 mg is to be administered as a 2-h IV infusion q12h (or a total daily dose of 15 × the CL_{CR} in mL/min distributed q12h), from study Day 1 until EOT.
- CL_{CR} 30 – <70 mL/min: vancomycin 1000 mg, or 15 × the CL_{CR} in mL/min, is to be administered as a 2-h IV infusion q24h, from study Day 1 until EOT.
- CL_{CR} <30 mL/min: vancomycin 500 mg, or 15 × CL_{CR} in mL/min, is to be administered as a 2-h IV infusion q24h, from study Day 1 until EOT.

A patient who develops the need for hemodialysis must be discontinued from the study before hemodialysis commences.

Dose adjustment in morbidly obese and hypermetabolic patients

If dictated by local standards of care, adjustments to the dose of vancomycin are permitted, for example in obese and hypermetabolic patients; adjustments to dosing in the morbidly obese (e.g., BMI >35) are encouraged if consistent with local standards of care.

For doses that exceed 1.2 g of vancomycin (i.e., >10 mg/min), care should be taken to adjust (prolong) the infusion time appropriately, or to consider a change in the dosing interval.

If adjustments to dosing for obese or hypermetabolic patients are standard at a site, the infusion rate and volume must be adjusted for all such patients at that site prior to first study drug administration, including those randomized to ceftobiprole who are receiving placebo-vancomycin.

Every effort should be made to maintain the blind if changes in the vancomycin infusion duration (i.e., >2-h infusion duration) or dosing schedule from twice daily to three times daily that are implemented during the study (after administration of first study drug administration), e.g., based on a change in renal function or based on vancomycin trough levels.

Vancomycin trough level determination in all patients prior to the fourth vancomycin dose (central laboratory)

A vancomycin trough level for central laboratory assessment is to be obtained approximately 30 min before administration of the fourth dose of vancomycin (i.e., on Day 2 for patients who receive vancomycin on a q12h schedule, and on Day 4 for patients who receive vancomycin on a q24h schedule). The central laboratory results will not be communicated to the study site.

Vancomycin trough level determination using local laboratories

When locally available, the vancomycin dosage may be adjusted by the unblinded pharmacist or delegate based on vancomycin trough testing (VTT), to maintain steady-state trough levels of 10–15 mg/L; adjustments are to be managed according to local standards at each site.

In study sites which use vancomycin trough level monitoring to guide vancomycin dosing using a local laboratory, a blood sample for local laboratory testing of the vancomycin trough level should be obtained in addition to the central laboratory blood sample before administration of the fourth dose of vancomycin. Additional local laboratory testing of vancomycin trough levels should be obtained according to institutional practices at the respective study site.

If the local practice at a site is to take blood samples for VTT, for blinding purposes these must be drawn from all patients at the site, regardless of study-drug treatment. The unblinded local laboratory technician must only provide the results of this testing to the unblinded pharmacist or delegate for patients randomized to vancomycin. If the patient is randomized to ceftobiprole, the local laboratory unblinded technician must discard samples and not report a vancomycin trough level.

Local VTT results will be entered in the unblinded eCRF by the unblinded pharmacist or delegate, together with the vancomycin dose.

3.4.3. Aztreonam

Aztreonam 1000 mg is to be administered as a 0.5-h IV infusion q12h. If CL_{CR} is <30 mL/min (i.e., severe renal impairment), the aztreonam dosage regimen may be adjusted by the unblinded pharmacist or delegate.

The requirement for aztreonam therapy will be reassessed at the 72-h study visit.

Prolonged serum levels of aztreonam may occur in patients with transient or persistent renal impairment. Accordingly, for patients with estimated CL_{CR} ≥10 and <30 mL/min, after an initial usual dose of 1000 mg, the maintenance dose of aztreonam should be reduced to 500 mg.

A patient who develops the need for hemodialysis must be discontinued from the study before hemodialysis commences.

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 / standard error will be displayed to two levels of precision greater than the data collected up to a maximum of 3 decimal places.

All comparisons will be for ceftobiprole versus vancomycin plus aztreonam. 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 vancomycin plus aztreonam group. All other statistical analyses will be performed using a two-sided hypothesis test at the overall 5% level of significance. 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.

When count data are presented, the percentage will be suppressed when the count is zero in order 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.

4.1. Sample Size

The study is designed to determine whether ceftobiprole is non-inferior to vancomycin plus aztreonam for the outcome measure of early clinical response at 48–72 h after start of treatment, defined as

1. a ≥20% reduction from baseline in the area (longest length × perpendicular width of erythema, edema, or induration) of the primary lesion,
2. survival for ≥72 h from the time of administration of the first dose of study drug,
3. no use of concomitant systemic antibacterial treatment or topical antibacterial administration on the primary lesion, and
4. no additional unplanned surgical procedure for the ABSSSI after start of therapy (other than debridement at bedside or local bedside wound care), with the exception of cellulitis where there is a conversion into an abscess within 48 h of study

treatment initiation, or, for post-surgery patients, when an extension of the original incision is indicated.

A sample size of 674 patients (337 per group) will provide at least 90% 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: $\pi_{\text{vancomycin/aztrenonam}} - \pi_{\text{ceftobiprole}} \geq 0.10$ versus

H_A: $\pi_{\text{vancomycin/aztrenonam}} - \pi_{\text{ceftobiprole}} < 0.10$.

Early clinical response rates of an at least 20% reduction in lesion area size (primary endpoint) and clinical cure rates at the TOC visit (main secondary endpoint) from recent Phase 3 studies in ABSSSI are summarized in tabular form in protocol Section 8.1. These clinical study data support an estimate of early clinical response rates of >80%.

The sample size estimate is therefore based on:

- a point estimate for early clinical response of 80% in each treatment group in the ITT and CE population.
- one-sided alpha level of 0.025.
- non-inferiority margin of 10 percentage points for the between-group difference of the primary endpoint.

Based on these assumptions, randomization of 337 patients per treatment group (total 674 patients) would provide >90% power to demonstrate the non-inferiority of ceftobiprole compared to vancomycin plus aztreonam. Patients with cutaneous abscesses will comprise ≤30% of those randomized.

With randomization of 337 patients per treatment group, the statistical power at a one-sided alpha level of 0.025 is 90% (ITT population) and 97% (CE population) for the key secondary endpoint, assuming that 85% of the ITT population is in the CE population using the same non-inferiority margin.

4.2. Randomization, Stratification, and Blinding

Eligible patients will be randomized in a 1:1 ratio to ceftobiprole or vancomycin/aztreonam, based on a computer-generated randomization schedule. The unblinded pharmacist or delegate will contact the IWRS to obtain the study treatment assignment, and dispense blinded therapy accordingly. The IWRS will associate that patient with the next available treatment in the appropriate stratum on randomization.

Randomization will be stratified at baseline, using block randomization, by:

- Study site

- Type of ABSSSI (cellulitis/erysipelas, major cutaneous abscess, or wound infection). Actual values (rather than IWRS strata values) will be used in all efficacy analysis.

Patients with a major cutaneous abscess must comprise ≤30% of the ITT population.

Detailed randomization instructions are provided in the IWRS manual.

The unblinded pharmacist or delegate will provide blinded and properly labeled study medication only to investigational staff. Only the unblinded pharmacist or delegate at the site, will have access to treatment codes via IWRS. Investigators, other site staff, sponsor employees, and others involved in the conduct of the study (with the exception of the above) will remain blinded to the treatment codes until the database has been locked for final analysis.

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 will include all randomized patients. All patients in the ITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different.

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

The mITT population will be the subset of patients in the ITT population who have had causative (infecting) pathogens identified by the central microbiology laboratory from skin lesion and blood cultures (local laboratory identification results will only be used if no causative (infecting) pathogen is identified by the central laboratory).

Patients with no pathogen isolated at baseline (microbiologically non-evaluable) will be excluded from the mITT population.

4.3.3. Clinically Evaluable (CE) Population

The CE population will be the subset of patients in the ITT population who have complied with important aspects of the study until TOC visit, i.e., with no major protocol deviations (e.g., a completed response outcome assessment, and no concomitant systemic antibacterial treatment or topical antibacterial applied to the primary lesion). Major protocol deviations will be identified prior to the database lock and study unblinding.

4.3.4. Microbiologically Evaluable (ME) Population

The ME population will be the subset of patients in the mITT population who are also in the CE population. Analysis at each timepoint will be performed on patients with available response at that timepoint (excluding those with a microbiological response of 'Not Evaluable' or missing).

4.3.5. Safety Population

The Safety population will include 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 actually received.

4.3.6. Pharmacokinetic (PK) Population

The PK population will include all patients who receive 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

Baseline for safety and efficacy is the last available value prior to or on the first dose of study drug date and time. In case the time of the first dose of study drug and/or the time of the assessment is unknown, assessments done the day of the dose of first study drug will be considered as baseline, unless otherwise specified. No data known to be collected post first study drug date will be used in determining the baseline value, unless otherwise specified.

For microbiological analysis, the identification of baseline pathogen(s) is based on all isolates collected from screening until 24 hours after first dose.

4.4.2. 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. All available data will be listed.

Analysis of the primary endpoint 48–72 h early-response analyses will be solely based upon actual elapsed time since first dose of study drug as discussed in Section 3.2.1 of this SAP. If multiple lesion measurements are taken within 48–72 h after the first dose of study drug, the last lesion measurement within this period will be used.

Likewise, analysis of Day 28 survival status and time until death will be based upon actual elapsed time since randomization as discussed in Section 8.3.6 of this SAP.

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.

4.4.3. 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 Imputation Algorithm for Partial and Missing Dates and Times.

4.4.4. Pre-specified Subgroups

Subgroup analyses will be performed for the primary and main secondary efficacy endpoints where applicable. For each specific subgroup, if there are not enough patients (i.e., <5% ITT population), the corresponding analyses will not be performed.

The subgroups analyses by causative (infecting) pathogen(s), minimal inhibitory concentration(s) and positive baseline blood culture will be determined in the mITT and ME populations.

Subgroup analyses will include the following factors:

- Age (years) (18–34 , 35–64, 65–74, ≥75)
- Sex (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 (North America, Europe)
- Causative (infecting) pathogen(s) and susceptibility phenotype of causative (infecting) pathogen(s) (e.g., MRSA, MSSA) overall and by baseline ABSSSI type.

Any group that has less than 10 organisms will not be included in the subgroup analyses.

- Study drug(s) minimal inhibitory concentration(s) for causative (infecting) pathogen(s)
- Positive baseline blood culture, overall and by causative (infecting) pathogen
- Baseline ABSSSI type (cellulitis/erysipelas, major cutaneous abscess, wound infection) (actual values)
- Diabetes mellitus (Yes, No)
- Illicit drug use (Current, Previous, Never)
- Injection drug use (Current, Previous, Never)
- Baseline creatinine clearance (mL/min) range (<30, 30 – <50, 50–80, >80)
- Baseline white blood cell (WBC) count [Normal (4.0×10^9/L ≤ WBC ≤ 10.0×10^9/L), Abnormal (WBC < 4.0×10^9/L or WBC > 10.0×10^9/L)]
- Baseline fever status (Fever [>38 °C / 100.4 °F, measured orally, >38.5 °C / 101.3 °F measured tympanically, >37.5 °C / 99.5 °F measured by the axillary method, or >39 °C / 102.2 °F measured rectally], No Fever [Formulae applicable to 'Fever' inverted, i.e., using ≤ in place of >])
- Baseline >10% immature neutrophils (band forms) (Yes, No)

4.4.5. 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.

4.4.6. Coding Dictionaries

Adverse events, medical history and prior and concomitant Non-drug treatment procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0 or later.

Previous and concomitant treatments will be coded with the World Health Organization Drug Dictionary Enhanced (WHO DDE) dated 01SEP2018 or later.

5. Subject Disposition

5.1. Disposition

A summary of the analysis sets includes the number and percentage of patients for the following categories: patients screened, patients who failed screening and the reasons for screen failure, 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, patients in the ME population, patients in the PK population**.** All percentages will be based on the number of patients randomized.

A summary of the patients excluded from mITT/CE population 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 CE populations. 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 TOC visit, patients who did not complete the TOC visit with overall reasons, patients who completed the LFU visit, patients who did not complete the LFU visit with overall reasons. All percentages will be based on the number of patients randomized.

The reason for study discontinuation, the reason for study treatment discontinuation and the overall reason the patient did not complete the EOT/TOC/LFU visit may include any of the following: adverse event, abnormal laboratory value, abnormal test procedure result, intercurrent illness, death, protocol deviation, lost to follow-up, administrative or logistical reasons, lack of efficacy, hemodialysis, pregnancy, investigator decision, withdrawal by patient, unblinding of treatment assignment or other.

Patient disposition data will also be presented in a listing.

A plot of time to early discontinuation of study drug and a summary will be provided using Kaplan-Meier. Time to study drug 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.

For patients with primary ABSSSI diagnosis change between screening and anytime thereafter during the study, the number and percentage of patients with change in diagnosis category (Wound Infection, Cellulitis, and Major Abscess) will be reported and the number of days until new diagnosis will also be presented using descriptive statistics. The number of days until new primary ABSSSI diagnosis is defined as the number of days from randomization until the date of new diagnosis.

A summary of enrollment will be provided for each geographical region, country and site for all randomized patients.

5.2. Protocol Deviations

Deviations from the protocol will be recorded appropriately. 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 for ITT Population. All the significant deviations will be presented in a listing.

6. Demographics and Baseline Characteristics

6.1. Demographics and Baseline Characteristics

The demographics and baseline characteristics will be presented in tables using descriptive statistics. The demographic characteristics consist of:

- Age (from eCRF)
- Age category (years) (<18, 18–34, 35–64, 65–74, ≥75)
- Sex (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)
- Geographic region (North America, Europe)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Baseline Weight
- Baseline Height
- Baseline Body Mass Index (BMI)
- Diabetes mellitus (Yes, No)
- Illicit drug use (Current, Previous, Never)
- Injection drug use (Current, Previous, Never)
- Baseline creatinine clearance (mL/min) (<30, 30 – <50, 50–80, >80)

- Baseline fever (Fever [>38 °C / 100.4 °F, measured orally, >38.5 °C / 101.3 °F measured tympanically, > 37.5 °C / 99.5 °F measured by the axillary method, or >39 °C / 102.2 °F measured rectally], No Fever [Formulae applicable to 'Fever' inverted, i.e., using ≤ in place of >])
- Baseline WBC count [Normal (4.0×10^9/L ≤ WBC ≤ 10.0×10^9/L), Abnormal (WBC < 4.0×10^9/L or WBC > 10.0×10^9/L)]
- Baseline >10% immature neutrophils (band forms) (Yes, No)
- Systemic Antibacterial medications prior to study drug (Yes, No)
- Topical Antibacterial medications prior to study drug (Yes, No)
- Concomitant antibacterial medications (Metronidazole)

A patient's age in years is recorded directly on the eCRF (integrated from IWRS). Age will be summarized using descriptive statistics and will be listed.

Demographics will be presented for ITT and CE analysis populations.

Demographics and baseline characteristics data will also be listed.

6.2. Female Reproductive System

Female reproductive system at screening will be presented for the ITT population and will consist of fertility status, number of months if post-menopausal, and method of birth control. Pregnancy test at screening will also be presented.

6.3. Medical/Surgical History

6.3.1. General Medical/Surgical History

The number and percentage of patients with any Medical history other than primary ABSSSI history will be summarized overall and for each system organ class and preferred term. Percentages will be calculated based on number of patients in the ITT population.

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

6.3.2. Disease-Specific History

The following medical/surgical history parameters related to primary ABSSSI will be summarized for the ITT population using descriptive statistics:

- Recent surgical procedure that resulted in the primary ABSSSI
- Days since most recent surgical procedure
- Recent trauma that resulted in the primary ABSSSI
- Days since most recent trauma

- Infection Site Assessment (erythema, induration, localized warmth, pain on palpation, tenderness on palpation, swelling, edema, fluctuance, incision required, incision performed, drainage required, drainage performed, purulent drainage, and seropurulent drainage)
- Description of Primary ABSSSI (days since symptoms onset, time since measurements, longest length, widest width perpendicular to the longest length, calculated surface area, measurement taken (before drainage vs. after drainage), days since most recent drainage, and maximum width of erythema or edema/induration from the edge of the wound or abscess)
- Location of primary ABSSSI (abdominal skin, arm, axilla, back, buttock, chest, face, foot, hand, inguinal region, leg, neck, scalp, shoulder)
- Microbiological causative (infecting) pathogen(s) isolated at baseline.

Incomplete symptom onset dates will be imputed as detailed Appendix 14.1.

Details of ABSSSI surgical procedures anticipated during the study and/or planned at baseline will also be listed.

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 eCRF.

Prior non-antibiotic medications are defined as medications with a stop date occurring before 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 preferred name.

Prior antibiotic medications are defined as medications with a stop date and time occurring before 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 drug class and preferred name.

At each level of summarization, a patient is counted once if he/she reports one or more medications at that level. Drug class will correspond to the Anatomical Therapeutic Classification (ATC) Level 4 term. All prior medications and concomitant medications will be summarized for the ITT population.

The imputation algorithm for partial and missing 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 before the first dose date. Concomitant non-drug procedures are defined as treatments 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.

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

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 of study drug (Day 1) to the last dose date of study drug (date of last known study drug administration as recorded on the Study Completion/Termination page on the eCRF) i.e., (Date of last dose of study drug - Date of first dose of study drug) + 1. If the last dose date of study drug on the Study Completion/Termination page is missing, or if a patient is lost to follow-up, then the last infusion end date recorded on the Exposure page on the eCRF will be used.

The duration of exposure to study drug by treatment group will be summarized for all patients in the Safety population and will be presented in a table by summary statistics. The duration of exposure will then be classified into one of the following categories: > 0–< 5 days, 5–10 days, > 10–14 days, and > 14 days and will be presented as the number and

percentage of patients in each duration category. Percentages will be computed from the number of patients in the Safety population.

Because study drug dose adjustment may occur during the study, the exposure to study drug will also be characterized by cumulative dose by treatment within each treatment group, which is defined as the sum of actual doses (mg) administered to a patient. The total cumulative dose (mg) will be summarized by descriptive summary statistics, by day and overall.

Also, the number of actual doses by treatment group will be defined as the number of occasions the dose is administered on a given day. The total number of actual doses will be summarized by day, and overall.

The overall compliance by treatment group will be summarized descriptively. 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.

A summary of each patient's exposure will be presented in a listing.

8. Efficacy Analysis

8.1. Primary Efficacy Analysis

8.1.1. Main Analysis

The main primary analysis will be based on the ITT population.

The numbers and percentages of responders and non-responders will be determined in each treatment group.

The weighted difference in percentage of responders at 48–72 h (ceftobiprole group minus the vancomycin plus aztreonam group), and the 95% CI for the weighted difference will be computed using CMH weights method adjusted for geographical region (North America and Europe), and actual type of ABSSSI. Estimates of the weighted risk ratio and weighted odds ratio will also be provided.

A bar graph showing the proportions of patients with early clinical response will be produced.

Test hypothesis for non-inferiority:

$H_0: \pi_1 - \pi_2 \leq -0.10$

$H_A: \pi_1 - \pi_2 > -0.10$

Where,

π_1 = Proportion of patient with early clinical response for ceftobiprole group

π_2 = Proportion of patient with early clinical response for vancomycin plus aztreonam group

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 response rates (ceftobiprole minus vancomycin plus aztreonam) in the ITT population is greater than -10%, the non-inferiority of ceftobiprole to vancomycin plus aztreonam will be concluded.

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

Test hypothesis for superiority:

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

$H_A: \pi_1 - \pi_2 > 0$

Where,

π_1 = Proportion of patient with early clinical response for ceftobiprole group

π_2 = Proportion of patient with early clinical response for vancomycin plus aztreonam 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).

The same analysis will be repeated on the CE population.

Subgroup analyses listed in Section 4.4.4 will be conducted for the primary efficacy outcome in the ITT and CE populations.

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 stratum (geographical region and actual type of ABSSSI when applicable), will be produced.

8.1.2. Sensitivity Analyses

To assess the robustness of the primary efficacy analysis results, the following sensitivity analyses will be performed for the primary outcome in ITT and CE populations:

- An unadjusted analysis by unstratified Wald Statistic will be provided, i.e., statistic will not be adjusted for the geographic region (North America and Europe) and actual ABSSSI type.
- Patients with missing surface area of primary lesion at baseline or 48–72 h will be excluded (Observed Cases analysis).
- The insufficient number of patients per site not warranting the investigation of the treatment by site interaction effect, only the heterogeneity of treatment effect across geographic regions (North America and Europe) will be evaluated. To assess the geographic region effect, the interaction between treatment and geographic region will be evaluated using Gail-Simon test with significance level of 0.10. In case the interaction is found to be significant, then further analysis of the primary endpoint will be performed to assess where these regional differences lie. This may include further subgroup analysis by site.
- Based on audit findings, a sensitivity analysis of the primary endpoint will be performed, excluding data from site 069.
- A forest plot by site showing the weighted treatment differences with associated 95% CI and p-values, computed using CMH weights statistics controlling actual type of ABSSSI will be produced.

8.2. Secondary Efficacy Analysis

8.2.1. Main Analysis

The main secondary analysis will be based on the ITT and CE populations.

The numbers and percentages of Success and No-Success will be determined in each treatment group at TOC visit.

The weighted difference in percentage of clinical success at TOC visit (ceftobiprole group minus the vancomycin plus aztreonam group), and the 95% CI for the weighted difference will be computed using CMH weights method, adjusted for geographical region (North America and Europe), and actual type of ABSSSI. Estimates of the weighted risk ratio and weighted odds ratio will also be provided.

A bar graph showing the proportions of patients with clinical success will be produced.

Test hypothesis for non-inferiority:

$H_0: \pi_1 - \pi_2 \leq -0.10$

$H_A: \pi_1 - \pi_2 > -0.10$

Where,

π_1 = Proportion of patient with clinical success for ceftobiprole group

π_2 = Proportion of patient with clinical success for vancomycin plus aztreonam group

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 clinical success rates (ceftobiprole minus vancomycin plus aztreonam) in the ITT and CE populations is greater than 10%, the non-inferiority of ceftobiprole to vancomycin plus aztreonam will be concluded.

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

Test hypothesis for superiority:

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

H_A: $\pi_1 - \pi_2 > 0$

Where,

π_1 = Proportion of patient with clinical success for ceftobiprole group

π_2 = Proportion of patient with clinical success for vancomycin plus aztreonam 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).

Subgroup analyses listed in Section 4.4.4 will be conducted for the primary efficacy outcome in the ITT and CE populations.

8.2.2. Sensitivity Analyses

In addition, the following sensitivity analyses will be performed for the main secondary endpoint:

- An unadjusted analysis by unstratified Wald Statistic will be provided, i.e., statistic will not be adjusted for the geographic region (North America and Europe) and actual ABSSSI type.
- Patients with missing investigator-assessed clinical success at the TOC visit will be excluded (Observed Cases analysis).
- The insufficient number of patients per site not warranting the investigation of the treatment by site interaction effect, only the heterogeneity of treatment effect across geographic regions (North America and Europe) will be evaluated. To assess the geographic region effect, the interaction between treatment and geographic region will be evaluated using Gail-Simon test with significance level of 0.10. In case the interaction is found to be significant, then further analysis of the primary endpoint will be performed to assess where these regional differences lie. This may include further subgroup analysis by site.

- Based on audit findings, a sensitivity analysis of the primary endpoint will be performed, excluding data from site 069.
- A forest plot by site showing the weighted treatment differences with associated 95% CI and p-values, computed using CMH weights statistics controlling for actual type of ABSSSI will be produced.
- Analysis will be performed to assess the association between the primary endpoint, i.e., early clinical response at 48–72 h, and the secondary endpoint, i.e., clinical responses at the TOC visits controlling for treatment group using CMH.

8.3. Other Secondary Efficacy Analysis

8.3.1. Clinical Response Defined as ≥80% Decrease in Lesion Area at the EOT Visit, ≥90% Decrease in Lesion Area at the TOC visit, and Clinical Success Achieved as per Secondary Endpoint Criteria Satisfied at EOT and TOC

The numbers and percentages of responders and non-responders will be determined in each treatment group at EOT, TOC, and EOT and TOC combined in the ITT and CE populations.

The weighted difference in percentage of responders at EOT and TOC visits (ceftobiprole group minus the vancomycin plus aztreonam group), and the 95% CI for the weighted difference will be computed using CMH weights method adjusted for geographical region (North America and Europe), and actual type of ABSSSI. Estimates of the weighted risk ratio and weighted odds ratio as well as the p-value for CMH test will also be provided.

8.3.2. Sustained Reduction in Lesion Size at the EOT and TOC Visits

The numbers and percentages of responders and non-responders for sustained reduction in lesion size at EOT and TOC visits will be determined in each treatment group in the ITT and CE populations.

The weighted difference in percentage of responders for sustained reduction in lesion size at EOT and TOC visits (ceftobiprole group minus the vancomycin plus aztreonam group), and the 95% CI for the weighted difference will be computed using CMH weights method adjusted for geographical region (North America and Europe), and actual type of ABSSSI. Estimates of the weighted risk ratio and weighted odds ratio as well as the p-value for CMH test will also be provided.

8.3.3. Investigator-assessed clinical success evaluated at 48–72 h after first treatment and the EOT visit, and sustained clinical success at the LFU visit.

The investigator-assessed the level of clinical success will be summarized at each given visit. Also, the weighted difference in percentage of clinical success (Cured + Improved) at each visit and the 95% CI for the weighted difference will be computed using CMH

weights method, adjusted for geographical region (North America and Europe), and actual type of ABSSSI. P-value for CMH test will also be provided.

The numbers and percentages of responders and non-responders for sustained clinical success at TOC and LFU visits will be determined in each treatment group in the ITT and CE populations.

The weighted difference in percentage of responders for sustained clinical success at TOC and LFU visits (ceftobiprole group minus the vancomycin plus aztreonam group), and the 95% CI for the weighted difference will be computed using CMH weights method adjusted for geographical region (North America and Europe), and actual type of ABSSSI. Estimates of the weighted risk ratio and weighted odds ratio as well as the p-value for CMH test will also be provided.

8.3.4. Microbiology

8.3.4.1. Microbiological Responses, Eradication Rate and Time to Eradication

Microbiological response (as defined in Section 3.2.3) at Day 3, Day 5, and the EOT, TOC and LFU visits will be determined in each treatment group in the mITT and ME populations.

The numbers and percentages of responders and non-responders will be determined in each treatment group. Eradication and presumed eradication will be grouped together as responders. Patients with microbiological response persistence, presumed persistence, superinfection, relapse or recurrence, or patients with missing data will be considered non-responders for the analysis. Proportion of patients achieving microbiological eradication or presumed eradication will be analyzed for each visit separately using the same statistical methods as for the primary endpoint.

The time to microbiological [presumed] eradication will be compared using Kaplan-Meier (KM) estimates. An unstratified log rank test will be performed to assess the difference between treatment groups. KM plot of time to microbiological [presumed] eradication will also be presented. Time to [presumed] eradication is defined as the actual elapse time from date of randomization to date of the first [presumed] eradication. Patients without [presumed] eradication records will be censored at the date of the last microbiological assessment date.

8.3.4.2. Microbiological Evaluations and Pathogen Identification

Causative (infecting) 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. Causative (infecting) pathogens include but

are not limited to the following bacterial species: *Enterobacter spp., Klebsiella pneumoniae, Staphylococcus aureus*, *Streptococcus viridans, Streptococcus pyogenes*.

The microbiological data will be summarized in the mITT and ME populations and analyzed as follows:

- Association between the clinical success achieved as per secondary endpoint criteria satisfied at TOC and the Microbiological [presumed] eradication rate at the TOC visit controlling for treatment group using CMH.
- Distribution of ceftobiprole and vancomycin MICs for pathogens isolated at baseline, including MIC50, MIC90 and MIC range, overall and by treatment group.

  MIC50 is the MIC value which inhibits 50% of pathogens isolated at baseline.

  MIC90 is the MIC value which inhibits 90% of pathogens isolated at baseline.

  MIC range is the minimum and maximum MIC values measured for pathogens isolated at baseline.

  Susceptibility interpretation results by Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria (Susceptible, Intermediate, Resistant) of pathogens isolated at baseline by tested drug, overall and by geographical region (North America, Europe).
- Microbiological eradication rate at TOC visit by baseline causative (infecting) pathogen.
- Patients with clinical and microbiological responses at TOC visit by baseline causative (infecting) pathogen.
- Shift in ceftobiprole and vancomycin MIC results from baseline to TOC for baseline causative (infecting) pathogens in the ceftobiprole group.
- Patients with baseline causative (infecting) pathogen classified as resistant (EUCAST and CLSI criteria), by region.

8.3.5. All-Cause Mortality (ACM)

The survival time between the two treatment groups will be compared using KM estimates for the ITT and CE populations.

An unstratified log rank test will be performed to assess the difference between treatment groups which will include all available mortality data as of the date of data cut, not just mortality data up to mortality day 28. Survival rates (Event-Free Probability Estimates) at Day 28 will be estimated using K-M estimate. Associated two-sided 95% CI will be calculated using Greenwood formula.

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

A Kaplan-Meier plot of survival time will also be provided.

8.3.6. Patient-Reported Pain

The pain scores will be summarized by treatment group in the ITT and CE populations at each time point with exception of Day 28.

The change from baseline will be calculated and summarized at all visits with exception of Day 28.

The difference in mean change from baseline of VAS and Wong-Baker Pain scale between treatment groups will be estimated using a mixed-model repeated measures (MMRM) analysis. The MMRM design will model the result on the treatment groups, visit, actual type of ABSSSI, geographical region (North America and Europe) and pain levels at baseline as covariates, with subjects as a random effect. The interaction term between treatment group and visit will also be included to allow the treatment group difference to differ over time. The variance-covariance matrix will be assumed to be unstructured and the Kenward-Rogers method will be used to calculate the degrees of freedom. If there are convergence problems with the MMRM analysis, other covariance structures will be examined to resolve the convergence issue, i.e., other additional variance-covariance structures would be evaluated, including compound symmetry (CS), heterogeneous compound symmetry (CSH), and auto-regressive [AR(1)]. In this eventuality, the Akaike's Information Criterion (AIC) will be used to determine the optimal variance-covariance structure matrix for the primary comparisons.

From this model, the Least Square (LS) mean treatment difference at each visit will be presented along with the 95% CI and the two-sided p-value for treatment effect at each visit.

Line plots of means and SEs will be created to display the change from baseline over the entire study period.

8.3.7. Health Economic Outcome Measures

Information on health economics outcome measures from baseline to the LFU visit will be collected at the LFU visit to perform summarization for total length of stay in hospital, location of treatment within the healthcare system and reason for healthcare encounter.

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

8.3.8. Lesion Area

The absolute and percentage change in lesion area size will be summarized by the treatment group in the ITT and CE populations.

The mean difference in absolute and percent change from baseline in lesion area size between treatment groups will be estimated using a MMRM analysis. The MMRM design will model the result on the treatment groups, visit, actual type of ABSSSI, geographical region (North America and Europe) and pain levels at baseline as covariates, with subjects as a random effect. The interaction term between treatment group and visit will also be included to allow the treatment group difference to differ over time. The variance-covariance matrix will be assumed to be unstructured and the Kenward-Rogers method will be used to calculate the degrees of freedom. If there are convergence problems with the MMRM analysis, other covariance structures will be examined to resolve the convergence issue, i.e., other additional variance-covariance structures would be evaluated, including compound symmetry (CS), heterogeneous compound symmetry (CSH), and auto-regressive [AR(1)]. In this eventuality, the Akaike's Information Criterion (AIC) will be used to determine the optimal variance-covariance structure matrix for the primary comparisons.

From this model, the LS mean treatment difference at each visit will be presented along with the 95% CI and the two-sided p-value for treatment effect at each visit.

The number and percentage of patients with percent reductions in lesion size area from baseline (e.g., ≥10%, ≥20%, ≥30%, ≥40%, ≥60% , ≥ 70% at 48–72 h after start of treatment; ≥40% ,≥ 50%, ≥60% , ≥70% ,≥80%, ≥90%, ≥95% at TOC) will be summarized by treatment group in the mITT and CE populations. The weighted difference in percentage of patients with specific percent reductions in lesion size area (the ceftobiprole group minus the vancomycin plus aztreonam group), and the 95% CI for the weighted difference will be computed using CMH weights method adjusted for geographical region (North America and Europe), and actual type of ABSSSI. P-value for CMH test and estimates of the weighted risk ratio and weighted odds ratio will also be provided.

Box plots will be provided to display the distribution of percent change in lesion size at each visit. In Addition, line plots of means and SEs will be created to display the absolute and percentage change in lesion area size over the entire study period.

8.3.9. Infection Site Assessment

The infection-site assessment including incision/drainage, erythema, heat/localized warmth, pain/tenderness to palpation, fluctuance, and swelling/induration will be summarized at each given visit.

9. Safety Analysis

All analysis of safety will be conducted using the Safety population. Statistical hypothesis testing will not be performed on any safety results.

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 AE (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

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 LFU 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 tabulated, according to the Medical Dictionary for Regulatory Activities (MedDRA®), system organ class (SOC), and preferred term (PT).

9.1.1. Incidence of Adverse Events

The incidence of AEs and SAEs tables 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, preferred terms 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.

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 will be listed.

9.1.2. Relationship of Adverse Events to Study Drug

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

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 relation to study drug other than "Not Related" or "Unlikely". 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 primary SOC and preferred term by treatment arm will be provided. 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.

9.2. Death

The summary of treatment-related AEs where the answer to "Outcome" is "Death Related to Adverse Event" will also be presented. 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".

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. Central laboratory safety parameters will be 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 central laboratory data using the standard international (SI) units provided by the central laboratory; in case of missing baseline results from the central laboratory, the local laboratory data will be used. Implausible central laboratory results were 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", "high" or "missing" relative to the normal ranges of the central laboratory. Each patient's categorical laboratory safety parameter values will be flagged as "abnormal" or "normal". This 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. In addition, laboratory values outside derived marked reference range values (multiplying the lower and upper ranges using the Basilea standard marked factors) will be summarized.

Laboratory results will be graded using the Division of AIDS (DAIDS) for Adverse Events Version 2.1. 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. Local and central laboratory results will be graded separately (e.g. baseline from local laboratory will not be compared to post baseline central laboratory results). The central laboratory 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.

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

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 14.2 will be included in hematology summary tables.

All hematology data by patient will be presented in a listing. Patients with abnormalities as per normal ranges in hematology will be listed.

9.3.2. Blood Chemistry

The laboratory tests listed in the Appendix 14.2 will be included in clinical chemistry summary tables.

All chemistry data by patient will be presented in a listing. Patients with abnormalities as per normal ranges in chemistry will be listed.

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

Also, the incidence of patients with abnormalities in ALT or AST associated to abnormalities in total bilirubin (TBILI) 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 x ULN will be listed showing all liver function tests (LFTs), i.e., ALT, AST, bilirubin (total, direct & indirect), alkaline phosphatase, and GGT observed across all visits.

Evaluation of drug-induced serious hepatotoxicity (eDISH) plots of maximum ALT/AST values versus total 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 following laboratory tests will be included: prothrombin time, international normalized Ratio, and activated partial thromboplastin time. All coagulation data by patient will be summarized and will be presented in a listing.

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.

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. Vancomycin Trough Level

Vancomycin trough level (central laboratory assessment): a vancomycin trough level for central laboratory assessment is to be obtained approximately 30 minutes before administration of the fourth dose of vancomycin (i.e., on Day 2 for patients who receive vancomycin on a q12h schedule, and on Day 4 for patients who receive vancomycin on a q24h schedule).

Vancomycin trough levels (local laboratory assessment): in study sites which use vancomycin trough level monitoring to guide vancomycin dosing and which perform vancomycin trough level testing using a local laboratory, an additional blood sample for local laboratory testing of the vancomycin trough level should also be obtained before administration of the fourth dose of vancomycin on Day 2 (vancomycin q12h schedule) or Day 4 (vancomycin q24 h schedule). If obtained, local laboratory testing of vancomycin trough levels should be obtained per institutional practices at the respective study site.

Vancomycin trough level results obtained from local and central laboratory will be listed.

9.3.8. 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 LFU visit it is at the discretion of the investigator whether a serum or urine pregnancy test is obtained, and subject 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 summarized and 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 twice daily (morning and evening) during the first 8 days of treatment, after which temperature measurements are to be taken once on each scheduled study visit day except Day 28. The same method of measuring temperature should be chosen within a site for all patients during course of the study. Pulse rates and blood pressures 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. A patient's height must only be assessed during the Screening visit.

Summary tables presenting observed values and changes from baseline will be presented for vital sign data, including weight (kg), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (°C) morning and evening, pulse (bpm), and respiration (breaths/minute), by treatment group at each visit on a given timepoint in the safety population. Changes from baseline to each scheduled post-baseline visit will be presented. 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. Summary table presenting minimum and maximum post-baseline values will also be provided.

All vital sign 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 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: < 40 or > 120 beats/min.
- Temperature: < 36 ^{0}C / 96.8 °F
- Temperature: > 38 °C / 100.4 °F measured orally.
- Temperature: > 38.5 °C / 101.3 °F measured tympanically.
- Temperature: > 37.5 °C / 99.5 °F measured by the axillary method.
- Temperature: > 39 °C / 102.2 °F measured rectally.

Each patient's continuous vital signs results values will be flagged as "low", "normal", "high" or "missing" relative to the marked reference ranges. This categorical data will be summarized in shift tables comparing the changes from baseline value as Low/Normal to post-baseline value as High or baseline value as High/Normal to post-baseline value as Low.

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. A brief physical examination will be performed for visits: Day 3, EOT, TOC, and LFU. Brief physical examination is to be focused on any changes from baseline.

A table will summarize physical examination results by treatment group and overall 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.

10. Pharmacokinetics

Plasma concentration data will be analyzed at each time point and will be presented as individual concentrations and with descriptive statistics (mean, standard deviation [SD], coefficient of variation [CV%], min, median and max). A retrospective population PK model will be developed as a separate study not performed by PPD. Pharmacokinetic analyses will be based on the population PK model and the effects on the PK parameters of demographic and baseline factors such as age, weight, sex, race, and renal function will be examined. The population PK analysis will derive the $fT > MIC$ and target attainment rate, and will analyze the relationship between exposure and efficacy/safety.

11. Interim analysis

The interim analysis was conducted involving a sample size re-estimation to

1. assess whether the initial sample size estimate is adequate for evaluating the primary endpoint as defined in Section 8.1.1, and
2. select a larger sample size, if warranted.

The interim analysis was blinded, i.e., conducted based solely on pooled information across the two treatment arms when early clinical response data were available for 60% of the patients planned to be randomized (approximately 404 patients). The number and percentage of responders and non-responders based on the primary endpoint mentioned in Section 8.1.1 and Clinical Success/No Success based on main secondary endpoint mentioned in Section 8.2.1 were provided. A summary table based on primary endpoint was provided on ITT population and tables based on secondary endpoint were provided on ITT and CE populations.

The final decision for sample size re-estimation was based on the overall response rates for primary and secondary endpoints, and was at the Sponsor's discretion.

The interim analysis was performed in November 2018. Following the blinded review of the primary and secondary endpoints, it was decided to keep the sample size specified in the protocol unchanged.

For safety monitoring, a DSMB will be utilized periodically throughout the study. Blinded interim safety assessments will be performed twice in each year after enrollment of the first patient.

Details will be provided in the DSMB Charter.

Note that investigators, sponsor employees, and others who are involved in the conduct and the analyses of the study (with the exception of the unblinded pharmacist or delegate) will remain blinded to the treatment codes and DSMB analysis results until all monitoring decisions have been made, and the database has been locked for final analysis.

12. Changes in the Planned Analysis from Protocol

- This SAP will be used for submission to the FDA and the EMA. No separate SAP will be written for EMA submission. In the EU, the main secondary objective listed in this SAP will be the primary objective, and the primary objective listed in this SAP will be the main secondary objective.
- The other secondary endpoint related to sustained reduction in lesion size at the EOT and TOC visits and all-cause mortality through day 28 will also be analyzed for CE population.
- The window of ±2 days was removed from the other secondary endpoint related to all- cause mortality through Day 28.
- The CE Population definition was updated to include the condition till TOC visit
- Other Secondary endpoint like patient-reported pain and lesion area will be analyzed using mixed-model repeated measures (MMRM) instead of ANCOVA as mentioned in protocol section 8.7.2.

13. References

LaVange, L., Durham, T., and Koch, G., (2005). Randomization-based nonparametric methods for the analysis of multicentre trials. *Statistical Methods in Medical Research* Vol. 14, 281-301.

O'Brien, P., and Fleming T. (1979). A multiple testing procedure for clinical trials. *Biometrics* Vol. 35, 549-556.

Peduzzi, P., Henderson, W., Hartigan, P., and Lavori, P. (2002). Analysis of randomized controlled trials. *Epidemiologic Reviews*, Vol. 24, No. 1, 26-38.

14. Appendices

14.1. Imputation Algorithm for Partial and Missing Dates and Time

Incomplete Dates of Primary ABSSSI Symptom onset

If day is missing, day will be set to 15th of the month.

If month is missing, month and day will be set to July 1st.

If either imputation above results in a date > informed consent, then impute it as the date of informed consent -1.

Missing Time for Lesion Size Assessments

In case assessment date is present but time is missing, time will be imputed to 12:00.

Medications and Non-Drug Procedures

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

If start date 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,

- 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 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.

Medications/Non-drug procedures with both missing start and end date after imputation will be considered as concomitant.

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

14.2. List of Clinical Central Laboratory Tests

Hematology	**Blood Chemistry**
Basophils (10^9/L)	Alanine Aminotransferase (U/L)
Eosinophils (10^9/L)	Albumin (g/L)
Erythrocytes (10^12/L)	Alkaline Phosphatase (U/L)
Hematocrit (%)	Aspartate Aminotransferase (U/L)
Hemoglobin (g/L)	Bilirubin (umol/L)
Leukocytes (10^9/L)	C Reactive Protein (nmol/L)
Lymphocytes (10^9/L)	Chloride (mmol/L)
Monocytes (10^9/L)	Creatinine (umol/L)
Neutrophils (10^9/L)	Direct Bilirubin (umol/L)
Platelets (10^9/L)	Gamma Glutamyl Transferase (U/L)
Reticulocytes/Erythrocytes/Leukocytes (%)	Glucose (mmol/L)
Direct Coombs	Glucose, Random (mmol/L)
	Indirect Bilirubin (umol/L)
	Lactate Dehydrogenase (U/L)
	Potassium (mmol/L)
	Protein (g/L)
	Sodium (mmol/L)
	Urate (mmol/L)
	Urea (mmol/L)
	Haptoglobin (g/L)