COVANCE

Motif BioSciences

Protocol No.: ICL-23-ABSSSI1

A Phase 3, randomized double-blind, multicenter study to evaluate the safety and efficacy of intravenous iclaprim versus vancomycin in the treatment of acute bacterial skin and skin structure infections suspected or confirmed to be due to Gram-positive pathogens. (REVIVE-1)

Covance Study ID: 000000145416

STATISTICAL ANALYSIS PLAN

Final Amendment 2.0
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Author: Alyssa Liu

Motif BioSciences
125 Park Avenue, 25th Floor, Suite 2622
New York, NY 10017

Covance Clinical Development Services
206 Carnegie Center
Princeton, NJ 08540

APPROVALS

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

Covance Approval:

Toyoko Oguri — 23 March 2017

Signature — Date

Toyoko Oguri/Senior Manager, Biostatistical and Statistical Programming

Printed Name/Title

Motif BioSciences Approval:

Rajesh Shukla — 23 March 2017

Signature — Date

Rajesh Shukla/Vice President of Clinical Operations

Printed Name/Title

VERSION HISTORY

Version Number	Version Date	Summary and rational of change(s)
Final 1.0	17-Aug-2016	
Amendment 1.0	12-Jan-2017	Section 2.3 (Sample Size and Power) • Revised power assumption related to TOC visit. Section 3.2 (Secondary Efficacy Endpoints) • The order of PP population and mCE population was changed. •Two definitions of "Persistent Infection" and "Recurrent Infection" were added when defining clinical failure. Section 5 (Analysis Population) • The order of PP population and mCE population was changed. Section 6.2 (Handling of Dropouts or Missing Data) • Added mITT efficacy analyses for primary endpoint, while patients who do not have an adequate assessment at the appropriate visit assumed as non-responders. Section 7.2 (Patient Disposition and Data Sets Analysed) • The order of PP population and mCE population was changed. Section 7.4 (Demographics and Other Baseline Characteristics) • The order of PP population and mCE population was changed. • Added two demographic variables, diabetes (present or absent) and geographic region (US vs ex-US). Section 7.7 (Measurements of Treatment Compliance and Exposure) • Clarify the treatment is started in the AM and completed in the PM when patients are administered with iclaprim q12h for 5 to 14 days. Section 7.8.2.2 (Time to Resolution of Signs and Symptoms of ABSSSI) • The order of PP population and mCE population was changed. Section 7.8.3 (Exploratory Analysis) • For primary endpoint, added exploratory analysis for ITT population with ≥50%, ≥75%, and ≥90% reduction in lesion size at ETP compared from baseline. • For the secondary endpoint of resolution or near resolution of ABSSSI at EOT and TOC, added exploratory analysis for ITT population with at least 50% and at least 75% reduction in lesion size at both EOT and TOC compared from baseline. • If it is concluded that Iclaprim is non-inferior to Vancomycin (i.e., the lower bound of two-sided 95% confidence interval of group difference in early clinical response is greater than -0.1), it may be concluded that Iclaprim is superior to Vancomycin if the entire 95% confidence interval is >0. Superiority may also be

Version Number	Version Date	Summary and rational of change(s)
		concluded for resolution of ABSSSI at TOC in a similar manner. Section 7.8.4 (Subgroup Analysis) • Added two demographic variables for subgroup analysis: diabetes (present or absent) and geographic region (US vs ex-US). Section 7.9.1 (Adverse Events) • Added another summary of TEAEs by diabetes (present or absent). • Added the definition of SAE. Section 7.9.2 (Laboratory Evaluations) • Parameter of CRP was updated from category of haematology to chemistry. Section 7.10 (Interim Analysis) • Clarified analysis for the primary endpoint under blinded interim data was using at least 20% reduction in lesion size at ETP when compared to baseline visit. Section 7.10.2 (Laboratory Evaluations) • Add another kind of shift table between baseline and post-baseline change, only applied for liver enzyme and renal function tests.
Amendment 1.0	15–Feb-2017	Table 1 Summary of Assessments was deleted. Same information is given in the text and it is a copy from protocol.
		Section 4 (Pharmacokinetics/ Pharmacodynamics Variables) • Deleted "After the study is complete, the database locked, and the data unblinded, patients randomized to iclaprim will have their samples assayed."
		Section 5 (Analysis Population) • Added details to Per Protocol population definition. • Table 1 reformatted to separate protocol deviation types that would exclude a patient from some visits and visits from deviation types that excludes a patient from all visits. • Deleted Type I A and Type III antiarrhythmic drugs from list of prohibited medications that would exclude a patient from per protocol analysis. • Added mITT subpopulation, strep-enriched mITT for exploratory analysis. • Added PP population for EMA analysis.
		Section 5.6.1 Important Protocol Deviations Leading to Exclusion from the mPP Analysis. • This section was deleted because it provides some

Version Number	Version Date	Summary and rational of change(s)
		information as in PP population.
		Section 6.1 (Time Points and Visit Widows) • Baseline for microbiology analysis was added.
		7.4 (Demographic and Other Baseline Characteristics) • Blood culture at baseline was defined; Geographic region subgroups were revised; • Geographic region subgroups were revised
		7.9.2 (Secondary Efficacy Analysis) • Added *S. pyogenes*-enriched mITT population and PP population for EMA to repeat the primary efficacy analysis.
		7.9.2.1 (Resolution or Near Resolution of ABSSSI) • Added *S. pyogenes*-enriched mITT at TOC to the analysis
		7.9.2.2 (Signs and Symptoms of ABSSSI) • Descriptive summary statistics for signs and symptoms will be limited to baseline display only.
		7.9.2.3 (Bacteriological response) • By-pathogen and by-patient bacteriological outcome section were moved from Section 3 to this section. • Added more description of analyses. • Added summary of MIC frequency and interpretation.
		7.10.1 (Adverse Events) • Treatment-emergent adverse event definition was clarified.
Amendment 2.0	10–Mar-2017	6.1 (Time Points and Visit Windows) • Added definition of baseline for microbiology data.
		6.2 (Handling of Dropouts or Missing Data) • Deleted general principle for imputing dates and clarified the imputing details refer to mockup.
		7.6 (Prior and Concomitant Medications) • Added the definition of prior medication.
		7.9.2.2 (Signs and Symptoms of ABSSSI) • Clarified patients are free of specific signs or symptoms at baseline should be out of that time-to-event analysis.

Version Number	Version Date	Summary and rational of change(s)
		7.9.3 (Exploratory Analysis) • Revised the definition for one exploratory analysis and added another exploratory analysis.
		7.10.1 (Adverse Events) • Treatment-emergent adverse event definition was clarified.

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASO	anti-streptolysin O
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BUN	blood urea nitrogen
CBC	complete blood count
CCLS	Covance Central Laboratory Services
CI	confidence interval
CO_2	carbon dioxide
CPK	creatine phosphokinase
CrCL	creatinine clearance
CRF	case report form
CRP	C-reactive protein
CTMS	Clinical Trial Management System
CV	Conventional units for laboratory results
ECG	Electrocardiogram
eCRF	electronic case report form
EOT	End of Therapy
EMA	European Medicines Agency
ETP	early timepoint
GGT	gamma glutamyl transferase
hCG	beta-human chorionic gonadotropin
ITT	intent-to-treat
IXRS	Interactive Phone and Web Response System
LDH	lactate dehydrogenase
LFT	Liver Function Test
LFU	Late Follow-Up
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MRSA	Methicillin-resistant Staphylococcus aureus
MSSA	Methicillin-sensitive Staphylococcus aureus
mCE	Modified clinically evaluable population
mITT	microbiological intent-to-treat
mPP	Per-protocol microbiologically evaluable population
N	analysis population

Abbreviation	Term
NI	non-inferiority
PK	pharmacokinetic
PP	Per-protocol population
PT	Preferred Term
Q12h	every 12 hours
QTc	QT interval corrected for heart rate
QTcB	QTc corrected according to Bazett
QTcF	QTc corrected according to Fridericia
RBC	red blood cell
SAE	serious adverse event
SCr	serum creatinine
SD	standard deviation
SI Units	International System of Units
SOC	system organ class (MedDRA classification)
TEAE	treatment-emergent adverse event
TFLs	Tables, Figures and Listings
TOC	Test of Cure
UA	Urinalysis
WBC	white blood cells

1 SOURCE DOCUMENTS

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	21 Oct 2015	Final 1.0
Protocol Amendment 1	3 Dec 2015	Amendment 1.0
eCRF	3 Feb 2016	Production 3.0

2 PROTOCOL DETAILS

2.1 Study Objectives

Primary Objective:

The primary objective of this study is to demonstrate that iclaprim is non-inferior to vancomycin in achieving a ≥20% reduction in lesion size at 48 to 72 hours (early timepoint, ETP) compared to baseline in all randomized patients (intent-to-treat, ITT).

Secondary Objectives:

The secondary objectives of this study are to demonstrate non-inferiority of iclaprim compared to vancomycin in the ITT, microbiological ITT (mITT), modified clinically evaluable (mCE), per protocol (PP), and microbiological PP (mPP) populations for the following:

1. Resolution or near resolution of acute bacterial skin and skin structure infection (ABSSSI) (clinical cure, defined by a ≥90% reduction in lesion size from the size at baseline, no increase in lesion size since ETP, and no requirement for additional antibiotics [except aztreonam and metronidazole] or unplanned significant surgical procedures after ETP other than bedside wound care) at Test of Cure (TOC) visit (7 to14 days after the end of treatment);
2. Resolution or near resolution (≥90%) of ABSSSI at End of Therapy (EOT);
3. Resolution or near resolution (≥90%) of ABSSSI at EOT and TOC among patients with severe infection at baseline defined by meeting one or more of the following criteria:
    a. fulfilled the published definition for systemic inflammatory response syndrome (SIRS) by having ≥2 of the following findings: body temperature >38°C or <36°C, heart rate >90 bpm, respiration rate >20 breaths/minute, and WBC >12000/mm^3 or <4000/mm^3 or >10% bands;
    b. Evaluated as having severe tenderness or severe erythema at the infection site; or
    c. Positive blood cultures at baseline.
4. Time to resolution of systemic and local signs and symptoms of ABSSSI.

Additional secondary objectives are to:

5. Assess microbiological outcome in the mITT, mCE, and mPP populations at EOT and TOC;
6. Establish the pharmacokinetic (PK) profile for iclaprim using population pharmacokinetics; and
7. Establish the safety profile of iclaprim in patients with ABSSSI.

2.2 Overall Study Design

This is a multicenter, randomized, double-blind study of the efficacy and safety of iclaprim compared to vancomycin. Patients will receive either iclaprim or vancomycin for 5 to 14 days, which comprises the range of total treatment duration. Patients will be evaluated daily up to ETP, then every 48 to 72 hours through the end of treatment. If the last dose of study drug falls on a day when an evaluation was not planned, an additional evaluation visit will need to be performed on that day (i.e. All EOT evaluations

should be performed on the last day [+2 days] of drug dose). Patients will also be evaluated at the TOC visit (7 to 14 days post-EOT) for both efficacy and safety, and will have a Late Follow-Up (LFU) phone call (28 to 32 days post-first dose) for safety only. Note, however, that patients with high liver function tests (LFTs) and unresolved adverse events (AEs) at TOC must be seen in person for an additional visit at LFU. The total duration of participation in the study for each patient is 29 to 33 days.

After completing screening procedures, including obtaining cultures from a clinical specimen prior to antibacterial therapy, a total of 600 patients (300 per treatment group) will be randomized (1:1) to receive either: (1) iclaprim 80 mg every 12 hours or (2) vancomycin 15 mg/kg. The duration of treatment for both groups will be 5 days (minimum duration) to 14 days (maximum duration). Assignment to study drug will be performed using a central randomization system. Approximately 80 active centers will be recruited.

Figure 1 displays a diagram of the study design.

The investigators, clinical study personnel, sponsor, and the patients will remain blinded with respect to the study drug treatment allocation. The unblinded pharmacist or his/her designee will be responsible for preparation of infusions. To account for the variable vancomycin dosing intervals, normal saline dummy infusions will be used to maintain the blind for patients who require a vancomycin dosing frequency other than every 12 hours (Q12h).

Concomitant antibiotics aztreonam and metronidazole used in compliance with their respective prescribing information are allowed at the discretion of the investigator during the study drug phase.

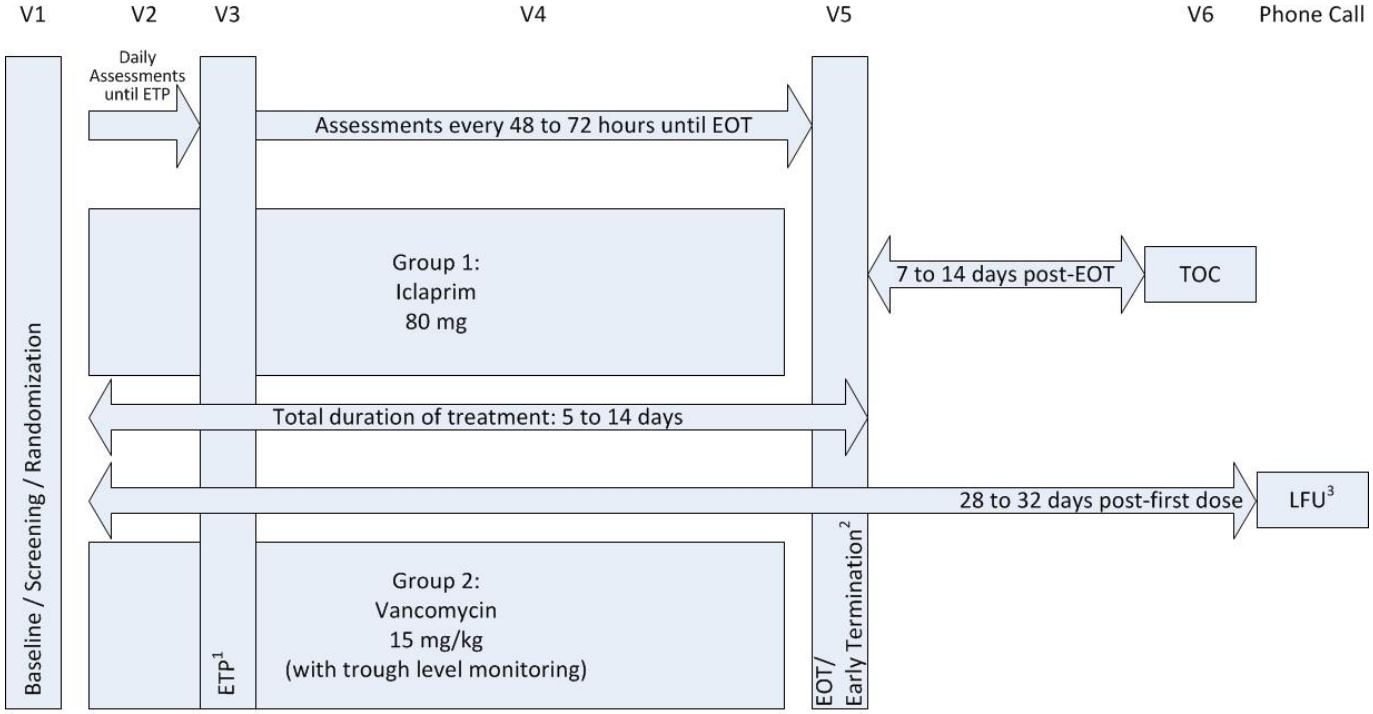
Systemic antibiotics (other than aztreonam and metronidazole) or topical antibiotics at the site of the ABSSSI under investigation, steroids >20 mg/day prednisolone or equivalent; and Type I A and Type III-antiarrhythmic drugs are prohibited.

2.3 Sample Size and Power

For non-inferiority (NI) testing with a 1-sided alpha of 0.025, assuming a 75% early clinical response rate in each group and a 10% NI bound delta, a sample size of 295 ITT patients per treatment group is required for 80% power. In addition, using similar methods of NI testing with a 1-sided alpha of 0.025, assuming a 90% clinical response rate at TOC in vancomycin and iclaprim group and a 10% NI bound delta, a sample size of 300 patients in the ITT population per treatment group is required for 98% power.

A total of 600 patients (approximately 300 per treatment group) will be randomized (1:1) for this study.

Figure 1: Study Design



Note: A window of +/- 2 hours is acceptable for infusion of study medication.
1. ETP assessment is 48 to 72 hours post-first dose
2. If the last dose of study drug falls on a day when an evaluation was not planned, an additional evaluation visit will need to be performed on that day (ie. All EOT evaluations should be performed on the last day [+/- 2 days] of drug dose).
3. If duration of therapy is 14 days, LFU may overlap with TOC. In this case, all LFU evaluations may take place at the TOC visit.
V*n*=Visit *n*; ETP=Early Time Point; EOT=End of Therapy; TOC=Test of Cure; LFU=Late Follow-up

3 EFFICACY AND SAFETY VARIABLES

3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of randomized patients who achieve an early clinical response (defined as reduction in the lesion size ≥20% compared to baseline) at 48 to 72 hours (ETP) and will be evaluated in ITT population.

3.2 Secondary Efficacy Endpoints

The primary efficacy endpoint will be repeated in mITT, PP, mCE and mPP populations.

The secondary endpoints are:

1. Resolution or near resolution of ABSSSI (i.e., clinical cure, defined by a ≥90% reduction in lesion size from the size at baseline, no increase in lesion size since ETP, and no requirement for additional antibiotics [except aztreonam and metronidazole] or unplanned significant surgical procedures after ETP other than bedside wound care) at TOC for iclaprim (80 mg q12h) compared with vancomycin (weight-based dose) for ITT, mITT, PP, mCE, and mPP populations
2. Resolution or near resolution (≥90%) of ABSSSI at EOT for ITT, mITT, PP, mCE, and mPP populations
3. Resolution or near resolution (≥90%) of ABSSSI at EOT and TOC among patients with severe infection at baseline for ITT, mITT, mCE, PP, and mPP populations
4. Time to resolution of signs and symptoms of ABSSSI from start of treatment for ITT, mITT, PP, mCE, and mPP populations
5. Patient-level bacteriological response rate at EOT and TOC for mITT, mCE, and mPP populations
6. Pathogen-level bacteriological response rate at EOT and TOC for mITT, mCE, and mPP populations

The clinical outcome will be evaluated at EOT and TOC (7 to 14 days post-EOT) programmatically for ITT, PP and mPP populations, and categorized as cure, failure, or indeterminate defined as follows:

- Cure: defined by a ≥90% reduction in lesion size from baseline, no increase in lesion size since ETP, and no requirement for additional antibiotics (except aztreonam and metronidazole) or unplanned significant surgical procedures;
- Failure: reduction in lesion size that is <20% for ETP and <90% for EOT and TOC compared to baseline, death related to the infection, persisting or recurrent infection, need for unplanned surgical procedure, or administration of rescue antibiotic therapy for the index infection before or at assessed visits or recurrence of index infection;
- Indeterminate: data inadequate for assessment of efficacy (there are no post-baseline local or systemic signs and symptoms data available to make this assessment [e.g., patient lost to follow up] after <2 days of treatment or <4 doses and no EOT evaluation), lost to follow-up prior to ETP, withdrawal of consent, receipt of effective antibiotic therapy for a cause other than the index infection before assessed visits, or death not attributed to the index ABSSSI or complication of ABSSSI.

  Noted: If a patient starts an antibiotic for an infection other than the primary ABSSSI at EOT visit date, they will still be included as “Clinical Cure” or “Clinical Failure” dependent on the size of

the lesion at EOT. The same rule will be applied to the evaluation of clinical outcome at TOC visit.

The definition of "Persistent Infection" and "Recurrent infection" when defining Clinical Failure are listed as follows:

1. Persistent Infection: If a patient has <90% reduction in lesion size at EOT compared to baseline, this represents "Persistent Infection" at EOT. The same rule applies when evaluating clinical failure at TOC visit.

2. Recurrent Infection: If a patient has Clinical Cure (≥90% reduction in lesion size from baseline) at EOT visit, and becomes Clinical Failure (<90% reduction in lesion size from baseline) at TOC visit, this represents "Recurrent infection". It means the lesion size becomes larger than EOT at TOC visit.

3.3 Safety Variables

Safety endpoints are AEs, serious adverse events (SAEs), electrocardiogram (ECG) results, liver function tests, hematology, coagulation, serum chemistry including creatinine and creatinine clearance, urinalysis (UA), vital signs, and physical examinations.

4 PHARMACOKINETIC/PHARMACODYNAMIC VARIABLES

Pharmacokinetic samples will be obtained from patients on 3 occasions: following the first dose of study medication, at ETP, and at EOT.

Iclaprim plasma concentrations will be used to determine population PK parameters with a non-linear mixed effect model. The potential influence of clinical characteristics (age, size, sex, hepatic function, renal function, concomitant medications, etc.) on PK parameters will be evaluated. Further details will be provided in a separate population PK analysis plan.

5 ANALYSIS POPULATIONS

The ITT population will be the primary population for analysis of primary endpoint. Microbiological response will be evaluated for mITT, mCE and mPP populations. All other efficacy analyses will be performed for each of the ITT, mITT, PP, mCE and mPP populations. All safety analysis will be performed in the Safety population. Enrolled patients are those who signed the inform consent form.

5.1 Safety Population

All patients who receive any study drug during the trial will be included in the Safety population. It is the primary population for safety analyses. Patients will be analyzed according to the treatment they receive.

5.2 Intent-to-treat (ITT) population

All randomized patients will be included in the ITT population. It is the primary population for efficacy analyses. Patients will be analyzed in the treatment group to which they are randomized.

5.3 Microbiological intent-to-treat (mITT) population

All randomized patients who have a Gram-positive baseline bacteria pathogen identified as the cause of ABSSSI will be included in mITT population.

A Gram-positive bacteria pathogen is identified as the cause of ABSSSI if the Gram-positive pathogen is identified from the lesion sample, and is subsequently confirmed by Covance Central Laboratory Services (CCLS).

5.4 Per Protocol (PP) Population

The PP population will consist of all patients in the ITT population who receive at least 80% of their planned doses and provide adequate data for assessment for each of the following time points: ETP, EOT, and TOC. This population excludes patients with Gram-negative bloodstream infections at baseline who are discontinued in order to treat the Gram-negative pathogen.

The data are considered adequate for inclusion in the PP population when the assessment of lesion size and clinical signs and symptoms are both performed at corresponding time point. To be included in the PP population, a patient must not have important protocol deviations.

5.4.1 Important Protocol Deviations Leading to Exclusion from the PP Analysis

Only those important protocol deviations considered to have a major effect on efficacy will lead to complete exclusion of the patient from the PP population. For the purposes of this study, the following criteria (Table 1) have been identified as important protocol deviations leading to exclusion from the PP population as it is considered that the occurrences of any of these criteria might have an important influence on the primary efficacy endpoint.

The majority of the important protocol deviations leading to exclusion from the PP population will be determined programmatically from the data. Those criteria which require clinical or medical monitoring interpretation will be reviewed prior to database lock, following discussion with the medical monitor and Sponsor.

Table 1: Important Protocol Deviations Leading to Exclusion from the PP population

Type	**Important Protocol Deviations Leading to Exclusion from the PP population**	**Method of Identification**
Discontinuation of study drug	Patients with Gram-negative bloodstream infections who are discontinued in order to treat the Gram-negative pathogen.	**Programmatic** check on blood culture results and patient disposition status. **Manual** review will be performed for identifying patients who discontinue the study drug.
Noncompliance	Received less than 80% of the planned study drug.	**Programmatic** check based on the exposure and drug accountability data. **Manual** review will be performed for identifying patients who miss the study drug.
Errors in Treatment Allocation	Patients that receive a wrong treatment at 1 or more study visits due to packaging or dispensing errors	**Programmatic** check based on unblinded IXRS database after the study is unblinded. The check will be done by comparing the package number that IXRS had assigned to the patient against the package number actually used.
Clinical Trial Management System (CTMS)	Covance Clinical will provide the list of protocol deviations based on the clinical monitoring	**Manual** review: This list will be reviewed and the important protocol deviations that will lead to exclusion from the PP population will be identified.
Type	**Important Protocol Deviations Leading to Exclusion at Affected Visits**	**Method of Identification**
Missing the required clinical evaluation	No adequate data at ETP, EOT and TOC	**Programmatic** check the missing assessment of lesion size, and the signs and symptoms at time points ETP, EOT and TOC
Prohibited medications	Systemic antibiotics (other than aztreonam and metronidazole) or topical antibiotics at the site of the ABSSSI under investigation, and steroids >20 mg/day prednisolone or equivalent (See Appendix A).	**Manual** review: List of preceding and concomitant medications will be reviewed by the study physician for potential prohibited medications occurring during the study up to and including TOC.

All important protocol deviations leading to exclusion from the PP population occurring during the study will be reviewed and approved by the Sponsor prior to database lock and unblinding. Should additional important protocol deviations leading to exclusion from the PP population, not anticipated at the time of preparing this SAP, be identified during the study (and prior to unblinding), they will be documented in a SAP amendment and included in all relevant protocol deviation reviews and approvals.

If a patient is one or more visits, the rule to determine if they are included in Per-protocol population for different time-point is summarized in the table below. For overall analysis, such as demographic summary, patients are included in the overall Per-protocol population if they are included in PP analysis at any visit.

ETP visit	EOT visit	TOC visit	Per-protocol Assessment
Missing	Missing or not missing	Missing or not missing	Patient is excluded from all visits even if EOT or TOC are not missing because lesion size difference from ETP cannot be determined.
Not missing	Missing	Missing	Evaluable at ETP only.
Not missing	Missing	Not missing	Evaluable at ETP and TOC, excluded from EOT.
Not missing	Not missing	Missing	Evaluable at ETP and EOT, excluded from TOC.
Missing	Missing	Missing	Non-evaluable at all visits

When analyzing efficacy endpoints, the following two rules will be applied to determine the clinical outcome for Per-protocol analysis:

1. If a rescue antibiotic is taken at a visit for clinical failure in ITT analysis, then the patient is still included for Per-protocol analysis at that timepoint and the outcome of failure is carried forward to subsequent visits and the patient is included at each of those visits for PP population.

2 If antibiotic is taken for a cause other than the index infection before assessed visits, the clinical outcome for this patient is Indeterminate for ITT population; however, this patient is excluded from PP population at that visit and subsequent visits.

5.5 Modified clinically evaluable (mCE) population

The mCE population will consist of all patients excluded from the PP population only because they have received prohibited concomitant or preceding antibiotics therapy active against Gram-positive pathogens.

5.6 PP microbiological evaluable (mPP) population

All mITT patients who receive at least 80% of their planned doses and provide adequate data for assessment for each of the following time points: ETP, EOT, and TOC.

5.7 *S. pyogenes*-enriched mITT (*S. pyogenes* mITT) population

S. pyogenes mITT include all mITT patients and patients who have infection site culture negative and ASO titer positive for *S. pyogenes* at baseline or TOC.

5.8 PP population for EMA sensitivity analysis

All PP patients without excluding any results at visits because of missing results at ETP.

6 DATA HANDLING

6.1 Time Points and Visit Windows

All analyses will use the nominal study visit as defined in the Study Schedule and eCRF. The study visit designations throughout tables and listings are listed as Baseline, Visit 2 (0-24 HRS), VISIT 2 (25-48 HRS), VISIT 2 (49-72 HRS), ETP, EOT, TOC, every 48 to 72 hours until EOT for Visit 4 and LFU. For microbiology data, baseline is defined within ±24 hours for first study treatment.

Study Visit in Protocol	Visit designations in tables and listings
Baseline/Screening/Visit 1 or Visit 2 (0-24 HRS)	Baseline
Visit 1	Visit 1
Daily until ETP for Visit 2	Visit 2.1, Visit 2.2 and Visit 2.3
ETP for Visit 3	ETP
Every 48 to 72 hours until EOT for Visit 4	Visit 4.1, Visit 4.2, Visit 4.3 and Visit 4.4
EOT for Visit 5	EOT
TOC for Visit 6	TOC
LFU phone call	LFU

6.2 Handling of Dropouts or Missing Data

For all ITT and mITT efficacy analyses, including the analysis of the primary endpoint, patients who do not have an adequate assessment at the appropriate visit will be assumed to be non-responders.

The safety evaluations will be performed on observed data only. Missing data will not be imputed for safety analyses except following rules to determine onset or stop dates of AEs or concomitant medications (see Section 1.4 in Appendix C – Table, Figure and Listing Shells for more details).

The imputed dates will not be listed. Study day relative to the first dose of treatment associated with missing or partial dates will not be displayed in AE listings.

The imputed dates of a medication will only be used to determine whether that medication will be classified as prior medication or concomitant medication.

7 STATISTICAL METHODS

7.1 General Principles

All data processing, summarization and analyses will be performed using Hosted SAS Environment / Version 9.3 (or later) of the SAS® (SAS Institute, Cary, NC) statistical software package.

Unless specified otherwise, data will be displayed using the following treatment group labels, in the order presented:

- Iclaprim
- Vancomycin
- Total (if applicable)

All data collected will be presented in listings by treatment group, country, center, patient, and visit (where applicable), unless otherwise specified.

Data will be presented in summary tables by treatment group, assessment and visit (where applicable). The category “Missing” will be presented if the number missing is greater than zero for at least one treatment group.

Descriptive summary statistics for continuous variables will include the number of observations (N), mean, standard deviation (SD), median and range.

Descriptive summary statistics for categorical variables will include frequency counts and percentages. Unless stated otherwise in the table shells, the denominator for percentage calculations will be the number of patients in the analysis population.

Dates will be displayed as DDMMMYYYY.

All significance tests will use a significance level of 5% for two-sided tests and a significance level of 2.5% for one-sided tests.

7.2 Patient Disposition and Data Sets Analyzed

Patient disposition will be listed and summarized by treatment group and overall, and will include the number and percentage of patients:

- enrolled;
- randomized (ITT population);
- treated (Safety populations);
- other study populations (mITT, PP, mCE, mPP, *S. pyogenes* mITT, safety).

In addition, the number and percentage of patients who complete the study, who discontinue from study early, including a breakdown of the primary reasons for discontinuation, will be presented for ITT and Safety populations. The number and percentage of patients who complete the treatment will be analyzed in a similar manner.

A summary of patient enrollment by country and center will also be provided by treatment group and overall for the ITT population.

The number of patients who complete study or complete each visit of ETP, TOC and TOC will be analyzed by treatment groups and study populations.

7.3 Protocol Deviations

All important protocol deviations leading to exclusion from the PP population (see Section 5.4.1) will be listed and summarized by treatment group for the ITT and mITT populations.

The deviations will be identified before data are unblinded.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall for ITT, mITT, PP, mCE, mPP and safety populations. Standard descriptive statistics will be presented for the continuous variables of:

- age (years) calculated as (calendar months between date of informed consent and date of birth – I(day of informed consent < day of birth))/12, where **I** is the indicator function. Months between dates in the same month will be 0. Age will be reported as whole years;
- weight (kg);
- height (cm);
- body mass index (BMI; kg/m^2) calculated as (weight/height^2) where weight is in kilograms and height is in meters;
- lesion size (cm^2)

The total counts and percentages of patients will be presented for the categorical variables of:

- age group (grouped as 18-39 years, 40-64 years, and 65 years and older);
- sex;

- race;
- ethnicity;
- creatinine clearance (CrCL) in mL/min (grouped as ≥90, 60-89, 30-59, 15-29, and <15 or hemodialysis);
- lesion type (major cutaneous abscess, cellulitis/erysipelas, and wound infection);
- Receipt of prior antibiotics (obtained from IXRS as Yes, No);
- Blood culture at baseline (positive, if anaerobic or aerobic blood culture has pathogen; negative, if culture taken and organism isolated but there is no pathogen or no organism was isolated)
- Gram-positive vs Gram-negative pathogen (mixed);
- Methicillin-resistant *Staphylococcus aureus* (MRSA) vs Methicillin-sensitive *Staphylococcus aureus* (MSSA);
- multiple pathogens vs single pathogen;
- *Streptococcus pyogenes* determined from ASO and either blood or infection site culture results from baseline (ASO positive only (> 330 IU/mL), culture positive only, ASO positive and culture positive, ASO negative (<= 330 IU/mL) and culture negative).
- severe infection (yes vs no), defined in Section 2.1
- diabetes (yes – if patient have medical history for diabetes, or baseline glucose > 200 mg/dL, or concomitant medications of either insulin or oral hypoglycemic; or no – no medical history for diabetes, baseline glucose <= 200 mg/dL, no concomitant medications of either insulin or oral hypoglycemic.)
- geographic region (US, Europe, Latin America).

Other baseline measurements, such as type of culture specimen / culture result, lesion type, blood culture by visit, baseline pathogens, vital signs, ECG, and laboratory evaluations, will be summarized by treatment group with the post-baseline measurements.

7.5 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 (or a later version if updated during the study). All medical history will be listed, and the number and percentage of patients with any medical history will be summarized for ITT population by system organ class (SOC) and preferred term (PT) for each treatment group and overall.

7.6 Prior and Concomitant Medications

Medications received prior to or concomitantly with treatment will be coded by Covance using the WHO Drug Dictionary, Version WHODRUG Enhanced 201509, DDEB2 (or a later version if updated during the study), Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications are those taken prior to the first dose date of treatment and within the preceding 30 days of the Informed Consent.

Concomitant medications are those with a start date on or after the first dose date of treatment, or those with a start date before the first dose date of treatment and a stop date on or after the first dose date of treatment, or with a start date before the first dose date of treatment and are reported as ongoing.

If a medication cannot be classified as “prior” or “concomitant” after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term.

Separate summaries will be presented for prior medications, concomitant medication excluding antibiotics, and concomitant antibiotic medications for ITT population. A patient listing of all prior and concomitant medications will be provided for ITT population.

7.7 Significant Procedures

The number and percentage of patients receiving any significant procedures, such as debridement or incision and drainage will be displayed by study visits and treatment groups for ITT population.

7.8 Measurements of Treatment Compliance and Exposure

Percentage compliance is calculated as:

100 * actual number of doses received / planned number of doses.

For example, patients are administered iclaprim q12h for 5 to 14 days, so the planned number of doses is 2 times the number of days in treatment period if the treatment is started in the AM. If a patient was treated for <5 days, the planned number of dosing days will be considered as 5 days. If a patient was treated for > 5 days, the planned number of dosing days is the actual number of days dosed. Missed doses will not be included in the actual number of doses for the compliance calculation.

The number and percentage of compliant patients will be presented for the Safety population, where compliant is defined as percentage compliance greater ≥ 80.0%. The category of percentage compliance < 80.0% will also be presented. The treatment compliance will be tabulated with three categories with number and percentage of patients: <80%, 80% to 100%, >100%.

The total treatment duration is defined as: Date of last dose – Date of first dose + 1 if treatment is started in the AM and completed in the PM. Treatment duration (days) will be summarized using descriptive statistics (n, mean, SD, median, minimum, and maximum) by treatment group for the Safety population.

7.9 Efficacy

7.9.1 Primary Efficacy Analysis

The primary efficacy analysis will be the NI (at significance level 0.025) of iclaprim (group 1) to vancomycin (group 2) for the proportion of ITT patients with a ≥20% reduction in lesion size at ETP compared to baseline. The NI bound will be 10%. Let P1 be the proportion for iclaprim and P2 be the proportion for vancomycin. Equivalently, if the lower bound of the two-sided 95% confidence interval (CI) for P1 – P2 is greater than -0.100 based on the Z test with unpooled variance estimate, NI will be concluded.

7.9.2 Secondary Efficacy Analysis

The primary NI efficacy analysis will be repeated in the mITT, mCE, PP, mPP populations, *S. pyogenes* enriched mITT population and PP population for EMA.

The secondary endpoints are resolution or near resolution of ABSSSI (i.e., clinical cure) at TOC for iclaprim compared with vancomycin, resolution or near resolution (≥90%) of ABSSSI at EOT, resolution or near resolution (≥90%) of ABSSSI at EOT and TOC among patients with severe infection at baseline,

time to resolution of signs and symptoms of ABSSSI, by-patient bacteriological response rate at EOT and TOC, and by-pathogen bacteriological response rate at EOT and TOC.

7.9.2.1 Resolution or Near Resolution of ABSSSI

For resolution or near resolution of ABSSSI at TOC, the NI test described in Section 7.9.1 will be used to demonstrate the non-inferiority of iclaprim to vancomycin in the ITT population EMA primary endpoint. The same NI test will be repeated for mITT, mCE, PP, mPP and *S. pyogenes* enriched mITT population at TOC. All above tests will then be repeated for resolution or near resolution of ABSSSI at EOT.

The NI test will be performed for resolution or near resolution of ABSSSI at TOC as well as EOT among patients with severe infection at baseline in ITT population, and repeated for mITT, PP populations.

A summary of clinical outcome, including the number and percent of patients with cure, failure and indeterminate outcomes at EOT and at TOC will be produced for the ITT, mITT, PP, and mPP.

7.9.2.2 Signs and Symptoms of ABSSSI

Baseline signs (tender to palpitations, erythema, edema, purulent drainage/discharge, fluctuance, induration, ulceration, and necrotic tissue) and baseline symptoms (localized pain, swelling, chills, and fever) will be summarized using descriptive statistics.

Time (in days) to resolution of each of the signs and symptoms of ABSSSI is defined as: first date with no specified sign/symptom of ABSSSI recorded on eCRF post treatment – date of first dose + 1. For patients who are not free of the specified sign/ symptom until the end of study, the last day recorded available sign/symptom on eCRF will be used as the censoring day. For patients free of any specific signs or symptoms at baseline (i.e. “none” of results for sign/symptom), please exclude these patients when analyzing time to resolution of that specific sign or symptom.

For each of the signs and symptoms, the hazard ratio of iclaprim vs vancomycin will be estimated in a Cox proportional hazard model for time to resolution of the specified sign/symptom, with the treatment group as the only covariate. The Kaplan-Meier (KM) method will be applied to estimate the distribution of the resolution time of each signs or symptom for each treatment group. The 95% CI of the hazard ratio will also be reported. This Cox regression will be performed in the ITT, mITT, PP populations.

7.9.2.3 Bacteriological response

Bacteriological response will be assessed at the patient level and at the microbiological level on the basis of results of the cultures, the susceptibilities of identified organisms, and the clinical outcome of the patient for the mITT, mCE and mPP populations.

For each assessment (ETP, EOT, and TOC), the by-pathogen bacteriological response for each causative organism identified at baseline will be defined as follows:

- Eradication: baseline causative organism cannot be isolated from any culture(s) at the assessment.
- Presumed eradication: The patient is a clinical cure at the assessment, and there is no appropriate material for culture from the original site of infection.
- Persistence: The baseline causative pathogen (based on susceptibility profile or molecular typing) is isolated at the assessment.
- Presumed persistence: The patient is a clinical failure at the assessment, and no appropriate material is available for culture from the original site of ABSSSI.
- Indeterminate: Clinical response was Indeterminate at the assessment and no appropriate material is available for culture from the original site of ABSSSI.

- Superinfection: A pathogen is isolated at the assessment that is different from the baseline causative pathogen.
- Recurrent infection: A pathogen is isolated only after the EOT visit that is different from the baseline pathogen(s).

By-pathogen bacteriological response categories will be summarized in a frequency table for each causative baseline pathogen per treatment group.

The by-patient bacteriological response will be determined according to the following definitions:

- Eradication: All baseline Gram-positive causative organism(s) have a response of Eradication.
- Presumed eradication: All baseline Gram-positive causative organism(s) have a response of Presumed Eradication or a combination of responses of Eradication and Presumed Eradication.
- Persistence: All or some baseline Gram-positive causative organism(s) have a response of Persistence or a combination of responses of Persistence and Presumed Persistence.
- Presumed persistence: All or some baseline Gram-positive causative organism(s) have a response of Presumed Persistence.
- Indeterminate: All baseline causative organism(s) have a response of Indeterminate.
- Superinfection: Any patient classified as a clinical failure who has a pathogen isolated during therapy that is different from the baseline causative pathogen.
- Recurrent infection: Any patient classified as a clinical failure who has a pathogen isolated after the EOT visit only, that is different from the baseline pathogen(s).

The by-patient bacteriological response will be determined by ordering the pathogen outcome for the patient by medical importance: persistence, presumed persistence, superinfection, recurrent infection, presumed eradication, and eradication. Patient bacteriological outcome is determined by the pathogen outcome of higher importance. For the combined rate of eradication or presumed eradication, 95% CI will be calculated per treatment group and for the difference as specified for the primary endpoint analysis, and number and percentages for all underlying by-patient bacteriological response categories will be tabulated.

Minimum inhibitory concentrations (MIC) will be summarized using EUCAST and CSLI methods for vancomycin and iclaprim antibiotics. The number and corresponding percentage for interpretation of the MIC result will be summarized for three categories: susceptible, Intermediate or resistance.

7.9.3 Exploratory Analysis

- Mortality rate within 28 days of first dose of treatment will be summarized overall and by treatment group for the ITT population.
- For early clinical response of ABSSSI, the NI test described for the primary endpoint analysis will be used to evaluate the proportion of ITT patients with a ≥50%, ≥75%, and ≥90% reduction in lesion size at ETP compared to baseline.
- For improvement of ABSSSI at EOT and TOC, the NI test described for the primary endpoint analysis will be used to evaluate the proportion of ITT patients with a ≥50% and ≥75% reduction in lesion size at EOT and TOC.
- In addition, sensitivity analyses for resolution or near resolution of ABSSSI will be evaluated as follows:

(1) Resolution and near resolution of ABSSSI excluding the criteria for lesion size reduction, but including the following considerations: Resolution or near resolution of ABSSSI (no requirement for additional antibiotics (except aztreonam and metronidazole), no death related to the infection, and no unplanned surgical procedure) for the ITT population at EOT and TOC.

(2) Resolution and near resolution of ABSSSI excluding the criteria for lesion size reduction at ETP, but including the following considerations:

- **Cure**: defined by a ≥90% reduction in lesion size from baseline and no requirement for additional antibiotics (except aztreonam and metronidazole) or unplanned significant surgical;

- **Failure**: reduction in lesion size that is <90% for EOT and TOC compared to baseline, death related to the infection, persisting or recurrent infection, need for unplanned surgical procedure, or administration of rescue antibiotic therapy for the index infection before or at assessed visits or recurrence of index infection.

- If it is concluded that Iclaprim is non-inferior to Vancomycin (i.e., the lower bound of two-sided 95% confidence interval of group difference in early clinical response is greater than -0.1), it may be concluded that Iclaprim is superior to Vancomycin if the entire 95% confidence interval is >0. Superiority may also be concluded for resolution of ABSSSI at TOC in a similar manner.

7.9.4 Subgroup Analysis

The primary endpoint, the proportion of patients with a ≥20% reduction in lesion size at ETP compared to baseline and the key secondary endpoint, proportion of patients with a clinical cure at TOC, will be presented for ITT and PP populations.

- age group (grouped as 18-39 years, 40-64 years, and 65 years and older);
- sex;
- race (white vs non-white);
- creatinine clearance (CrCL) in mL/min (grouped as ≥90, 60-89, 30-59, 15-29, and <15 or hemodialysis);
- blood culture at baseline (positive, if anaerobic or aerobic blood culture has pathogen; negative, if culture taken and organism isolated but there is no pathogen or no organism was isolated)
- MRSA vs MSSA;
- multiple pathogens vs single pathogen;
- *Streptococcus pyogenes* determined from ASO and either blood or infection site culture results from baseline (ASO positive only, culture positive only, ASO positive and culture positive, ASO negative and culture negative).
- diabetes (yes – if patient have medical history for diabetes, or baseline glucose > 200 mg/dL, or concomitant medications of either insulin or oral hypoglycemic; or no – no medical history for diabetes, baseline glucose <= 200 mg/dL, no concomitant medications of either insulin or oral hypoglycemic.)
- geographic region (US, Europe and Latin America).

The difference in the proportions of the two treatment groups and 95% CI will be calculated for each subgroup, and forest plots will be used to display these intervals graphically.

7.10 Safety

7.10.1 Adverse Events

All adverse events (AEs) recorded on the eCRF will be coded using the MedDRA dictionary Version 18.1 (or a later version if updated during the study) and classified as either pre-treatment AEs or treatment – emergent AEs (TEAEs) as follows:

- Pre-treatment AEs are events that start prior to the date of first dose of treatment.
- TEAEs are events with start date on or after the date of first dose of treatment (using dates and times as recorded on the medication administration log) through TOC visit, or events with start date prior to the date of first dose of treatment whose severity worsens on or after the date of first dose of treatment. SAEs will be reported through end of study as TEAE.

If any incomplete date/time of AE onset or start of first infusion is not sufficient to exclude that the AE is treatment emergent, then the AE will be considered to be a TEAE.

All AE data will be listed by treatment group with Pre-treatment AEs and TEAEs presented separately. Treatment-emergent status will be flagged in the listing. In addition, corresponding listings of SAEs, AEs leading to discontinuation of treatment and AEs resulting in death will be produced.

The severity of all AEs is recorded as mild, moderate, or severe. If severity is missing for a TEAE, it will be considered severe only in the overall category in the summary tables.

The relationship between an AE and treatment is assessed as related, probably related, probably not related, or not related. A drug-related AE is an AE considered by the investigator as related or probably related to the study drugs, or with unknown/missing relationship to treatment.

Each AE must be assessed and recorded in the eCRF as serious or not serious. Serious AEs must be reported as described in the protocol

An overview table will summarize the number and percentage of patients with at least one of the following TEAEs for Safety population, where patients with more than one TEAE in a particular category are counted only once in that category:

- any TEAE;
- any TEAE by severity (mild, moderate, severe);
- drug-related TEAEs;
- TEAEs leading to discontinuation of the study drug;
- SAEs;
- drug-related SAEs;
- SAEs leading to death.

The number and percentage of patients reporting each TEAE, including TEAE by age (<65 and ≥65), TEAEs by CrCL (≥90, 60-89, 30-59, 15, 29, and < 15 or hemodialysis), TEAEs by diabetes (present or absent), TEAEs leading to discontinuation, SAEs, drug related SAEs, and SAEs leading to death, will be summarized for each treatment group and overall, by SOC (sorted alphabetically) and PT (sorted by descending overall total) for Safety population. The analogous summaries will also be given for study drug related TEAEs, all TEAEs by severity and for all SAEs. TEAEs with missing severity will not be included in the counts of patients within a SOC or PT. For counting the number of events, the same rule for multiple events in one category will be applied as specified above. There will also be summaries of the

most common TEAEs (>5%) and SAEs (>5%) by PT in descending order of frequency in the iclaprim group.

No statistical comparisons of AEs, deaths, AE leading to discontinuation, or SAEs between treatment groups will be performed.

7.10.2 Laboratory Evaluations

Data for the following hematology, blood chemistry, and urinalysis analytes received from central laboratory as well as LFT results (Table 2) recorded in the eCRF will be listed (see Appendix B for the scheduled data collection) and summarized by treatment group and visit. Data received from local laboratories will be listed with the original units. If data for any additional analytes are also received then these will be listed only.

All central laboratory data will be reported in International System of Units (SI Units) and Conventional Units (CV Units). Out-of-reference-range values will be flagged as high (H) or low (L) in the data listings.

Table 2: Laboratory Evaluations

Hematology (CBC)	Chemistry [Fasted] (Chem-20)	Urinalysis (UA)
Hematocrit Hemoglobin MCH MCHC MCV Platelet count Red Blood Cell Count White Blood Cell Count White Blood Cell Differential (% & ABS): Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Albumin ALP ALT AST BUN Chloride Creatinine GGT Glucose LDH Potassium Sodium Magnesium Total Bilirubin Total CO_2 (measured as bicarbonate) Total protein CPK CRP	pH and specific gravity Glucose Ketones Occult blood Proteins Microscopic examination of sediment (including RBCs and WBCs) Bilirubin/Urobilinogen
Source: Protocol Appendix A – Clinical Laboratory Evaluations		

Laboratory test variables will be summarized by treatment group and visit using descriptive statistics (number of patients, mean, SD, minimum, maximum, as well as mean change from baseline, standard error for mean change, minimum, median, and maximum). For each laboratory analyte, the baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of treatment. The descriptive statistics will be summarized for both SI and CV units.

The number and percentage of patients with values below, within and above the corresponding extended normal range will be tabulated per visit. Shift tables (i.e., cross-tabulations of below the lower limit of the normal range, within the limits of the normal range and above the upper limit of the normal range at baseline versus scheduled visits) will be presented by laboratory test.

In addition, shift tables for 6 liver enzyme tests (AST, ALT, alkaline phosphatase, GGT, total and direct bilirubin) and 3 renal function tests (BUN, creatinine, creatinine clearance) for post-baseline change in grade categories ⩽3x ULN, >3x-5x ULN, >5x-10x ULN, >10x-20x ULN, >20x ULN will be presented. For bilirubin, the category is presented as two categories, <2x ULN, >2x ULN. The maximum change through all study will be presented as overall results and results will also be presented by visit.

Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries, but will be listed. Data obtained from laboratory tests not required by the protocol will not be summarized, but will be listed.

7.10.3 Vital Signs

The following vital signs will be listed and summarized by treatment group and visit (see Appendix B for the scheduled data collection).

- systolic and diastolic blood pressure (mmHg);
- heart rate (bpm);
- respiration rate (breaths/min);
- body temperature (°C).

Vital signs data and changes from baseline in vital signs will be summarized by visit using standard descriptive statistics for the Safety population. The baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of treatment. Assessments carried out on day of first treatment administration are considered to have taken place before the treatment administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

7.10.4 Electrocardiograms

The following quantitative ECG measurements will be taken and read centrally during the study (see Appendix B for the scheduled data collection):

- heart rate (bpm);
- RR interval (msec);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- Bazett corrected QT (QTcB) interval (msec);
- Fridericia corrected QT (QTcF) interval (msec).

Triplicate ECG measurements will be listed for every ECG measurement, and the median value of the triplicate measurements will be summarized using descriptive statistics.

Based on 12-lead triplicate ECG results as reported on the case report form (CRF) that are read centrally the number and percentage of patients whose median QTcF value is >500 msec **and/or** is >60 msec different from the predose baseline value will be provided for every visit. For every visit with ECG

measured, the median QTcF and QTcB values will be summarized with descriptive statistics for the following categories:

- > 450 msec;
- > 480 msec;
- > 500 msec;
- increase from baseline > 30 msec;
- increase from baseline > 60 msec.

The central ECG measurements at all pre-planned visits and time points and changes from baseline in ECG will be listed and summarized by treatment group and visit using standard descriptive statistics for the Safety population.

The baseline value will be defined as last scheduled or unscheduled median value collected prior to the first dose of treatment. Assessments carried out on day of first treatment administration are considered to have taken place before the treatment administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

7.10.5 Physical Examination

Physical examination results (normal/abnormal) and details of abnormalities will be listed for each patient (see Appendix B for the scheduled data collection).

7.11 Interim Analysis

When 75% of the randomized patients have undergone the 48- to 72-hour (ETP) response assessment, a blinded interim analysis is planned to estimate the percentage of patients in the study who classify as having a reduction in the lesion size ≥20% at the 48- to 72-hour visit compared to baseline. Based on the observed overall percentage, the sample size will be re-estimated as N_1 using z-test with unpooled variance estimate. The new total sample size will be the maximum of 300 and N_1, following Friede T et al (2007). The sponsor may increase the total sample size to attempt to ensure that an adequate number of ITT patients are included in the study. Since the review is blinded and the efficacy analyses will not be reviewed by treatment group, no adjustment of p-values is required. Nevertheless, the sponsor will take steps to minimize the distribution of results to avoid introducing any bias.

8 REFERENCES

1 Friede T, Mitchell C, Müller-Velten R. *Blinded Sample Size Reestimation in Non-Inferiority Trials with Binary Endpoints*. Biometrical Journal. 2007; 49: 903-916.

9 APPENDICES

Appendix A – Prohibited Medicines

The following medications are prohibited:

- Systemic antibiotics (other than aztreonam and metronidazole) or topical antibiotics at the site of the ABSSSI under investigation;
- Steroids >20 mg/day prednisolone or equivalent;
- Type IA and Type III anti-arrhythmic drugs; and
- Local antiseptics.

Appendix B – Schedule of Events

Procedure	**Baseline/ Screening/ Randomization Visit 1** (up to 24 hours prior to first dose)[1]	Daily until ETP **Visit 2**	**ETP** (48 to 72 hours post-first dose) **Visit 3**	Every 48 to 72 hours until EOT **Visit 4**	**EOT**/ Early Termination **Visit 5** (treatment duration: minimum 5 days, maximum 14 days)	**TOC** 7 to 14 days post-EOT **Visit 6**	**LFU** 28 to 32 days post-first dose **Phone Call**[2]
Informed consent	X						
Medical history	X						
Prior medications (preceding 30 days)	X						
Concomitant medications		X	X	X	X	X	
Review of inclusion & exclusion criteria	X						
Complete physical examination[3]	X						
Limited physical examination[4]		X	X	X	X	X	
Assessment of signs & symptoms of ABSSSI with digital photography[5]	X		X		X	X	
Assessment of signs & symptoms of ABSSSI without digital photography[5]		X		X			
Evaluation of adverse events[6]	X	X	X	X	X	X	X
Significant procedures (incision & drainage, debridement, amputation, suture removal, etc.)		X	X	X	X	X	
Creatinine clearance (estimated)	X						
LFT safety	X	X	X		X	X	
C-reactive protein	X		X		X	X	
Hematology[7]	X		X	X	X	X	
Clinical chemistry[7]	X		X	X	X	X	
Urinalysis[7]	X		X	X	X	X	
Serum pregnancy test (females of childbearing potential)[8]	X						
Blood cultures (aerobic/anaerobic)	X[9]	X[10]	X[11]	X[11]			
Study medication administration[12]		X	X	X[13]	X[14]		
Blood sample for PK analysis		X[15]	X[16]		X[16]		
ECG (at each timepoint 3 ECGs at least 1 minute apart will be performed)	X	X[17]	X[18]				
Infection site cultures[19]	X		X		X	X	
ASO antibody titers	X					X	
Draw trough levels[20]				X[21]			
Central randomization	X						
Clinical efficacy assessment					X	X	
Day 28 mortality							X

Abbreviations: ASO = anti-streptolysin O; EOT = End of Therapy; ETP = Early Timepoint; LFT=liver function test; LFU = Late Follow-up; TOC = Test of Cure.
[1] Must be performed during the baseline visit and completed within 24 hours of study entry (first dose of study drug).
[2] Patients with high LFTs and unresolved AEs at TOC will be required to come in for an additional visit at LFU (for LFTs, blood samples will be obtained to document normalization). If duration of therapy

is 14 days, LFU may overlap with TOC. In this case, all LFU evaluations may take place at the TOC visit.

[3] Complete physical examination, including vital signs (includes determination of body temperature), height, weight, and a review by body systems.

[4] Limited physical examination, including vital signs (includes determination of body temperature) and excluding weight and height.

[5] Eight signs (tenderness to palpitation, erythema, edema, purulent drainage/discharge, fluctuance, induration, ulceration, and necrotic tissue) and four symptoms (localized pain, swelling, chills, and fever) of infection will be assessed at each evaluation and graded on a scale of 0 to 3 (0=none, 1=mild, 2=moderate, or 3=severe). The extent of the infection (to include width, length, and depth and diagram of the infection site) will be determined via photography at baseline, ETP, EOT, and TOC only. Photography procedures outlined in protocol Appendix B will be followed. Acetate based planimetric tracing will follow the procedures outlined in Appendix C. (Planimetry measurements are based upon automatic detection of pixels inside of the traced skin infection area. Pixels are converted to calibrated units based on the scanned resolution [e.g., 300 DPI]. Skin infection measurements will be provided in cm^2.). Patients who have a worsening of clinical signs and symptoms of ABSSSI during study medication treatment such that additional or alternative systemic antibacterial therapy is warranted must be withdrawn from study medication.

[6] All adverse events will be recorded throughout the study period, up to and including the LFU phone call.

[7] Hematology comprises a complete blood count (RBC count, WBC count with differential counts, platelet count, hemoglobin, and hematocrit), MCH, MCHC, MCV, and CRP. Clinical chemistry comprises creatinine, BUN, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, glucose, sodium, potassium, chloride, bicarbonate, LDH, GGT, and CPK. Urinalysis comprises determination of pH, specific gravity, presence of blood, glucose, protein, ketones, and bile, and microscopic examination of sediment.

[8] Serum pregnancy test must be obtained immediately prior to randomization. If obtaining the serum pregnancy result would cause a delay in treatment, the patient can be entered on the basis of a negative urine pregnancy test result. The urine pregnancy test must be sensitive to at least 50 mU/mL of beta-hCG, pending results of the serum test. The patient must inform the investigator if she becomes pregnant, and study medication must be withdrawn.

[9] Obtain two sets of blood cultures (aerobic and anaerobic) 10 minutes apart from two separate peripheral sites.

[10] If patient has a blood culture that grows a Gram-negative pathogen from Visit 1 blood cultures, the patient must be withdrawn from study medication and started on the appropriate antibiotics for complicated bacteremia. If patient has signs of bacteremia, obtain two sets of aerobic/anaerobic blood cultures 10 minutes apart that are collected at different sites.

[11] If patient has a blood culture that grows a Gram-negative pathogen from Visit 2 blood cultures, the patient must be withdrawn from study medication and started on the appropriate antibiotics for complicated bacteremia. If patient has a blood culture that grows a Gram-positive pathogen from Visit 1 and/or Visit 2 blood cultures, another 2 sets of blood cultures must be obtained at both Visit 3 and Visit 4. If these are positive, the patient must be withdrawn from study medication and started on the appropriate antibiotics for complicated bacteremia.

[12] A window of +/- 2 hours is acceptable for infusion of study medication. For patients randomized to receive vancomycin, vancomycin dosing will be adjusted based on trough levels to maintain a trough of either 10 to 15 mg/L for patients with an organism whose MIC is ≤1 mg/L or 15 to 20 mg/L for patients with an organism whose MIC is >1 mg/L. Dose adjustments made due to trough monitoring will need to be performed in such a manner as to ensure that the blind is maintained.

[13] If the last dose of study drug falls on a day when an evaluation was not planned, an additional evaluation visit will need to be performed on that day (i.e., all EOT evaluations should be performed on the last day [+2 days] of drug dose).

[14] If clinically indicated (i.e., investigator may decide on a given day that a patient no longer needs treatment. In these cases, medication will not be administered, but all other EOT assessments must be performed.)

[15] On Day 1, before the start of first study medication infusion and within 5 to 15 minutes, 1 to 3 hours, and 5 to 7 (ensure last PK sample is taken prior to next dose) hours after the infusion.

[16] Before the start of study medication infusion at ETP and EOT, and within 5 to 15 minutes, 1 to 3 hours, and 5 to 7 hours (ensure last PK sample is taken prior to next dose) after the ETP and EOT infusions.

[17] On Day 1, before the start of first study medication infusion and within 10 minutes of the end of the first study medication infusion. If the median QTcF value is >500 msec and/or is >60 msec different from the predose baseline value, follow-up ECG tests should be performed every 1 to 2 hours until they are below these threshold values.

[18] At ETP, an ECG should be performed before the start of study medication infusion and within 10 minutes of the end of the study medication infusion.

[19] Prior to randomization, all patients (regardless of the disease type) should have appropriate cultures obtained. Deep culture samples, such as from a biopsy, needle aspiration, surgically obtained specimens, or punch biopsies of an area contiguous to the infected wound should be obtained. Swabs are not acceptable; cultures will be performed locally, where isolates will be retained for transport to a central microbiology laboratory for susceptibility testing according to CLSI-approved methodology. Note that only target pathogens will be sent to the central microbiology laboratory (therefore, contaminants/Gram-negative isolates [from mixed wound infections] in blood cultures do not need to be sent). If the patient is discontinued from the study due to treatment failure, a clinical specimen will be obtained at that time only. Additional clinical specimens will be obtained, if clinically feasible and if the patient has persistent clinical signs or symptoms, at ETP, EOT, and TOC.

[20] For vancomycin patients with a CrCL < 25mL/min, a daily level should be obtained and the unblinded team should monitor and re-dose the patient when that level is below 20 mg/L.

[21] Vancomycin patients with a CrCL ≥25 mL/min should have their vancomycin level checked with the 5th dose due to difficulty interpreting levels checked prior to achieving steady state.

Appendix C – Table, Figure and Listing Shells

The table, figure, and listing shells and corresponding Table of Contents will be created in a separate file.