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This study will be performed in compliance with Good Clinical Practices.

A Phase 3, **r**andomized, double-blind, multicenter study to **e**valuate the safety and efficacy of intra**v**enous **i**claprim versus **v**ancomycin in the tr**e**atment of acute bacterial skin and skin structure infections suspected or confirmed to be due to Gram-positive pathogens.

REVIVE-1

Product: **Iclaprim**
Protocol/Amendment No.: **ICL-23-ABSSSI1-01**
Phase: **3**

for

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by

Covance, Inc.

Date of Original Protocol: 21 OCT 2015
Date of Amendment 1: 3 DEC 2015

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SUMMARY OF CHANGES

Synopsis (Objectives)

- Added mCE population to secondary objectives numbers 1 to 5.
- Added the following secondary objective:
  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; and
  c. Positive blood cultures at baseline.

Synopsis (Methodology/Study Design)

- Changed window for EOT evaluations from "+/- 2 days" to "+2 days."
- Clarified that normal saline dummy infusions will be used to maintain the blind where vancomycin is dosed at a different interval than q12h.
- Added text from protocol body indicating that for patients in whom Gram staining of culturable material or cultures indicates that Gram-negative coverage is required, and for patients in whom anaerobic pathogens are suspected or confirmed as pathogens at the infected site, aztreonam and metronidazole may be administered, respectively.

Synopsis [Number of Patients (planned and analyzed)]

- Provided justification for adequate power with current sample size for secondary endpoint of clinical cure at TOC.

Synopsis (Exclusion Criteria)

- Updated exclusion criteria to clarify that patients who receive more than one dose of a short-acting (i.e., q12h dosing or less) systemic antibiotic(s) active against Gram-positive pathogens within the last 7 days would be excluded from the study, unless there is documented evidence of treatment failure OR demonstrated resistance of Gram-positive pathogens to the prior antibiotic therapy.

Synopsis (Study Medication)

- Changed volume of iclaprim and vancomycin from 300 to 500 mL.
- Clarified that iclaprim subjects with moderate hepatic impairment (Child-Pugh Class B) will be administered 40 mg of iclaprim (in 500 mL normal saline, infused over 2 hours q12h for 5 to 14 days).
- Updated vancomycin infusion time to 2 hours.
- Updated information regarding vancomycin dosing intervals and how blind will be maintained. Dosing interval will be every q12h, q24h, q48h, or dosed by daily level based on creatinine clearance. Patients randomized to vancomycin who require dosing intervals of q24h, q48h, or dosed by daily level due to renal impairment will receive dummy infusions (normal saline) at 12 hour intervals when they are not to receive vancomycin.
- Clarified that vancomycin patients with an organism whose MIC is ≤1 mg/L should maintain a trough of 10 to 15 mg/L.
- Updated use of dummy infusions, which will be used for patients randomized to vancomycin who have a dosing frequency other than q12h (no longer for differing infusion times).

Synopsis (Study Populations)

- Added description of mCE population: all patients excluded from the PP population only because they have received prohibited concomitant or preceding antibiotic therapy active against Gram-positive pathogens.

- Clarified that PP population excludes patients with Gram-negative bloodstream infections who were discontinued in order to treat the Gram-negative pathogen.

Synopsis (Evaluation: Efficacy)

- Added mCE population to secondary endpoints.
- Added resolution or near resolution (≥90%) of ABSSSI at EOT and TOC as a secondary endpoint.

Synopsis (Statistical Methods)

- Added mCE population to secondary efficacy analyses.
- Added resolution or near resolution (≥90%) of ABSSSI at EOT and TOC as a secondary endpoint.

Section 5.4.3 (Rationale for Iclaprim dose regimen)

- Added justification for 50% reduction in dose for iclaprim patients with moderate hepatic impairment.

Section 5.4.4 (Rationale for choice of comparator)

- Clarified that the maintenance of a trough of 10 to 15 mg/L is the recommendation for vancomycin patients with an organism whose MIC is ≤1 mg/L.
- Added justification for maximum vancomycin dose of 1750 mg.

Section 6 (Study Objectives)

- Added mCE population to secondary objectives numbers 1 to 5.
- Added the following secondary objective:
  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; and
  c. Positive blood cultures at baseline.

Section 7.1 (Overall Study Design and Plan Description)

- Changed window for EOT evaluations from "+/- 2 days" to "+2 days."
- Updated use of dummy infusions, which will be used for patients randomized to vancomycin who have a dosing frequency other than q12h (no longer for differing infusion times).

Section 7.2.1 (Efficacy Endpoints)

- Added mCE population to secondary endpoints.
- Added resolution or near resolution (≥90%) of ABSSSI at EOT and TOC as a secondary endpoint.

Section 7.3.2 (Exclusion Criteria)

- Added exclusion criteria "recurrent cellulitis treated with oral suppressive therapy" (as an ABSSSI category under exclusion criterion #1).
- Updated exclusion criterion #6 to clarify that patients who receive more than one dose of a short-acting (i.e., q12h dosing or less) systemic antibiotic(s) active against Gram-positive pathogens within the last 7 days would be excluded from the study, unless there is documented evidence of treatment failure OR demonstrated resistance of Gram-positive pathogens to the prior antibiotic therapy (antibiotics given for surgical prophylaxis are not included in this). Clarified that patients with prior short-acting systemic antibiotic(s) (i.e., q12h dosing or less) should not comprise >25% of the clinical trial population.
- Removed the following exclusion criterion: Infections due to a Gram-positive organisms known to be resistant to vancomycin and/or mixed ABSSSI in which the Gram-negative organisms are known to be resistant to aztreonam.

- For exclusion criterion #14, changed bradycardia from <50 bpm to <40 bpm and changed QC/QTcF normal range from QTcF >470 msec to QTcF >500 msec.

Section 7.3.3.2 (Withdrawal from study medication and termination of study participation)

- Added criteria for study treatment discontinuation for patients with a baseline blood culture that is growing a Gram-negative organism.
- Added criteria for study treatment discontinuation for patients with treatment-emergent acute kidney injury: Patients who have a confirmed increase in serum creatinine (SCr) of 0.5 mg/dL from baseline, if SCr was normal at baseline, or (2) a 50% increase in SCr from baseline, if the upper limit of SCr was not normal at baseline. This does not apply to patients on hemodialysis, continuous renal replacement therapy (e.g., CVVH, CVVHD), or peritoneal dialysis

Section 7.4.1.1 (Investigational product, dosage and mode of administration)

- Changed volume of iclaprim from 300 to 500 mL.
- Clarified that iclaprim subjects with moderate hepatic impairment (Child-Pugh Class B) will be administered 40 mg of iclaprim (in 500 mL normal saline, infused over 2 hours q12h for 5 to 14 days).

Section 7.4.1.2 (Reference therapy, dosage, and mode of administration)

- Added maximum vancomycin dose of 1750 mg.
- Clarified that vancomycin dosing would be based on actual body weight.
- Changed volume of vancomycin from 300 to 500 mL.
- Updated vancomycin infusion time to 2 hours.
- Updated information regarding vancomycin dosing intervals and how blind will be maintained. Dosing interval will be every q12h, q24h, q48h, or dosed by daily level based on creatinine clearance. Patients randomized to vancomycin who require dosing intervals of q24h, q48h, or dosed by daily level due to renal impairment will receive dummy infusions (normal saline) at 12 hour intervals when they are not to receive vancomycin.
- Clarified that patients who are on intermittent hemodialysis will be dosed after dialysis based on their pre-hemodialysis level. Patients who are on continuous renal replacement therapy will be dosed q24h.
- Clarified that patients with an organism whose MIC is ≤1 mg/L should maintain a trough of 10 to 15 mg/L.
- Updated use of dummy infusions, which will be used for patients randomized to vancomycin who have a dosing frequency other than q12h (no longer for differing infusion times).
- Clarified process for determining initial dosing interval for patients with renal impairment (including the addition of a table).
- Provided details for monitoring trough levels in patients with a creatinine clearance of ≥25 mL/min and in patients with a creatinine clearance < 25 mL/min.

Section 7.4.2 (Identity of Investigational Product)

- Changed formulation from “10 mL vial” to “two 5 mL ampule.”
- Added iclaprim mesylate concentration (16.3 mg/mL)

Section 7.5.1 (Schedule of Study Procedures)

- Row for “Draw trough levels” was added to Schedule of Study Procedures, as well as associated footnotes (footnotes 20 & 21).
- Clarified that 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.
- Clarified that if a 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.

- Clarified that if a 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.
- Clarified that if a 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.
- Clarified that vancomycin patients with an organism whose MIC is ≤1 mg/L should maintain a trough of 10 to 15 mg/L.
- Changed window for EOT evaluations from "+/- 2 days" to "+2 days."

Section 7.5.2.1 [Baseline/screening/randomization (Visit 1)]

- Clarified that the Principal Investigator, Study Coordinator or designee may enter and randomize patients after contacting the central randomization system.

Section 7.5.3.1.1 [Daily assessments until ETP (Visit 2)]

- Clarified that 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.
- Clarified that if a 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.
- Clarified that for vancomycin patients with a creatinine clearance < 25mL/min, a daily trough level should be obtained and the unblinded team should monitor and re-dose the patient when that level is below 20 mg/L.

Section 7.5.3.1.2 [Early timepoint (Visit 3)]

- Clarified that 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.
- Clarified that if a 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.
- Clarified that if a 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.

Section 7.5.3.1.3 [Assessments until EOT every 48 to 72 hours (Visit 4)]

- Clarified that 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.
- Clarified that if a 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.
- Changed window for EOT evaluations from "+/- 2 days" to "+2 days."
- Clarified that vancomycin patients with a creatinine clearance ≥25 mL/min should have their vancomycin level checked with the 5th dose due to difficulty interpreting levels checked prior to achieving steady state.

Section 7.6.1 (Efficacy Assessments)

- Added mCE row to Table 4 (Summary of Assessments).
- Added resolution or near resolution (≥90%) of ABSSSI at EOT and TOC as a secondary endpoint.

Section 7.6.1.2 (Secondary Efficacy Assessments)

- Added resolution or near resolution (≥90%) of ABSSSI at EOT and TOC as a secondary endpoint.

Section 7.6.1.2.3 (Microbiology Assessment)

- Clarified that if a 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.
- Clarified that if a patient has signs of bacteremia at any Visit, 2 sets of aerobic/anaerobic blood cultures that are collected at different sites should be obtained 10 minutes apart.
- Clarified that if a 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.
- Clarified that if a 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.

Section 7.6.2.2.2 (Reporting Serious Adverse Events)

- Updated telephone numbers and fax numbers.

Section 7.6.2.5 (Safety Laboratory Determinations)

- Corrected "pharmacy manual" to "Laboratory Manual."

Section 7.6.2.6.3 (Electrocardiogram)

- Corrected "pharmacy manual" to "ECG Manual."

Section 7.9.1 (Determination of Sample Size)

- Provided justification for adequate power with current sample size for secondary endpoint of clinical cure at TOC.

Section 7.9.2 (Patient Populations Analyzed)

- Added description of mCE population: all patients excluded from the PP population only because they have received prohibited concomitant or preceding antibiotic therapy active against Gram-positive pathogens.
- Clarified that PP population excludes patients with Gram-negative bloodstream infections who were discontinued in order to treat the Gram-negative pathogen.

Section 7.9.3.2 (Secondary Efficacy Outcome Measures)

- Added mCE population to secondary endpoints.
- Added resolution or near resolution (≥90%) of ABSSSI at EOT and TOC as a secondary endpoint.

Section 10 (References)

- Added reference numbers 7, 12-15, and 19-21

Appendix A (Clinical Laboratory Evaluations)

- Changed "Bile" to "Bilirubin/urobilinogen."

Appendix D (Vancomycin Dosing Nomogram)

- Added general text regarding iclaprim and vancomycin dosing.
- In "Creatinine Clearance" column, changed ">75" to "≥ 75" and changed "35-50" to "35-49."
- Removed infusion duration table.
- Clarified that vancomycin dosing would be based on actual body weight.
- Added graphic of a sample dosing sequence to clarify how blind will be maintained at different vancomycin dosing intervals.

Appendix E (Child-Pugh Scoring System)

- Corrected Albumin range of "2.8-2.5" to "2.8-3.4."
- Added point total interpretation.

Appendix F (Short-Acting Systemic Antibiotics Active Against Gram-Positive Pathogens)

- Added appendix to supplement Exclusion Criterion #6.

Additional minor editorial updates were also made but not detailed in the Summary of Changes.

SYNOPSIS

Study Number:	ICL-23-ABSSSI1
Title of Study:	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)
Indication:	Acute bacterial skin and skin structure infections (ABSSSIs) suspected or confirmed to be due to Gram-positive pathogens.
Number of Investigators and Study Centers:	Approximately 80 study centers in the United States, the EU, and other countries around the world.
Development Phase:	3
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 Time Point [ETP]) compared to baseline in all randomized patients (ITT). **Secondary Objectives:** The secondary objectives of this study are to demonstrate non-inferiority of iclaprim compared to vancomycin in the ITT, mITT, mCE, PP, and mPP populations for the following: 1. Resolution or near resolution of 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; and 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 PK profile for iclaprim using population pharmacokinetics; and 7. Establish the safety profile of iclaprim in patients with ABSSSI.
Study Population:	Patients ≥18 years of age of either gender with ABSSSIs suspected or confirmed to be due to Gram-positive pathogens.
Methodology/ 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. 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 (ie. 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), and will have a Late Follow-Up (LFU) phone call (28 to 32 days post-first dose). 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) weight-based vancomycin. The duration of treatment for both groups will be 5 days (minimum duration) to 14 days (maximum duration). 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. Normal saline dummy infusions will be used to maintain the blind where vancomycin is dosed at a different interval than q12h. For patients in whom Gram staining of culturable material or cultures indicates that Gram-negative coverage is required, and for patients in whom anaerobic pathogens are suspected or confirmed as pathogens at the infected site, aztreonam and metronidazole may be administered, respectively. Concomitant antibiotics aztreonam and metronidazole will be used in compliance with their respective prescribing information at the discretion of the investigator during the study treatment 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. **Clinical Assessments:** The primary endpoint for clinical response (defined as the reduction in lesion size ≥20% compared to baseline) will be evaluated in all randomized patients at ETP (48 to 72 hours post-first dose). Patients who have died or who received rescue antibacterial therapy prior to that time will be included as treatment failures. In addition, clinical outcome will be evaluated by the investigator at EOT and TOC (7 to 14 days post EOT). The assessments of clinical outcome will be categorized as cure, failure, or indeterminate. **Microbiological Assessments:** An adequate clinical specimen for microbiologic evaluation will be obtained at baseline prior to randomization. Additional clinical specimens will be obtained, if clinically feasible and if the patient has persistent clinical signs or symptoms, at ETP, EOT and TOC. If the patient is discontinued from the study due to treatment failure, a clinical specimen will be obtained at that time. Specimens will be evaluated by the local microbiology laboratory; in addition, isolates will be subcultured and sent to a central microbiology laboratory for confirmation of pathogen identity and minimum inhibitory concentrations (MICs). Two sets of blood samples for aerobic/anaerobic cultures 10 minutes apart from different sites peripherally will be obtained within 24 hours prior to the first dose of study drug. Blood cultures from intravascular devices are not permitted.

	Any potential pathogen will be subcultured and the isolates shipped to the central laboratory. Anti-streptolysin O titers will also be taken within 24 hours of the start of treatment. Microbiological 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. Microbiological response by patient will be determined at ETP, EOT, and TOC visits and categorized as eradication, presumed eradication, persistence, presumed persistence, indeterminate, superinfection, or recurrent infection in patients with a Gram-positive pathogen isolated at baseline. **Pharmacokinetic Assessments:** Pharmacokinetic samples will be obtained from patients on 3 occasions, following the first dose of study medication, at ETP, and at EOT. After the study is complete, the database locked, and the data unblinded, patients randomized to iclaprim will have their samples assayed. **Safety and tolerability assessments:** All patients who receive any study drug will be evaluated for safety on the basis of medical history and physical examinations, reports of clinical AEs, routine electrocardiography, and clinically significant findings from routine liver function tests, serum chemistry, hematology, coagulation, and urinalysis (UA) tests. All adverse events will be recorded throughout the study period, up to and including the LFU phone call. While blinded to treatment assignment, the investigator will categorize the severity of each AE and the potential for relationship to study drug. Serious AEs (SAEs) include those that were life threatening, led to prolongation of the existing hospitalization, a congenital anomaly/birth defect, or caused persistent or significant disability, incapacity, or death. Treatment-emergent AEs (TEAEs) will be defined as those that start or worsen in severity during or after the first dose of study drug administration through end of study.
Number of Patients (planned and analyzed):	A total of 600 patients (approximately 300 per treatment group) will be randomized (1:1) for this study. Using Farrington and Manning's method 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% non-inferiority 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% early clinical response rate at TOC in each group and a 10% NI bound delta, a sample size of 300 patients in the ITT population per treatment group is required for 82% power. If the initial endpoint of clinical response at ETP does not achieve statistical significance, no further statistical testing will be done.
Diagnosis and Main Criteria for Inclusion:	The following are the main inclusion criteria: written informed consent; ≥18 years of age; a bacterial infection of the skin with a lesion size area of at least 75 cm^2 with major cutaneous abscess, cellulitis/erysipelas, and/or wound infections (caused by external trauma [eg, needle sticks or insect bites]); and the presence of purulent or seropurulent drainage before or after surgical intervention of a wound or at least 3 of the following signs and symptoms: discharge, erythema (extending at least 2 cm beyond a wound edge in one direction), swelling and/or induration, heat and/or localized warmth, and/or pain and/or tenderness to palpation.

Exclusion Criteria:	The following are the main exclusion criteria: ABSSSI of the following categories: severely impaired arterial blood supply such that amputation of the infected anatomical site is likely, infected diabetic foot ulcers, infected decubitus ulcers, infected human or animal bites, necrotizing fasciitis or gangrene, uncomplicated skin or skin structure infection, self-limiting infections, skin and/or skin structure infection that can be treated by surgery alone, infections associated with a prosthetic device, and suspected or confirmed osteomyelitis; known or suspected concurrent infection or conditions requiring systemic anti-microbial treatment, prophylaxis, or suppression therapy; received more than one dose of a short-acting (i.e., q12h dosing or less) systemic antibiotic(s) active against Gram-positive pathogens within the last 7 days, unless there is documented evidence of treatment failure OR demonstrated resistance of Gram-positive pathogens to the prior antibiotic therapy.
Study Medications:	Iclaprim will be administered at a dose of 80 mg in 500 mL normal saline, infused over 2 hours q12h (every 12 hours) for 5 to 14 days. For subjects with moderate hepatic impairment (Child-Pugh Class B), iclaprim will be administered at a dose of 40 mg in 500 mL normal saline, infused over 2 hours q12h for 5 to 14 days. Vancomycin will be dosed as follows: 15 mg/kg body weight in 500 mL normal saline infused over 2 hours for 5 to 14 days. Dosing interval will be every q12h, q24h, q48h, or dosed by daily level based on creatinine clearance. Patients randomized to vancomycin who require dosing intervals of q24h, q48h, or dosed by daily level due to renal impairment will receive dummy infusions (normal saline) at 12 hour intervals when they are not 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. Normal saline dummy infusions will be used to maintain the blind for patients randomized to vancomycin who have a dosing frequency other than Q12h.
Dose and Regimen:	Iclaprim is a dihydrofolate reductase inhibitor being studied for the treatment of ABSSSI. The dosing regimen of iclaprim is 80 mg q12h via an intravenous administration. Each dose will be infused over 2 hours, and the duration of treatment will be 5 days (minimum duration) to 14 days (maximum duration).
Duration of Treatment:	The total duration of treatment in the study for each patient is 5 to 14 days.
Duration of Patient Participation in Study:	The total duration of participation in the study for each patient is 29 to 33 days.

Study Populations:	Intent-to-treat (ITT) population — All randomized patients (primary population for efficacy analyses). Patients will be analyzed in treatment group to which they were randomized. Microbiological intent-to-treat (mITT) population — All randomized patients who have a Gram-positive baseline bacterial pathogen identified as the cause of ABSSSI. Modified clinically evaluable (mCE) population consists of all patients excluded from the PP population only because they have received prohibited concomitant or preceding antibiotic therapy active against Gram-positive pathogens. Per-protocol (PP) population — ITT patients who receive at least 80% of their planned doses and provide adequate data for assessment for each of the following timepoints: ETP, EOT and TOC. This excludes patients with Gram-negative bloodstream infections who were discontinued in order to treat the Gram-negative pathogen. PP microbiologically evaluable population (mPP) — mITT patients who receive at least 80% of their planned doses and provide adequate data for assessment for each of the following timepoints: ETP, EOT, and TOC. Safety population — All patients who receive any study drug during the trial (primary population for safety analyses). Patients will be analyzed according to the treatment they received.
Evaluation: Efficacy	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 among all randomized patients (ITT population). The primary efficacy analysis will be the non-inferiority (NI) of iclaprim (group 1) to vancomycin (group 2) for the proportion of patients with a ≥20% reduction in lesion size at ETP compared to baseline. The primary NI efficacy analysis will be repeated in the mITT, mCE, the PP, and the mPP populations as secondary outcomes. The secondary endpoints are: 1. Resolution or near resolution of ABSSSI (ie, 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, mCE, PP, and mPP populations 2. Resolution or near resolution (≥90%) of ABSSSI at EOT for ITT, mITT, mCE, PP, 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, mCE, PP, 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
Evaluation: Safety	Treatment emergent AEs, SAEs, hematology, clinical chemistry, UAs, vital signs, physical examinations, electrocardiograms (ECGs), and liver function tests will be evaluated.
Evaluation: Pharmacokinetics	Iclaprim plasma concentrations will be used to determine population PK parameters, including C_{max}, AUC to infinity ($AUC_{0-\infty}$), clearance, and volume of distribution. Interindividual variability (IIV) will be determined for PK parameters, as well as residual variability. 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 detailed in a separate population PK analysis plan.
Statistical Methods:	In general, statistical tests will be two-sided, and at the level of significance alpha = 0.05. The non-inferiority assessment will be made with a one-sided test at significance level of 0.025. Confidence intervals (CIs) will be calculated at a 95% confidence level. Continuous data will be summarized by treatment group using the number of patients in the analysis population (N), mean, standard deviation (SD), median, and range, and categorical data will be summarized by treatment group using N and percentage. **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% CI for P1 – P2 is greater than -0.100 based on the Z test with unpooled variance estimate, NI will be concluded. **Secondary Efficacy Analyses:** The primary NI efficacy analysis will be repeated in the mITT, mCE, the PP, and the mPP populations. The secondary endpoints are resolution or near resolution of ABSSSI (ie, clinical cure) at TOC for iclaprim (80 mg q12h) compared with vancomycin (weight-based dose), 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. **Safety Analyses:** All patients who received any amount of iclaprim or vancomycin during the trial will be evaluated for safety. Safety evaluation include incidence of TEAEs, laboratory test results (including liver function tests), vital signs, ECG results, and physical examination findings. All summaries of safety data will be based

	on the safety population (all treated patients). No formal statistical analysis of the safety data will be performed. Summary tables will be provided for all AEs by treatment group. The incidence of AEs, related AEs, SAEs, and AEs leading to discontinuation of the study treatment will be presented by Medical Dictionary for Regulatory Activities system organ class (SOC) and preferred term. In addition, the incidence of AEs by severity will be presented by SOC and preferred term. The AE summary tables will include patient counts. Therefore, if a patient experiences more than one episode of a particular AE, the patient will be counted only once for that event. If a patient has more than one AE that is coded to the same preferred term, the patient will be counted only once for that preferred term. Similarly, if a patient has more than one AE within a SOC, the patient will be counted only once in that SOC. 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, SD for mean and standard error for mean change, minimum, median, maximum, and number and percent of patients within specified categories). Shift tables (ie, 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. 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. Descriptive statistics of vital signs and ECG results at each visit will be presented by treatment group. Physical examination findings will be listed for each patient.

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1. CONTACTS

1.1 Emergency Contacts

Contact the person indicated below for questions concerning serious adverse events and other emergencies:

CRO Medical Monitor:

Name: Patrick McLeroth
Country: USA
Phone: +1 609 216-4187
Fax: +1 609 987-9262
Business Hours: 8 am to 6 pm Eastern Standard Time

2. INVESTIGATOR/SPONSOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I understand that the study may be terminated or enrolment suspended at any time by the sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients. I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

Principal Investigator	Date

Sponsor Signature:

Name David Huang Motif, Chief Medical Officer	Date

3. LIST OF ABBREVIATIONS

List of Abbreviations

Abbreviation	Definition
ABSSSI	acute bacterial skin and skin structure infection
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASO	anti-streptolysin O
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC∞	area under the concentration-time curve to infinity
b.i.d.	twice daily
BL	Baseline
BUN	blood urea nitrogen
CBC	complete blood count
CD4	cluster of differentiation
CFR	US Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
C_{min}	minimum concentration
CO_2	carbon dioxide
CPK	creatine phosphokinase
CrCL	creatinine clearance
CRF	case report form
CRO	clinical research organization
CRP	C-reactive protein
CSA	clinical study agreement
cSSSI	complicated skin and skin structure infections
CYP	cytochrome P450
DHFR	dihydrofolate reductase
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOT	End of Therapy
ETP	early timepoint
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
hCG	beta-human chorionic gonadotropin
HIV	human immunodeficiency virus
IC50	inhibitory concentration at 50%
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IXRS	Interactive Phone and Web Response System
LDH	lactate dehydrogenase
LFU	Late Follow-Up
MCH	mean corpuscular hemoglobin

List of Abbreviations

Abbreviation	Definition
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
mITT	microbiological intent-to-treat
mPP	Per-protocol microbiologically evaluable population
MRSA	methicillin-resistant staphylococci
N	analysis population
NI	non-inferiority
NSVT	nonsustained ventricular tachycardia
PP	Per-protocol
PK	pharmacokinetic
PV&DSS	Covance Pharmacovigilance & Drug Safety Services
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
REB	Regional Ethics Board
SAE	serious adverse event
SCr	serum creatinine
SD	standard deviation
SOC	system organ class (MedDRA classification)
T > MIC	time above the minimum inhibitory concentration
TEAE	treatment-emergent adverse event
TOC	Test of Cure
UA	urinalysis
US	United States
WBC	white blood cells

4. ETHICAL CONSIDERATIONS

4.1 Institutional Review Board or Independent Ethics Committee

In accordance with the United States (US) Code of Federal Regulations (CFR) Title 21 Section 56 (21 CFR 56), the protocol, advertisement, and Informed Consent Form (ICF) will be reviewed and approved by the Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Regional Ethics Board (REB). The sponsor will supply relevant material for the investigator to submit to the IRB for the protocol's review and approval. Verification of the IRB's unconditional approval of the protocol and the written ICF statement will be transmitted to the investigator.

The IRB will be informed by the investigator of subsequent protocol amendments and of Suspected Unexpected Serious Adverse Reactions. Approval for protocol amendments will be transmitted in writing to the investigator. If requested, the investigator will permit audits by the IRB and regulatory inspections by providing direct access to source data/documents.

The investigator will provide the IRB with progress reports at appropriate intervals (not to exceed one year) and a Study Progress Report following the completion, termination, or discontinuation of the investigator's participation in the study.

4.2 Ethical Conduct of the Study

The study procedures outlined in this protocol will be conducted in accordance with the CFR governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), IRBs (21 CFR 56), Investigational New Drug Application (21 CFR 312), and Applications for Food and Drug Administration (FDA) Approval to Market a New Drug (21 CFR 314), as appropriate. As such, these sections of US Title 21 CFR, along with the applicable International Conference on Harmonisation (ICH) Guidelines, are commonly known as Good Clinical Practices (GCP), which are consistent with the Declaration of Helsinki.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirements.

4.3 Patient Information and Consent

Written informed consent for the study will be obtained from all patients before protocol-specific procedures are carried out. The ICF generated by the sponsor will be approved (along with the protocol) by the IRB.

The investigator (or designee) will explain the nature of the study and the action of the test product. The patients will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the designated IRB and will be signed by the patient prior to protocol-specific procedures being performed.

The patient will be given a copy of the signed ICF and the original will be maintained with the patient's records.

5. INTRODUCTION

5.1 Acute Bacterial Skin and Skin Structure Infections

Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) are predominantly caused by the following Gram-positive pathogens: *Staphylococcus aureus*, including methicillin-resistant staphylococci (MRSA), beta hemolytic streptococci (most commonly *S. pyogenes* and *S. agalactiae*), enterococcus spp., and viridans group streptococci.

Due to the rapid emergence of hospital- and community-acquired strains of resistant bacteria, there is an urgent need to identify and develop compounds that are active against drug-resistant and emerging pathogens, such as MRSA, which are associated with increased rates of morbidity and mortality and, therefore, with significantly increased pharmacoeconomic costs.

5.2 Properties of Iclaprim

Iclaprim (MTF-100) is a potent and selective inhibitor of dihydrofolate reductase (DHFR) of important bacterial pathogens, including antibiotic-resistant strains. Iclaprim inhibits human DHFR minimally, resulting in a selectivity index of more than 4 orders of magnitude. These results, together with more than 2 decades of clinical experience with trimethoprim (a related diaminopyrimidine), provide the proof of concept that selective DHFR inhibitors are safe and efficacious.

A major advantage of iclaprim over many existing antibiotics is its potent bactericidal activity against a broad spectrum of Gram-positive bacteria, including MRSA, vancomycin-intermediate *S. aureus*, vancomycin-resistant enterococci (VRE), and quinolone-resistant strains. Moreover, iclaprim exhibits potent activity against most trimethoprim-resistant strains. Iclaprim is active against the majority of the Gram-positive pathogens in ABSSSI.

Further details about iclaprim can be found in the Investigator's Brochure.

5.3 Overview of Nonclinical and Clinical Studies

5.3.1 Nonclinical studies

Iclaprim is rapidly bactericidal against Gram-positive clinical isolates and displays a significant postantibiotic effect. Based on in vitro data, the propensity for resistance development is predicted to be low. Iclaprim was active against pathogens susceptible and resistant to standard antibiotics when administered by either intravenous (IV) or oral (p.o.) routes in in vivo rodent infection models.

In a 4-week toxicity study in male and female rats, single daily IV bolus doses up to 60 mg/kg were given. Little evidence of systemic toxicity was observed, even at the highest dose tested (60 mg/kg/day). However, poor local injection site tolerability precluded the determination of a no observed adverse effect level (NOAEL). However, the Non-Toxic-Effect level was at least 30 mg/kg/day. In a 4-week toxicity study in male and female marmosets, single daily infusions up to 30 mg/kg over 20 minutes were well tolerated, with the exception of a slight irritation response at the injection site. Therefore, the NOAEL was considered to be 30 mg/kg/day.

In safety pharmacology studies with IV bolus doses up to 30 mg/kg in rats, no behavioral changes or effects on spontaneous locomotor activity were observed. Telemetric monitoring of cardiovascular effects in the conscious dog with single IV bolus doses up to 10 mg/kg showed no signs of any gross electrocardiogram (ECG) waveform abnormality or rhythm disturbance. Iclaprim reversibly inhibited the human ether-a-go-go related gene mediated potassium current in transfected Chinese hamster ovary cells with an inhibitory concentration at 50% (IC50) of 0.9 μM. Iclaprim did not significantly inhibit the sodium and calcium channels, with an IC50 of 95 μM and 46 μM, respectively. Iclaprim was not mutagenic in the Ames test and showed no mutagenic or clastogenic activity in the mouse lymphoma, rat micronucleus, or

mammalian chromosome aberration tests.

5.3.2 Phase 1 Clinical studies

Iclaprim has been administered in single-dose studies up to 3.2 mg/kg and in repeated escalating IV dose studies up to 1.6 mg/kg.

Following IV administration, iclaprim rapidly and extensively distributes into tissues and shows a terminal elimination half-life of about 3 hours. Pharmacokinetic (PK) properties are independent of the dose; maximum concentration (C_{max}) and area under the concentration-time curve (AUC) increased proportionately with the dose. Iclaprim is excreted, mainly in the urine, as conjugated metabolites.

In a single-dose ECG-study with 1.6 mg/kg and 3.2 mg/kg infused over 30 minutes, iclaprim prolonged the QTc interval (QT interval corrected for heart rate) in a dose-dependent manner. Maximal increases coincided with C_{max} levels and were rapidly reversible. Dosing with 1.6 mg/kg was assessed as acceptable for clinical purposes, whereas dosing at 3.2 mg/kg was associated with relevant QTc prolongations (>60 msec) and nonspecific T-wave alterations.

In a second single-dose ECG study using doses of 0.4 mg/kg and 0.8 mg/kg iclaprim base infused over 30 minutes and 1.6 mg/kg infused over 60 minutes, evaluation of the QTc interval showed a reversible dose-dependent effect of iclaprim on the duration of the QTc interval at 0.8 mg/kg and 1.6 mg/kg. Importantly, at both the 0.8-mg/kg and 1.6-mg/kg doses, no subject had a maximal QTc value >500 msec. When QTc was corrected according to Fridericia (QTcF), no subject exhibited any postinfusion QTcF prolongation of >60 msec from Baseline (BL). In addition, in both of the ECG studies, no gender differences concerning QTc prolongations were observed, nor were any cardiovascular adverse events (AEs) reported.

A transient C_{max}-related mean increase in QTc corrected according to Bazett (QTcB) of approximately 10 msec was observed after infusion of 0.8 mg/kg iclaprim over 30 minutes. This transient QTc prolongation is similar to or less than QTc prolongations observed with other antibiotics, eg, 51 msec for IV erythromycin [1], 3 to 11 msec for clarithromycin [2,3,4]; moxifloxacin showed QTc prolongations of 9 to 17 msec in several studies submitted in their New Drug Application [5].

Iclaprim was safe and well tolerated; no treatment-related severe AEs were observed in any of the subjects exposed to iclaprim in Phase 1 studies. Safety and tolerability were acceptable at the highest doses tested, 3.2 mg/kg as a single dose and multiple doses of 1.6 mg/kg twice daily (b.i.d.) for 10 days.

5.3.3 Phase 2 cSSSI Study

In a Phase 2 clinical study of patients with complicated skin and skin structure infections (cSSSI), patients were randomized to receive either iclaprim base at a dose of 0.8 mg/kg or 1.6 mg/kg infused over 30 minutes every 12 hours or vancomycin 1 g every 12 hours. Clinical cure rates in all groups were >90% at Day 10 and at the Test of Cure (TOC) visit.

Drug-related AE rates were 0%, 6%, and 10%, for the 0.8 mg/kg, 1.6 mg/kg, and vancomycin 1 g regimens, respectively. Both doses of iclaprim were well tolerated. No treatment-related serious adverse events (SAEs) were observed. In 48 patients who had ECGs performed during the study medication administration period, central evaluation of these data revealed an increase in QTcB interval >60 msec immediately following study medication infusion in 2 patients (1 patient in each of the iclaprim 1.6 mg/kg and vancomycin groups), but the corresponding QTcF increases were below 60 msec. No QTc interval recorded immediately following completion of the infusion exceeded 480 msec. Furthermore, no treatment-emergent cardiac rhythm disturbances were observed.

5.3.4 Phase 3 cSSSI Studies

Iclaprim was administered at a dose of 0.8 mg/kg b.i.d. for 10 to 14 days in two Phase 3 cSSSI studies. The cure rates in the intent-to-treat (ITT) and Per-protocol (PP) populations, respectively, in both studies were as follows:

Table 1: ASSIST-1 & ASSIST-2 Cure Rates

	ASSIST-1		**ASSIST-2**		**Combined**	
	Iclaprim	**Linezolid**	**Iclaprim**	**Linezolid**	**Iclaprim**	**Linezolid**
ITT	N = 249	N = 248	N = 251	N = 243	N = 500	N = 491
Clinical cure, n (%)	207 (83.1%)	220 (88.7%)	204 (81.3%)	199 (81.9%)	411 (82.2%)	419 (85.3%)
95% CI	78.0% – 87.3%	84.2% – 92.1%	75.9% – 85.9%	76.5% – 86.5%	78.6% – 85.5%	81.9% – 88.4%
Treatment difference (iclaprim - linezolid) and 95% CI	-5.6% [-11.72% to 0.6%]		-0.6% [-7.7% to 6.5%]		-3.1% [-7.9% to 1.6%]	
PP	N = 206	N = 213	N = 209	N = 195	N = 415	N = 408
Clinical cure, n (%)	195 (94.7%)	211 (99.1%)	188 (90.0%)	188 (96.4%)	383 (92.3%)	399 (97.8%)
95% CI	90.7% – 97.0%	96.6% – 99.7%	85.1% – 93.7%	92.7% – 98.5%	89.3% – 94.7%	95.9% – 99.0%
Treatment difference (iclaprim - linezolid) and 95% CI	-4.4% [-8.4% to -1.0%]		-6.5% [-11.8% to -1.2%]		-5.5% [-8.7% to -2.4%]	
The CI presented in this table were calculated using SAS-generated 95% CI. The ASSIST-1 analysis used the Newcombe-Altman formula						

For the pivotal Phase 3 studies, ASSIST-1 and ASSIST-2, in the combined data set, the incidence of possibly or probably treatment-related AEs was 22.6% for the iclaprim treatment group, compared to 27.9% for the linezolid group. No treatment-related SAEs were observed in ASSIST-1; 1 SAE in ASSIST-2 was considered to be possibly treatment related (elevated alanine aminotransferase [ALT] in one iclaprim-treated patient). In general, iclaprim was safe and well tolerated with a similar AE profile to the comparator drug linezolid.

With respect to cardiac effects, results from the combined Phase 3 clinical studies indicated that the incidence of QTc prolongations of concern (QTcF >60 ms) in the iclaprim treatment arms were similar to those observed in the linezolid treatment arms (3 patients each). Adverse events of QTc prolongation were reported infrequently (4 cases in the iclaprim arms and 2 cases in the linezolid arms) and no cases of QTc prolongation related cardiac effects classified as treatment related AE were observed in these studies. Iclaprim led to a mean increase of the QTc interval by about 5 to 6 msec greater than that observed with linezolid, which is considered clinically well tolerated.

The analysis of liver enzyme level increases in cSSSI patients was complex, as in addition to study drug treatment a number of other conditions can contribute to such effects, such as general state of health, underlying inflammatory condition, HCV, HBV and HAV, lifestyle (ie, drug / alcohol abuse), besides the effects of treatment with the study drug. Overall, the increases in ALT and aspartate aminotransferase (AST) levels observed upon IV exposure using the therapeutic dose in the cSSSI population were similar to those observed with linezolid treatment and were considered not to be of major clinical significance, since they were asymptomatic and without significant concomitant increase in bilirubin: no Hy's law cases were

observed.

5.4 Rationale

5.4.1 Rationale for the Current Study

Iclaprim is an antibiotic (DHFR) designed to be effective against bacteria that have developed resistance to other antibiotics, including trimethoprim. Iclaprim exhibits potent activity against Gram-positive clinical isolates of many genera of staphylococci, including methicillin sensitive staphylococci, MRSA, and beta-hemolytic streptococci (eg, Group A and B streptococci). It is also effective against vancomycin-intermediate resistant *Staphylococcus aureus*, vancomycin-resistant Enterococci, and quinolone-resistant strains.

In 2008, following a Phase 3 trial, Arpida submitted a request to the FDA and the EMA (European Medicines Agency) for approval to market the compound. On the basis of submitted data, iclaprim was not approved and ceased to be developed. Motif has reviewed all preclinical and clinical data, including the US and European regulatory correspondences. Compared to the previous ASSIST protocols, the current study (protocol ICL-23-ABSSSI1) will employ a different dosing strategy (fixed iclaprim dose instead of weight-based iclaprim) and will use a different comparator (vancomycin instead of linezolid). This study will also be larger, recruiting 100 more patients, and will be conducted in more sites from a number of different countries. Protocols ICL-23-ABSSSI1 and ICL-23-ABSSSI2 will also use a new early timepoint (ETP) to evaluated early response as a primary efficacy endpoint, as recommended by the new FDA guidance for developing ABSSSI drugs [6].

Liver function test elevations of uncertain significance were seen in the previous ASSIST protocols. There is a need for additional clinical studies to further demonstrate iclaprim's safety and efficacy. For this reason, this Phase 3 clinical study is intended to demonstrate that the safety, tolerability, and efficacy of iclaprim are non-inferior to that of vancomycin. This adequate and well-controlled study will thus provide important evidence for the marketing approval application of iclaprim for the treatment of ABSSSIs.

5.4.2 Rationale for patient population

Iclaprim is active against the major pathogens associated with ABSSSI. Therefore, adult patients with signs and symptoms of wound infection (caused by external trauma [eg, needle sticks or insect bites]), cellulitis, or major cutaneous abscess with surrounding cellulitis are eligible for this study. Evaluation of patients with these major infection subtypes of ABSSSI will provide support for the use of iclaprim in the broader ABSSSI population.

5.4.3 Rationale for Iclaprim dose regimen

Therapy for ABSSSI is generally 5 to 14 days. An iclaprim dose of 80 mg administered over 2 hours every 12 hours (q12h) is selected as the dosing regimen to be progressed in pivotal studies based upon exposure projections. The selected dose is designed to optimize the efficacy and safety profiles of iclaprim based on the following considerations

- When iclaprim was tested in standard rodent models of infection, good efficacy was observed. The primary PK/PD predictors for efficacy were determined to be (1) the ratio of the area under the curve (AUC) to the minimum inhibitory concentration (MIC), ie, AUC/MIC, and (2) the time above the MIC, ie, T > MIC, expressed as a percent of the dosing interval. Thus, optimization of these two parameters would be expected to maximize the efficacy of the drug.

- A thorough QTc (TQTc) study indicated that there was an association between the maximum QTc value and the maximum plasma iclaprim concentration (C_{max}). Thus, minimization of C_{max} would be expected to correspond to optimal cardiovascular safety of iclaprim. In the TQTc study, doses of 1 mg/kg and 2 mg/kg administered over 0.5 hours led to dose related increases in the QTc, whereas

0.5 mg/kg administered over 0.5 hours did not. The increases in QTc for the 1 mg/kg dose were considered to be mild, with a mean (95% confidence interval) change in the placebo- and baseline-corrected QTcB of 10.3 (3.3, 17.3) msec. This dose was associated with a geometric mean (95% confidence interval) C_{max} of 792 (682, 919) ng/mL. A reference Cmax of 800 ng/mL was therefore used for the evaluation of potential dosing regimens with respect to the risk of QTc prolongation.

- Iclaprim was administered at a dose of 0.8 mg/kg over 0.5 hours g12h in the ASSIST-1 and ASSIST-2 to 470 patients. Iclaprim was well tolerated in both studies at this dose. Adverse events related to QTc prolongation were reported infrequently (4 cases in the iclaprim arms and 2 cases in the linezolid arms) and no cases of QTc prolongation-related cardiac effects classified as treatment related AEs were observed in these studies. Iclaprim led to a mean increase of the QTc interval by about 5 to 6 msec greater than that observed with linezolid, a drug that is considered to be clinically well tolerated.

- A population pharmacokinetic (PK) analysis of the data from the ASSIST studies demonstrated no relationship between the clearance (CL) of iclaprim and body weight, suggesting that a fixed rather than weight-based dose should be used.

The ASSIST-1 and ASSIST-2 studies used sparse sampling with a population PK analysis. The post-hoc estimates of the individual patient PK parameters were used to simulate the plasma iclaprim concentration-time profiles for each patient and from those profiles, the corresponding values for $Cmax_{ss}$, $AUC(0\text{-}24)_{ss}$, AUC/MIC, and T > MIC. In these analyses, the MIC value used was based on the MIC_{90} of *S. aureus* of 120 ng/mL identified in worldwide surveillance studies. Various fixed dose regimens were examined with respect to maximizing AUC/MIC and T > MIC while minimizing the probability of a steady-state C_{max} ($Cmax_{ss}$) ≥800 ng/mL. The results of these simulations form the basis for the selection of the dose in proposed pivotal studies.

The data from the simulations of the fixed dose regimens (64 mg, 72 mg, and 80 mg) based on the post-hoc estimates of iclaprim PK in 470 patients indicate that administration of 80 mg as a 2 hour infusion should provide a 28% increase in AUC/MIC and a 32% increase in the T > MIC compared to the dosing regimen used in the previous ASSIST trials, while keeping $Cmax_{ss}$ below the reference Cmax of 800 ng/mL from the TQTc study and lower than the observed mean values for Cmax at doses > 0.5 mg/kg in the TQTc studies. Therefore, the regimen of 80 mg administered over 2 hours q12h would be expected to maximize the likelihood of antibacterial efficacy while minimizing the potential for QTc prolongation.

An iclaprim dose of 40 mg administered over 2 hours every 12 hours (q12h) is selected as the dosing regimen for patients with moderate hepatic impairment (Child-Pugh Class B [Appendix E]). An open-label, parallel, single dose study to investigate the pharmacokinetics of iclaprim in subjects with hepatic or renal dysfunction and in obese subjects showed a 2.5-fold increase in AUC and a 1.4-fold increase in C_{max}. Since iclaprim clearance was reduced by 50%, a 50% reduction in dose will be used for patients with moderate hepatic impairment [7].

5.4.4 Rationale for choice of comparator

In this study, patients will be randomized in a 1:1 ratio to receive fixed-dose iclaprim (group 1) or weight-based vancomycin (group 2).

Vancomycin is a glycopeptide antibiotic and is active against many Gram-positive bacteria, including *Staphylococcus aureus* [8]. It is indicated in potentially life-threatening infections, is used for therapy of severe staphylococcal infections, and remains as the recommended first-line empiric therapy for ABSSSIs (purulent and nonpurulent) [8,9]. It is widely available, is cost-effective, and its safety has been well established over years of use [9].

Vancomycin has been chosen as the comparator in this double-blind study because it is the standard of care Gram-positive treatment for ABSSSI according to Infectious Diseases Society of America guidelines, most commonly used empiric Gram-positive treatment for ABSSSI, it will help facilitate blinding (compatible

infusion times), and recent FDA-approved ABSSSI treatments used vancomycin as the treatment comparator during clinical trials.

According to the most recent recommendations for vancomycin dosing compiled by the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists, it is recommended that dose adjustments be based on monitored trough levels to maintain the required therapeutic concentration levels [10]. This is the most practical and accurate method of assessing vancomycin effectiveness [10]. The recommended trough serum concentrations are either 10 to 15 mg/L for patients with an organism whose minimum inhibitory concentration (MIC) is ≤1 mg/L or 15 to 20 mg/L for patients with an organism whose MIC is >1 mg/L [11]. Normal saline dummy infusions will be used to maintain the blind.

Vancomycin dosing will be capped at 1750 mg per dose; in morbidly obese patients (above 100 kg of body weight), there is little additional increase in creatinine clearance at doses >1750 mg [12,13,14,15].

6. 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 (ETP) compared to baseline in all randomized patients (ITT).

Secondary Objectives:

The secondary objectives of this study are to demonstrate non-inferiority of iclaprim compared to vancomycin in the ITT, mITT, mCE, PP, and mPP populations for the following:

1. Resolution or near resolution of 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; and

    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 PK profile for iclaprim using population pharmacokinetics; and

7. Establish the safety profile of iclaprim in patients with ABSSSI.

7. INVESTIGATION PLAN

7.1 Overall Study Design and Plan Description

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 (ie. 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), and will have a Late Follow-Up (LFU) phone call (28 to 32 days post-first dose) Note, however, that patients with high LFTs and unresolved 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 treatment 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 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 treatment 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.

Regulatory guidances that have been taken into account while designing this protocol included:

- Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. Center for Drug Evaluation and Research (CDER) Draft Guidance, October 2013.

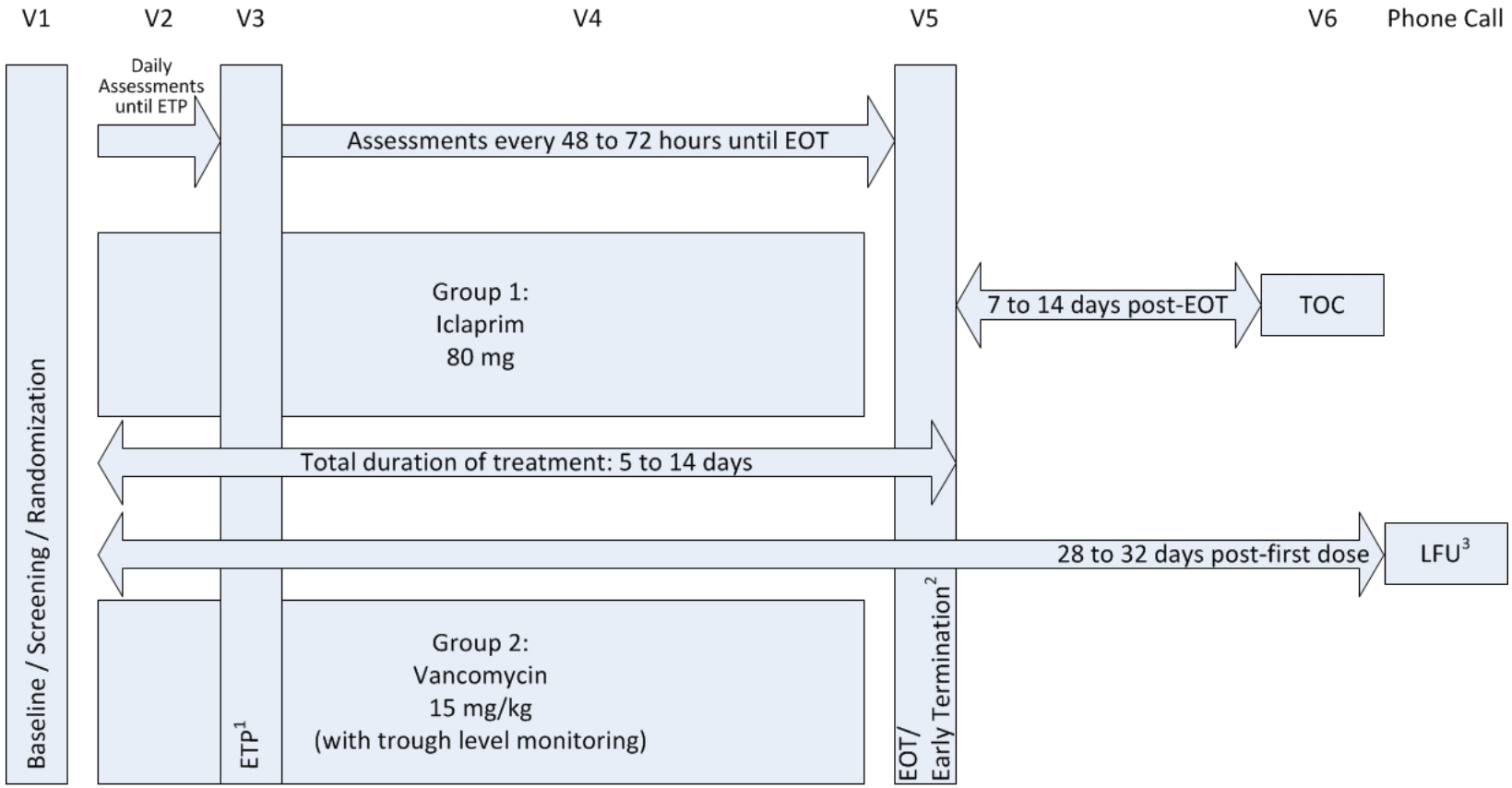
- Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. (EMA/CHMP/351889/2013) EMEA, October 2013;

- Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. (CPMP/EWP/558/95 rev 2) European Medicines Agency (EMEA), December 2011;

- ICH EI4 Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-anti-arrhythmic drugs. (CHMP/ICH/2/04) EMEA, May 2005; and

- Developing anti-microbial drugs - general considerations for clinical trials. CDER Draft Guidance, July 1998.

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

7.2 Study Endpoints

7.2.1 Efficacy Endpoints

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 among all randomized patients (ITT population).

The secondary endpoints are:

1. Resolution or near resolution of ABSSSI (ie, 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, mCE, PP, and mPP populations

2. Resolution or near resolution (≥90%) of ABSSSI at EOT for ITT, mITT, mCE, PP, 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, mCE, PP, 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

7.2.2 Safety Endpoints

Safety endpoints are AEs, SAEs, ECG results, liver function tests, hematology, coagulation, serum chemistry, urinalysis (UA), vital signs, and physical examinations.

7.3 Selection of Study Population

7.3.1 Inclusion Criteria

Patients will be considered for further screening procedures only if they meet **all** of the following criteria:

1. At least 18 years of age

2. Written informed consent to participate in the study before any study-specific screening procedures are performed. If any patient is unable to give consent, it may be obtained from an acceptable representative.

3. A bacterial infection of the skin with a lesion size area of at least 75 cm^2 (lesion size measured by the area of redness, edema, or induration) and clinical evidence of at least 1 of the following:

    a) Major cutaneous abscess,

    b) Cellulitis/erysipelas, and/or

    c) Wound infections (caused by external trauma [eg, needle sticks or insect bites]).

4. Presence of purulent or seropurulent drainage before or after surgical intervention of a wound within 24 hours of randomization (because surgical incision and drainage might influence treatment outcomes among patients with major cutaneous abscesses; note that patients with major cutaneous abscesses should not comprise >30% of the clinical trial population) OR

   At least 3 of the following signs and symptoms within 24 hours of randomization:

   a) Discharge,

   b) Erythema (extending at least 2 cm beyond a wound edge in one direction),

   c) Swelling and/or induration,

   d) Heat and/or localized warmth, and/or

   e) Pain and/or tenderness to palpation.

5. At least 1 of the following conditions within 24 hours of randomization considered to be pathogen-related:

   a) Fever (>38°C/100.4°F orally, rectally, or tympanically),

   b) Enlarged and/or tender proximal lymphadenopathy and/or lymphangitis,

   c) Elevated total peripheral white blood cells (WBCs) >10,000/mm^3,

   d) >10% immature neutrophils (bands), regardless of total peripheral WBC count, or

   e) A non-specific C-reactive protein greater than the upper limits of normal.

6. Venous access available for IV dosing.

7. Accessible infection site for culture.

8. If female, must either:

   a) be post-menopausal for at least 1 year; or

   b) have had a hysterectomy or tubal ligation; or

   c) if of childbearing potential:

      i. have maintained her normal menstrual pattern for the 3 months prior to study entry, and have taken hormonal contraceptives for at least 3 months prior to study entry;

         or

      ii. agree to use two adequate methods of birth control defined as: intrauterine device plus a barrier method (diaphragm plus spermicide, condom used by partner, vasectomized partner, or contraceptive sponge) or use 2 adequate barrier methods (condom use by partner or vasectomized partner plus diaphragm and spermicide);

         or

      iii. must be using another medically acceptable method of contraception and agrees to

continue with the same method during the study; and

d) have a negative serum pregnancy test (serum beta-human chorionic gonadotropin [hCG]) result 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.

There are no male contraceptive requirements.

7.3.2 Exclusion Criteria

Any of the following will exclude a patient from enrolling in this study:

1. ABSSSI of the following categories:

   a) Severely impaired arterial blood supply such that amputation of the infected anatomical site is likely,

   b) Infected diabetic foot ulcers

   c) Infected decubitus ulcers,

   d) Infected human or animal bites (insect bites that cause an infection are permitted),

   e) Necrotizing fasciitis or gangrene,

   f) Uncomplicated skin or skin structure infection (eg, simple abscesses, folliculitis, impetigo, furunculosis, or superficial cellulitis),

   g) Recurrent cellulitis treated with oral suppressive therapy,

   h) Self-limiting infections such as isolated folliculitis or other infection that has a high surgical incision cure rate or furunculosis or carbunculosis that is not associated with a cellulitis at least 1 cm in radius,

   i) Skin and/or skin structure infection that can be treated by surgery alone,

   j) Infections associated with a prosthetic device (ie, suspected or confirmed prosthetic joint infection), and

   k) Suspected or confirmed osteomyelitis or septic arthritis

2. Known or suspected concurrent infection or conditions requiring systemic anti-microbial treatment, prophylaxis, or suppression therapy;

3. Known or suspected human immunodeficiency virus (HIV)-infected patients with a cluster of differentiation (CD4) count <200 cells/mm^3 recorded in the last 30 to 60 days;

4. Absolute neutrophil count (ANC) <500 cells/mm^3;

5. Organ transplant within the preceding 6 months;

6. Received more than one dose of a short-acting (i.e., q12h dosing or less) systemic antibiotic(s)

active against Gram-positive pathogens (Appendix F) within the last 7 days, unless there is documented evidence of treatment failure OR demonstrated resistance of Gram-positive pathogens to the prior antibiotic therapy (antibiotics given for surgical prophylaxis are not included in this). Note that patients with prior short-acting systemic antibiotic(s) (i.e., q12h dosing or less) should not comprise >25% of the clinical trial population;

7. ABSSSI suspected or documented as being exclusively due to Gram-negative or anaerobic organisms based on epidemiological grounds or on direct examination of a specimen with Gram stain (mixed ABSSSI in which both Gram-positive and Gram-negative pathogens are isolated may be enrolled if the clinician suspects that the predominant causative pathogen is a Gram-positive organism);

8. ABSSSI known or suspected to be due to a fungal, parasitic or viral infection;

9. Concomitant morbidity of such severity that the patient is likely to die or present with serious medical conditions within 30 days of study entry;

10. Known or suspected local or systemic hypersensitivity to trimethoprim, iclaprim, vancomycin, or related compounds;

11. Pregnant or lactating female;

12. Severe hepatic disease (Child-Pugh Class C) or known aspartate aminotransferase (AST) or alanine transaminase (ALT) >5 times the upper limit of normal and/or bilirubin >2 times the upper limit of normal;

13. Requirement for corticosteroids >20 mg/day prednisolone or equivalent, or received corticosteroids >20 mg per day prednisolone or equivalent in the past 3 days;

14. Cardiovascular conditions and treatments:

    a) Patients known to have congenital or sporadic syndromes of QTcF prolongation;

    b) Type I A or III anti-arrhythmic drugs;

    c) Nonsustained ventricular tachycardia (NSVT) defined as >10 consecutive ventricular beats at a rate of >120 beats per minute (bpm) with a duration of <30 seconds,

    d) Bradycardia (<40 bpm), and

    e) QT/QTcF interval outside the normal range defined as: QTcF >500 msec.

15. Clinically significant abnormal blood electrolyte levels, as defined below, <u>that cannot be corrected</u> prior to study inclusion:

    a) Potassium <3.0 mmol/L (after correction has been attempted), and/or

    b) Magnesium <0.5 mmol/L (1.2 mg/dL) (after correction has been attempted)

16. Previous enrollment in Study ICL-23-ABSSSI1 or Study ICL-24-ABSSSI2;

17. Receipt of any investigational agent or device within 30 days of study medication administration; or

18. Patient unable or unwilling to adhere to the study-designated procedures and restrictions.

7.3.3 Withdrawal of Patients

7.3.3.1 Replacement Procedures

Patients withdrawn from the study or prematurely discontinued from study medication treatment will not be replaced.

7.3.3.2 Withdrawal from study medication and termination of study participation

Reasons for withdrawal of study drug:

- Death of patient;
- Patient withdraws consent to participate in the study; and
- At the request of the investigator or the sponsor:
    - General or specific changes in the patient's condition that render him or her unacceptable for further treatment in the judgment of the investigator;
    - Patient noncompliance, defined as refusal or inability to adhere to the prescribed dosing and follow-up regimen.

Termination of study participation:

Patients must be withdrawn from the study if they withdraw consent to participate. They are not required to state their reasons for withdrawing consent.

Patients must have study treatment discontinued for any of the following reasons:

- Infection-related reasons:
    - Baseline bacteriological cultures of acceptable specimen(s) demonstrate exclusively Gram-negative pathogens and/or fungi (patients with no growth in their baseline cultures may continue if they are improving clinically);
    - Worsening of clinical signs and symptoms of ABSSSI during study medication treatment such that additional or alternative systemic antibacterial therapy is warranted;
    - Treatment with a prohibited concomitant antibiotic (Section 7.4.4.2);
    - Treatment with antibiotics other than those specified in the protocol;
    - Development of a confirmed concomitant infection that is not an ABSSSI such that additional or alternative systemic antibacterial treatment is warranted; and
    - Diagnosis of osteomyelitis made while the patient is receiving study medication.
    - A baseline blood culture that is growing a Gram-negative organism.
- Treatment-emergent cardiovascular abnormalities:
    - QTcF values that both exceed an absolute QTcF value of 520 msec and exceed the baseline QTcF value by >60 msec;

- Ventricular arrhythmia; and
- Requirement for Type IA or III anti-arrhythmic drugs.

- Treatment-emergent LFT abnormalities (see Section 7.6.2.6.4 for expected evaluations):
  - Patients who have confirmed AST or ALT elevations of > 5X ULN should be discontinued from study medication and followed through LFU for safety; and
  - Patients who have a bilirubin ≥ 2X ULN with an AST or ALT ≥ 3X ULN and with an alkaline phosphatase (ALP) < 2X ULN should be immediately discontinued from study medication and followed through LFU.

- Treatment-emergent acute kidney injury:
  - Patients who have a confirmed increase in serum creatinine (SCr) of 0.5 mg/dL from baseline, if SCr was normal at baseline, or (2) a 50% increase in SCr from baseline, if the upper limit of SCr was not normal at baseline. This does not apply to patients on hemodialysis, continuous renal replacement therapy (e.g., CVVH, CVVHD), or peritoneal dialysis [12].

7.3.3.3 Follow-up of Patients Prematurely Discontinued from the Study Treatment Regimen or Withdrawn from Study

If a patient must be discontinued from the study treatment prior to the EOT evaluation, premature termination procedures should be performed at the time of withdrawal and appropriate standard of care therapy instituted. The reason for discontinuation, if known, and the antibacterial therapy must be recorded on the case report form (CRF). All patients will be requested to return for the TOC visit irrespective of whether randomized study treatment is completed.

7.4 Treatment of Patients

7.4.1 Treatments Administered

7.4.1.1 Investigational product, dosage and mode of administration

Iclaprim will be administered at a dose of 80 mg in 500 mL normal saline, infused over 2 hours q12h for 5 to 14 days. A window of +/- 2 hours is acceptable.

Iclaprim must not be administered as a bolus injection, undiluted solution, intramuscular injection, or subcutaneous injection.

For subjects with moderate hepatic impairment (Child-Pugh Class B [Appendix E]), iclaprim will be administered at a dose of 40 mg in 500 mL normal saline, infused over 2 hours q12h for 5 to 14 days.

7.4.1.2 Reference therapy, dosage, and mode of administration

Vancomycin will be dosed as follows: 15 mg/kg body weight (to a maximum of 1750 mg; using actual body weight) in 500 mL normal saline infused over 2 hours for 5 to 14 days. Dosing interval will be every q12h, q24h, q48h, or based on daily levels based on creatinine clearance. Patients randomized to vancomycin who require dosing intervals of q24h, q48h, or dosed by daily level due to renal impairment will receive dummy infusions (normal saline) at 12 hour intervals when they are not to receive vancomycin.

Patients who are on intermittent hemodialysis will be dosed after dialysis based on their pre-hemodialysis level. Patients who are on continuous renal replacement therapy will be dosed q24h.

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. Trough levels should be drawn at Dose 5 for patients with normal renal function. For patients with renal impairment (creatinine clearance < 75 mL/min), the following table should be used for the initial dosing interval:

Table 2
Vancomycin Dosing Intervals Based on Renal Clearance

Creatinine Clearance (mL/min)	Dosing Interval (hours)
≥ 75	Q12H
50-74	Q12H
35-49	Q24H
25-34	Q48H
< 25	Dose by daily level
Intermittent Hemodialysis	Dose after dialysis
CRRT	Q24H
Abbreviations: CRRT = continuous renal replacement therapy; Q*n*H=every *n* hours	

Patients with a creatinine clearance ≥25 mL/min should have their vancomycin level checked with the 5th dose due to difficulty interpreting levels checked prior to achieving steady state.

For patients with a creatinine clearance < 25 mL/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.

See Appendix D for the vancomycin dosing nomogram.

7.4.2 Identity of Investigational Product

Generic name: Iclaprim

Trade name: Not applicable

Formulation: Two 5 mL ampule containing sterile concentrate for IV infusion

Concentration: 12.8 mg/mL iclaprim base (16.3 mg/mL iclaprim mesylate)

Manufacturer: Wulfing GmbH, Germany

7.4.2.1 Packaging and Labeling

Packaging and labeling will be performed by the sponsor in accordance with all local and federal legal and regulatory requirements.

7.4.2.2 Clinical Supplies Disclosure

The Interactive Phone and Web Response System (IXRS) should be used to unblind patients and to unmask drug identity. Drug identification information is to be unmasked ONLY if necessary for the welfare of the patient. Every effort should be made not to unblind the patient unless necessary. Any unblinding that occurs at the site must be documented.

7.4.2.3 Storage and Stability

Unopened ampoules of iclaprim should be stored at room temperature, below 25°C. Any unused contents of the opened ampoules must be discarded. The contents of the diluted solution for infusion may be stored

for up to 24 hours at room temperature. Until dispensed to the patients, the study medication will be stored in a securely locked area, accessible to authorized personnel only.

Vancomycin or allowed concomitant antibiotics must be prepared and stored in accordance with the manufacturer's specifications, separately from iclaprim.

7.4.2.4 Study Drug Accountability, Reconciliation, and Return

The sponsor will provide each investigator with sufficient amounts of the study medication. The investigator will confirm receipt of all batches of study medication in writing.

The investigator will administer the study medication only to patients enrolled in this study and according to the procedures in this study protocol. Each patient will be given only the study medication carrying his or her randomization number. Each administration of study medication will be documented in the electronic case report form (eCRF).

All supplies must be accounted for at the end of the study. The investigator’s unblinded designee must maintain accurate and adequate records, including dates; lot numbers; quantities received; individual usage, etc. The investigator’s designee must also return all unused supplies to the sponsor (or designee), noting the exact amount used in the study, regardless of whether the study was completed or terminated prematurely. At the time of return, the investigator’s unblinded designee must verify that all unused or partially used study medication supplies have been returned and that no remaining supplies are in the investigator's possession.

7.4.3 Method of Assigning Patients to Treatment Groups and Measures to Minimize/Avoid Bias

7.4.3.1 Randomization/Patient Identification

Once a signed and dated consent form and the patient’s medical history have been obtained, the inclusion and exclusion criteria have been met, appropriate information has been obtained (including demographics, such as age and gender, as well as creatinine value), a complete physical examination has been completed (including weight), the biological samples have been collected, and ECGs have been obtained, the patient will be assigned a patient number and drug assignment via a centralized randomization system (IXRS). Randomization will occur in a 1:1 ratio into 1 of the 2 treatment groups: fixed-dose iclaprim or weight-based vancomycin. The IXRS will calculate the weight-based vancomycin dose (including CrCL considerations).

As this is a double-blind study, all individuals except the unblinded pharmacist (and delegated unblinded staff) at the study site must remain blinded to the IV study therapy regimen. The unblinded pharmacist will access the IXRS and will receive open-labeled clinical supplies from Motif to prepare each dose of IV study therapy for each individual patient.

A single patient cannot be assigned more than 1 allocation number.

7.4.3.2 Blinding

This is a double-blind study (operating under in-house blinding procedures) in which the patient enrolled, the study investigator, study center personnel, and the sponsor will be blinded to which clinical material is received until all patients have completed the study, the data have been screened for completeness and accuracy, the database has been locked, and protocol violators have been identified. There will be an unblinded pharmacist (and delegated unblinded staff) at each study center who will prepare and account for the infusion bags of active study therapy according to guidelines provided in the pharmacy manual. Vancomycin weight-based dosing levels, as well as adjustments made during the study as a result of trough monitoring, will only be known to the unblinded study team. The unblinded pharmacist and his/her delegated staff will not be involved in any management or evaluation of the safety and efficacy parameters

in the patient. All study personnel involved with patient eligibility and evaluation of safety and efficacy outcomes, including the study coordinator(s), investigator, or subinvestigator(s), must not have access to the treatment group assignment or the preparation of the infusion.

Study blinding is employed to ensure the integrity of the data being collected. However, the safety of the patients participating in the study must not be compromised. If unblinding is urgently required to guide the immediate medical management of the patient, the investigator will be able to access the IXRS to determine the patient's treatment group assignment. The IXRS unmasking feature is intended to be used only in situations in which emergency unblinding of the patient (eg, knowledge of the exact treatment group required for treatment of a serious adverse experience) is deemed medically necessary. If any patient is unblinded prior to the completion of the study (either accidental unblinding or emergency unblinding for a serious adverse experience), the investigator must promptly contact the appropriate sponsor representative to document the circumstances on the appropriate eCRF.

Study medication accountability will be noted by the unblinded CRA during site visits and at study completion.

7.4.4 Prior and Concomitant Medications

Any medication the patient takes other than study medications is considered a concomitant medication. All concomitant medications (except parenteral or enteral nutrition or IV solutions solely for the purpose of hydration or keeping the vein patent, and all nondrug therapy [surgeries, debridements, etc.]) must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: trade name, route of administration, dates of administration, dosage, and indication.

At baseline, patients will be asked what medications they have taken during the previous 30 days. From first dose to TOC, patients will be asked what concomitant medications they are currently taking or changes since their previous study visit.

7.4.4.1 Permitted

Aztreonam and metronidazole are allowed concomitant antibiotics at the discretion of the investigator. No synergism or antagonism has been observed with these antibiotics and iclaprim or vancomycin. They must be used in compliance with their respective package insert. For patients in whom Gram staining of culturable material or cultures indicates that Gram-negative coverage is required, and for patients in whom anaerobic pathogens are suspected or confirmed as pathogens at the infected site, aztreonam and metronidazole may be administered, respectively. Treatment with these agents should be continued for at least 5 days and should not be required for longer than the treatment duration of study medication.

The use of aztreonam therapy was selected because it has activity against a wide spectrum of Gram-negative aerobic bacteria without cross-coverage of Gram-positive pathogens and provides, in combination with iclaprim or vancomycin, adequate empirical coverage for common aerobic Gram-positive, and Gram-negative pathogens associated with ABSSSI. Please refer to the country-specific package insert for recommendations about aztreonam dosing.

Metronidazole was selected as a permitted concomitant antibiotic therapy because it has activity against anaerobic bacteria without cross-coverage of aerobic Gram-positive pathogens. The investigator has the discretion to determine if IV or p.o. metronidazole is administered. Please refer to the country-specific package insert for recommendations about metronidazole dosing.

No other systemic antibiotics or topical antibiotics at the site of the ABSSSI under investigation may be used.

In the event of suspected *Clostridium dificile* colitis, vancomycin may be administered orally.

Hormonal contraceptives for female patients are permitted.

7.4.4.2 Prohibited

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.

7.4.5 Treatment Compliance

Records of study medication used, dosages administered, and intervals between visits will be maintained during the study. Study medication accountability will be noted by the unblinded CRA during site visits and at study completion.

7.5 Study Procedures

7.5.1 Schedule of Study Procedures

A schedule of procedures and assessments to take place during the study is shown in Table 3.

Table 3: Schedule of Study Procedures

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 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 [eg, 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 (ie, all EOT evaluations should be performed on the last day [+2 days] of drug dose).

[14] If clinically indicated (ie, 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, l 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 creatinine clearance < 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 creatinine clearance ≥25 mL/min should have their vancomycin level checked with the 5^{th} dose due to difficulty interpreting levels checked prior to achieving steady state.

7.5.2 Screening Procedures

7.5.2.1 Baseline/screening/randomization (Visit 1)

The following procedures will be performed during the baseline visit, within 24 hours of study entry (first dose of study drug):

- Obtain informed consent;
- Record medical history (pre-existing conditions);
- Prior medications (within the preceding 30 days)
- Verify inclusion and exclusion criteria;
- Perform complete physical examination, including vital signs (includes determination of body temperature), height, weight, and a review by body systems;
- Assess clinical signs and symptoms of ABSSSI; including photography (procedure outlined in Appendix B). 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 [eg, 300 DPI]. Skin infection measurements will be provided in cm^2;
- Assess AEs;
- Estimate CrCL;
- LFT safety assessment;
- C-reactive protein (CRP) assessment;
- Obtain blood and urine samples for clinical chemistry, hematology, and UA;
- 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;
- Obtain two sets of blood cultures (aerobic and anaerobic) 10 minutes apart from two separate peripheral sites;
- Perform and assess 12-lead ECG (3 ECGs at least 1 minute apart);
- Obtain sample for culture from infection site. 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;
- Obtain anti-streptolysin O (ASO) antibody titers; and

- Contact the central randomization system to enroll the patient and receive blinded assignment of patient number and study arm allocation:
    - Contact the central randomization system to enroll the patient
    - Principal Investigator, Study Coordinator or designee may enter and randomize
    - Unblinded pharmacist or designee is the only individual who may access treatment assignment and prepare study infusions

7.5.3 Treatment Period Procedures

A window of +/- 2 hours is acceptable for infusion of study medication.

7.5.3.1 Study treatment period from 5 to 14 days

7.5.3.1.1 Daily assessments until ETP (Visit 2)

During the initial 48 to 72 hours of treatment, a V2 assessment will be performed daily which includes the following:

- Record concomitant medications;
- Perform limited physical exam, including vital signs (includes determination of body temperature) and excluding weight and height;
- Assess clinical signs and symptoms of ABSSSI without digital photography. 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;
- Assess AEs;
- Record any significant procedures performed that require surgical intervention (incision and drainage, amputation, suture removal, etc. [debridement and incisions at bedside are permitted]);
- LFT safety assessment;
- 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;
- Study medication administration
- Blood samples for PK should be obtained on the first day of treatment before the start of first study medication infusion and 5 to 15 minutes, l to 3 hours, and 5 to 7 hours after the infusion; and
- Perform and assess12-lead ECG (3 ECGs at least 1 minute apart) before the start of first study medication infusion and within 10 minutes of the end of the first study medication infusion on Day l.
- For vancomycin patients with a creatinine clearance < 25mL/min, a daily trough level should be obtained and the unblinded team should monitor and re-dose the patient when that level is below

20 mg/L.

7.5.3.1.2 Early timepoint (Visit 3)

Between 48 and 72 hours from first dose, an ETP visit should be performed and should include:

- Record concomitant medications;
- Perform limited physical exam, including vital signs (includes determination of body temperature) and excluding weight and height;
- Assess clinical signs and symptoms of ABSSSI; including photography (procedure outlined in Appendix B). 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 [eg, 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;
- Assess AEs;
- Record any significant procedures performed that require surgical intervention (incision and drainage, amputation, suture removal, etc. [debridement and incisions at bedside are permitted]);
- LFT safety assessment;
- CRP assessment;
- Obtain blood and urine samples for clinical chemistry, hematology, and UA;
- 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;
- Study medication administration;
- PK blood sample (before the start of study medication infusion and 5 to 15 minutes, l to 3 hours, and 5 to 7 hours after the infusion);
- Perform and assess 12-lead ECG (3 ECGs at least 1 minute apart) before the start of study medication infusion and within 10 minutes of the end of the study medication infusion; and
- Obtain sample for culture from infection site (if clinically feasible and if the patient has persistent clinical signs or symptoms).

7.5.3.1.3 Assessments until EOT every 48 to 72 hours (Visit 4)

During the patient's remaining time on therapy, the following V4 assessments should take place every 48 to 72 hours:

- Record concomitant medications;
- Perform limited physical exam, including vital signs (includes determination of body temperature) and excluding weight and height;
- Assess clinical signs and symptoms of ABSSSI without digital photography. 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;
- Assess AEs;
- Record any significant procedures performed that require surgical intervention (incision and drainage, amputation, suture removal, etc. [debridement and incisions at bedside are permitted]);
- Obtain blood and urine samples for clinical chemistry, hematology, and UA;
- 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; and
- Study medication administration. 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).
- Vancomycin patients with a creatinine clearance ≥25 mL/min should have their vancomycin level checked with the 5th dose due to difficulty interpreting levels checked prior to achieving steady state.

7.5.3.2 End of Therapy/Early Termination (Visit 5)

The following procedures will be performed on the last day of therapy (duration of therapy: minimum 5 days, maximum 14 days):

- Record concomitant medications;
- Perform limited physical examination, including vital signs (includes determination of body temperature) and excluding weight and height;
- Assess clinical signs and symptoms of ABSSSI; including photography (procedure outlined in Appendix B). 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 [eg, 300 DPI]. Skin infection measurements will be provided in cm^2.);
- Assess AEs;
- Record any significant procedures performed that require surgical intervention (incision and drainage, amputation, suture removal, etc. [debridement and incisions at bedside are permitted]);
- LFT safety assessment
- CRP assessment;

- Obtain blood and urine samples for clinical chemistry, hematology, and UA;
- Study medication administration if clinically indicated (ie, 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.);
- PK blood sample (before the start of study medication infusion and 5 to 15 minutes, l to 3 hours, and 5 to 7 hours after the infusion);
- Obtain sample for culture from infection site (if clinically feasible and if the patient has persistent clinical signs or symptoms); and
- Perform clinical efficacy assessment.

7.5.3.3 Test of Cure (Visit 6)

The following procedures will be performed at the TOC visit, 7 to 14 days post-EOT:

- Record concomitant medications;
- Perform limited physical examination, including vital signs (includes determination of body temperature) and excluding weight and height;
- Assess clinical signs and symptoms of ABSSSI; including photography (procedure outlined in Appendix B). 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 [eg, 300 DPI]. Skin infection measurements will be provided in cm^2.);
- Assess AEs;
- Record any significant procedures performed that require surgical intervention (incision and drainage, amputation, suture removal, etc. [debridement and incisions at bedside are permitted]);
- LFT safety assessment;
- CRP assessment;
- Obtain blood and urine samples for clinical chemistry, hematology, and UA;
- Obtain sample for culture from infection site (if clinically feasible and if the patient has persistent clinical signs or symptoms);
- Obtain ASO antibody titers; and
- Perform clinical efficacy assessment.

7.5.3.4 Late Follow-Up (phone call)

Late follow-up will be performed via a telephone call to the patient 28 to 32 days post-first dose.

- Assess AEs; and
- Documentation of Day 28 mortality.

Patients with high liver function tests and unresolved AEs at TOC will be required to come in for an additional visit at LFU. 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.

7.5.4 Procedures for Premature Discontinuation from the Study Treatment Regimen

All patients who discontinue early from the study medication must have an Early Termination Assessment. This assessment should take place as soon as possible after the patient stops taking study medication. The observations and procedures scheduled for EOT should be performed at the Early Termination Assessment.

7.6 Efficacy and Safety Variables

7.6.1 Efficacy Assessments

Table 4 displays a summary of all assessments.

Table 4: Summary of Assessments

Population	Definition	Analyses
ITT	All randomized patients	Primary efficacy analysis: Patients with early clinical response at ETP Secondary efficacy analyses: • Resolution or near resolution of ABSSSI at TOC • Resolution or near resolution of ABSSSI at EOT • Resolution or near resolution of ABSSSI at EOT and TOC among patients with severe infection at baseline • Time to resolution of signs and symptoms of ABSSSI
mITT	ITT with causative Gram-positive organism at baseline	Secondary efficacy analyses: • Supportive analysis of primary efficacy endpoint • Resolution or near resolution of ABSSSI at TOC • Resolution or near resolution of ABSSSI at EOT • Resolution or near resolution of ABSSSI at EOT and TOC among patients with severe infection at baseline • Time to resolution of signs and symptoms of ABSSSI • Pathogen-level bacteriological response rate at EOT and TOC • Patient-level bacteriological response rate at EOT and TOC
mCE	All patients excluded from the PP population only because they have received prohibited concomitant or preceding antibiotic therapy active against Gram-positive pathogens	Secondary efficacy analyses: • Supportive analysis of primary efficacy endpoint • Resolution or near resolution of ABSSSI at TOC • Resolution or near resolution of ABSSSI at EOT • Resolution or near resolution of ABSSSI at EOT and TOC among patients with severe infection at baseline • Time to resolution of signs and symptoms of ABSSSI • Pathogen-level bacteriological response rate at EOT and TOC • Patient-level bacteriological response rate at EOT and TOC
PP	ITT with ≥80% of planned doses + provide adequate data for assessment	Secondary efficacy analyses: • Supportive analysis of primary efficacy endpoint • Resolution or near resolution of ABSSSI at TOC • Resolution or near resolution of ABSSSI at EOT

		• Resolution or near resolution of ABSSSI at EOT and TOC among patients with severe infection at baseline • Time to resolution of signs and symptoms of ABSSSI
mPP	mITT with ≥80% of planned doses + provide adequate data for assessment	Secondary efficacy analyses: • Supportive analysis of primary efficacy endpoint • Resolution or near resolution of ABSSSI at TOC • Resolution or near resolution of ABSSSI at EOT • Resolution or near resolution of ABSSSI at EOT and TOC among patients with severe infection at baseline • Time to resolution of signs and symptoms of ABSSSI • Pathogen-level bacteriological response rate at EOT and TOC • Patient-level bacteriological response rate at EOT and TOC
Safety	All patients who received study drug	All safety analyses
Abbreviations: ABSSSI = acute bacterial skin and skin structure infection; EOT = End of Therapy; ETP = Early Timepoint; ITT = Intent-to-treat; mCE = modified clinically evaluable; mITT = Microbiological intent-to-treat; PP = Per-protocol population; mPP = Per-protocol microbiologically evaluable population; TOC = Test of Cure.		

7.6.1.1 Primary Efficacy Assessments

The primary efficacy endpoint will be 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) as measured by planimetric tracing (See Appendix C).

7.6.1.2 Secondary Efficacy Assessments

The secondary endpoints are resolution or near resolution of ABSSSI (ie, 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.

7.6.1.2.1 Clinical Assessment

The primary endpoint for clinical response (defined as the reduction in lesion size ≥20% compared to baseline) will be evaluated in all randomized patients at ETP (48 to 72 hours post-first dose). Patients who have died or who received rescue antibacterial therapy prior to that time will be included as treatment failures. In addition, clinical outcome will be evaluated by the investigator at EOT and TOC (7 to 14 days post-EOT). The assessments of clinical outcome will be 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 or recurrence of index infection; or

- Indeterminate: data inadequate for assessment of efficacy (there are no post-baseline local or systemic signs and symptoms data available to make this assessment [eg, 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, or death not attributed to the index ABSSSI or complication of ABSSSI.

7.6.1.2.2 Clinical Signs and Symptoms of Infection

Eight signs (tenderness to palpitation, erythema, edema, purulent drainage/discharge, fluctuance, induration, ulceration, and necrotic tissue) and 4 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).

7.6.1.2.3 Microbiology Assessment

An adequate clinical specimen for microbiologic evaluation (eg, pus from a wound or abscess, an aspirate or skin biopsy specimen from the leading edge of cellulitis) will be obtained at baseline prior to randomization. Additional clinical specimens will be obtained, if clinically feasible and if the patient has persistent clinical signs or symptoms, at ETP, EOT, and TOC. If the patient is discontinued from the study due to treatment failure, a clinical specimen will be obtained at that time. Specimens will be evaluated by the local microbiology laboratory; in addition, isolates will be subcultured and sent to a central microbiology laboratory for confirmation of pathogen identity and MICs

Two sets of blood samples for aerobic/anaerobic cultures 10 minutes apart from different sites peripherally will be obtained within 24 hours prior to the first dose of study drug. 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 at any Visit, 2 sets of aerobic/anaerobic blood cultures that are collected at different sites should be obtained 10 minutes apart. 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. Blood cultures from intravascular devices are not permitted. Any potential pathogen will be subcultured and the isolates shipped to the central laboratory. The data generated by the central laboratory will be used for the primary analysis. Anti-streptolysin O titers will also be taken within 24 hours of the start of treatment.

Microbiological 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. In patients with a Gram-positive pathogen isolated at baseline, microbiological response by patient will be determined at ETP, EOT, and TOC visits and categorized as eradication, presumed eradication (no material available for culture in clinically cured patients), persistence, presumed persistence (no material available for culture in patients who had clinical failure), indeterminate (those patients with clinical outcome of indeterminate), superinfection (ie, the emergence of a new isolate documented at the site of infection with worsening signs and symptoms of infection–identified after completion of therapy), or recurrent infection (pathogen that is different from baseline pathogen[s] is isolated).

The protocol for shipment of isolates from the local laboratory to the central laboratory, and details of the environmental conditions under which specimens and isolates will be stored, can be found in the

Laboratory Manual.

7.6.1.2.3.1 By-Pathogen Bacteriological Response

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).

7.6.1.2.3.2 By-Patient Bacteriological Response

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).

7.6.2 Safety Assessments

All patients who receive any study drug will be evaluated for safety on the basis of medical history and physical examinations, reports of clinical AEs, routine electrocardiography, and clinically significant

findings from routine liver function tests, serum chemistry, hematology, coagulation, and UA tests. All adverse events will be recorded throughout the study period, up to and including the LFU phone call. While blinded to treatment assignment, the investigator will categorize the severity of each AE and the potential for relationship to study drug. Serious AEs include those that were life threatening, led to prolongation of the existing hospitalization, a congenital anomaly/birth defect, or caused persistent or significant disability, incapacity, or death. Treatment-emergent AEs (TEAEs) will be defined as those that start or worsen in severity during or after the first dose of study drug administration through end of study.

The guidance for grading the severity of adverse events can be found in Appendix G.

7.6.2.1 Adverse Events

7.6.2.1.1 Definitions

The term "adverse event," as used by the sponsor, is synonymous with the term "adverse experience," which is used by the FDA.

An AE is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a human being participating in a clinical study with a sponsor test article, regardless of causal relationship. This includes the following:

- Any clinically significant worsening of a pre-existing condition.
- Note: Emergence of a new pathogen associated with a clinical event during therapy at a site other than the initial site of infection will be considered to be an AE.
- Any recurrence of a pre-existing condition.
- An AE occurring from overdose of a sponsor study drug whether accidental or intentional (ie, a dose higher than that prescribed by a health care professional for clinical reasons).
- An AE occurring from abuse of a sponsor study drug (ie, use for nonclinical reasons).
- An AE that has been associated with the discontinuation of the use of a sponsor study drug.

A procedure is not an AE, but the reason for a procedure may be an AE.

A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the patient signs the ICF. Pre-existing conditions will be recorded on the Medical History/Current Medical Conditions page of the eCRF.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a TEAE. An AE is considered to be treatment emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or (2) it is present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the last follow-up visit.

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms or require therapy, and are recorded on the AE page of the eCRF under the signs, symptoms, or diagnosis associated with them.

7.6.2.1.2 Reporting of Adverse Events

All AEs, including intercurrent illnesses, must be documented. Volunteered, observed, and elicited AEs will be recorded in the eCRF. This includes AEs the patient reports spontaneously, those the investigator observes, and those the patient reports in response to open-ended questions.

At each visit the investigator, or delegate, will determine whether or not any AEs have occurred. The patient will be questioned in a general way and no specific symptoms will be suggested. The patient will be asked an open-ended question such as, "How have you been feeling since your last study assessment/visit?"

All AEs, regardless of relationship to study medication, must be recorded in the patient's medical records and on the AE page(s) of the eCRF. If known, the diagnosis should be recorded, and the individual signs and symptoms should be listed. All AE entries should contain the date of onset; time of onset (if known); a brief description of the event; duration of event; severity; treatment required; relationship to study medication; action taken with regard to study medication; outcome; date and time of resolution (if applicable); and whether the event is classified as serious by the investigator. Each AE will be assessed by the investigator with regard to seriousness, severity, and relationship to study medication.

Adverse event reporting begins from the time of informed consent and ends at LFU.

7.6.2.1.3 Assessment of Severity

The severity of each AE must be assessed by the investigator and recorded in the eCRF as mild, moderate, or severe defined as the following:

- **Mild**: An AE that does not interfere with usual activities.
- **Moderate**: An AE that interferes with usual activities.
- **Severe**: An AE that is intense or debilitating and interferes with usual activities.

7.6.2.1.4 Relationship to Study Treatment

The relationship of each AE to study medication must be assessed and recorded by the investigator as not related, probably not related, probably related, and related.

- **Not related**: Clinical event with an incompatible time relationship to drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
- **Probably not related**: Clinical event whose time relationship to drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
- **Probably related**: Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.
- **Related**: Clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

7.6.2.1.5 Follow-up of Adverse Events

Patients with high LFTs and unresolved AEs at TOC must be seen in person for an additional visit at LFU. The investigator must continue to follow all non-serious AEs (and SAEs) until they resolve or until the investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

7.6.2.2 Serious Adverse Events

Each AE must be assessed and recorded in the eCRF as serious or not serious. Serious AEs must be reported as described in Section 7.6.2.2.2. International Conference on Harmonisation Guidelines and the Code of Federal Regulations (CFR; 21 CFR 312.32, revised as of 01 April 2014) define an SAE as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;

- A life-threatening adverse event;

- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events not considered to be SAEs are:

1. Clinical failure, which is the primary study endpoint/variable;
2. Routine treatment or monitoring of the studied indication not associated with any deterioration in condition;
3. Elective or preplanned treatment for a pre-existing condition that did not worsen; and
4. Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

7.6.2.2.1 Review of Serious Adverse Events

The investigator and the sponsor (or designee) will review each SAE report and evaluate the relationship of the SAE to study treatment. Based on the investigator's and sponsor's assessment of the SAE, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical study. If the discovery of a new SAE related to the study medication raises concern over the safety of continued administration of the study medication to patients, the sponsor will take immediate steps to notify the US FDA/other regulatory authorities and all investigators participating in clinical studies of the study medication.

Further action that may be required includes the following:

- Modification of the protocol;
- Discontinuation or suspension of the study;
- Modification of the existing consent form and informing current study participants of new findings;
- Addition of any newly identified study medication-related AEs to the list of expected AEs.

7.6.2.2.2 Reporting Serious Adverse Events

All SAEs, occurring after the signing of the ICF until LFU, and regardless of study drug relationship, must be reported by telephone to Covance within 24 hours of obtaining knowledge of the event. The caller's name and telephone number, as well as the name of the drug and study, should be recorded.

SAEs in **North America** - Covance Pharmacovigilance & Drug Safety Services (PV&DSS)

Telephone number – +1 888-724-4908
Fax number - +1 888-887-8097

SAEs in **Asian-Pacific** - Covance PV&DSS

Telephone number – +61 2 8879 2000
Fax number - +61 2 9888 8322

SAEs in **Europe & Middle East/Africa** - Covance PV&DSS

Telephone number – +44 1628 548000
Fax number - +44 1628 540028

SAEs in **Latin America** - Covance PV&DSS

Telephone number – +55 11 3750-3900
Fax numbers – Columbia – 01800 518 1218
Chile – 1230-020-5597

The site must also complete the Clinical Safety Event Report (CSER) Form and fax to Covance PV&DSS. The CSER Form will collect data surrounding the event, eg, the nature of the symptom(s), time of onset in relation to initiation of therapy, duration, intensity, and whether or not therapy was interrupted or discontinued. The investigator's assessment of the probable cause of the event will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic tests reports, and procedures as well as all pertinent medical information related to the event will also be collected.

Covance PV&DSS will forward SAE queries directly to the investigator requesting incomplete or missing information. It is the investigator's responsibility to be diligent in providing this information back to Covance PV&DSS as soon as it is available.

If event qualifies for expedited reporting (serious, related, or unexpected events), the CRO will submit a report to the FDA by Day 15. If the event is also fatal or life-threatening, the FDA will be notified by Day 7 via phone, fax, or email (note that the date of first receipt is considered to be Day 0). Expected safety reports will also be distributed to the investigators by Day 15.

Investigators will be notified by the CRO of all SAEs that require prompt submission to their IRB/IEC. Investigators should provide written documentation of IRB/IEC notification for each report to the CRO. The CRO will ensure that all SAEs are reported to the appropriate regulatory authorities. For sites using the central IRB, the CRO will submit reports to the central IRB on behalf of those sites.

7.6.2.2.3 Follow-up of Serious Adverse Events

The investigator must continue to follow all SAEs (and non-serious AEs) until they resolve or until the investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

7.6.2.3 Pregnancy

Pregnancy (of a female patient, or of a woman impregnated by a male patient during the study), although not itself an SAE, should be reported on a Clinical Pregnancy Report Form and be followed up to determine the outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities. Pregnancy follow-up should be done until the infant is at least 6 months of age.

7.6.2.4 Protocol Deviations due to an Emergency or Adverse Event

Departures from the protocol may occur in the event of an emergency. In such cases, the investigator or other physician in attendance must contact the CRO Medical Monitor as soon as possible to discuss the circumstances of the emergency. All protocol deviations and the reasons for such deviations must be reported accordingly.

7.6.2.5 Safety Laboratory Determinations

Investigative sites will use local laboratory results to confirm patient eligibility (inclusion/exclusion criteria). A central laboratory will receive samples for all safety laboratory evaluations as described in Table 3.

Procedures for the collection, preparation, and transportation of samples to the central laboratory for evaluation are detailed in the Laboratory Manual.

Although the results of these analyses will be provided to the respective investigators on a regular basis, investigators should use their local laboratories to generate data necessary for the routine management of the patient's medical conditions, since central laboratory results will not be available in a timely manner for patient management.

Clinical hematology and chemistry tests and UA will be performed on certain study days as shown in the Schedule of Study Procedures (Table 3). In addition, a serum or urine pregnancy test will be performed immediately prior to randomization for female patients of childbearing potential. (Patients who are pregnant will be excluded or withdrawn from the study. Patients who become pregnant during the study must inform the investigator and be withdrawn from study medication.)

Clinical hematology tests will include hematocrit, hemoglobin, red blood cell (RBC) count, WBC count, platelet count, and WBC differential including neutrophils, lymphocytes, monocytes, eosinophils, basophils, MCH, MCHC, MCV, and CRP.

Clinical chemistry tests will include creatinine, blood urea nitrogen (BUN), AST, ALT, ALP, gamma glutamyl transferase, lactate dehydrogenase, creatine phosphokinase, total bilirubin, albumin, total protein, glucose, sodium, potassium, chloride, and bicarbonate.

Urinalysis will include determination of pH, specific gravity, presence of blood, glucose, protein, ketones, and bile, and microscopic examination of sediment.

7.6.2.6 Vital Signs, Physical Examination, and Other Safety Evaluations

7.6.2.6.1 Vital Signs

Systolic and diastolic blood pressure, heart rate, and respiration rate will be assessed on each study visit.

7.6.2.6.2 Physical Examination

A complete physical examination, including vital signs (includes determination of body temperature), height, weight, and a review by body systems, will be conducted at baseline.

Limited physical examinations, including vital signs (includes determination of body temperature) and excluding weight and height, will be conducted at all post-baseline visits.

7.6.2.6.3 Electrocardiogram

Twelve-lead ECGs will be performed at screening, Day 1, and at ETP. On Day 1 and at ETP, the triplicate ECGs will be taken prior to study medication administration and within 10 minutes of the end of the first study medication dose. In addition, a 12-lead ECG will be performed at ETP within 10 minutes after the end of infusion, as specified in the Schedule of Study Procedures (Table 3).

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.

Fredericia's formula is as follows:

$$QTcF = QT / RR^{1/3}$$

All ECG recordings will be taken as triplicates at least 1 minute apart and the median QTcF value will be evaluated at the respective study site for exclusion criterion 15 (Section 7.3.2), for compliance with study protocol-defined procedures (see above) and safety.

Furthermore, all ECG tests will also be transmitted to, and electronically stored at, a central center specialized in the standardized evaluation of ECG tests. Procedures for performing ECG tests and subsequent transmission to and interpretation by the central ECG laboratory are detailed in the ECG Manual.

7.6.2.6.4 Liver Function Tests

Liver function tests will be taken at screening, and patients with severe hepatic disease (Child-Pugh Class C) or known AST or ALT >5 times the upper limit of normal and/or bilirubin >2 times the upper limit of normal will be excluded from the study. During the course of the study, liver function tests will also be taken at V2 visits, ETP, EOT, and TOC. Patients with high liver function tests at TOC will be required to come in for an additional visit at LFU. Blood samples will be obtained to document normalization.

For patients who meet 1 of the 2 LFT discontinuation criteria (Section 7.3.3.2), an appropriate evaluation of causes for the liver enzyme abnormalities should be initiated and the LFTs should be followed every 48-72 hours until normalization or stability. The following evaluations should be considered:

- History, including alcohol and other drugs of abuse;
- Clinical symptoms – RUQ pain, nausea etc.;
- Viral hepatitis serologies;
- Autoimmune hepatitis serologies;
- Concomitant medication review to eliminate possible heptatotoxic medications where possible;
- Ethanol and acetaminophen/paracetamol levels; and
- Abdominal ultrasound.

7.6.2.7 Reporting Safety Information

The investigator must promptly report to his or her IRB/IEC/ REB all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs associated, or possibly associated, with the use of the study medication.

7.7 Pharmacokinetic Analysis

Pharmacokinetic samples will be obtained from patients on 3 occasions: following the first dose of study medication, at ETP, and at EOT. After the study is complete, the database locked, and the data unblinded, patients randomized to iclaprim will have their samples assayed.

7.7.1 Collection and Handling of Samples

Pharmacokinetic blood samples (5 mL) for determination of iclaprim concentrations will be collected on Day 1, ETP and EOT at the following timepoints: before study medication infusion, and within 5 to 15 minutes, 1 to 3 hours, and 5 to 7 hours after the end of study medication infusion (see Table 3). Per patient, a total of 12 samples, for a total of 60 mL blood, will be obtained for PK analysis. All samples will be labeled to indicate the clinical study number, patient number, actual relative time after study medication administration, and sampling number. Processing, storage, and shipping instructions are provided in the pharmacy manual. Plasma concentrations of iclaprim will be measured by a validated liquid chromatography tandem mass spectrometric detection assay [16].

7.8 Data Handling and Record Keeping

7.8.1 Data Quality Assurance

Before study initiation, at a site initiation visit, or at an investigator's meeting, a sponsor representative will review the protocol and CRFs with the investigators and their staff. During the study, the CRA will visit the site regularly to check the completeness of patient records, the accuracy of entries in the CRFs, the adherence to the protocol and to GCP, the progress of enrollment, and also to ensure that study medication is being stored, dispensed, and accounted for according to specifications. Key study personnel should be available to assist the monitor during these visits.

Subsequently, information entered into the database is systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors, eg, simple spelling errors, will be corrected by Data Management personnel. Other errors or omissions will be entered on Data Query Forms, which will be returned to the investigational site for resolution. A copy of the signed Data Query Form is to be kept with the CRFs, and, once the original is received at the sponsor (or designee), the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be made after entering data from each visit.

When the database has been declared to be complete and accurate, the database will be locked and unblinded. Any changes to the database after that time can only be made by joint written agreement among the Clinical Study Leader, the Study Statistician, and the Data Manager.

Further details are defined in the separate guidelines for data entry and data management personnel.

7.8.2 Case Report Forms and Source Documentations

Investigators must enter the information required by the protocol onto the CRFs in accordance with procedures described in the pharmacy manual.

The investigator must complete the CRFs and transmit the data as instructed by the sponsor (or designee) and must store a copy of the source documents with other study documents, eg, the protocol, the investigators' brochure, and any protocol amendments, in a secure place. All entries to the CRFs must be made as described in the CRF Completion Guideline or as instructed by the sponsor (or designee) at study initiation.

Patient data collected within the eCRFs during the study will be documented in an anonymous fashion and the patient will only be identified by the patient number, and by his/her birth date if also required. If, as an

exception, it is necessary for safety or regulatory reasons to identify the patient, both the sponsor (or designee) and the investigator are bound to keep this information confidential.

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, ECG tests, etc., and keep a copy of the signed ICF. All information on CRFs must be traceable to these source documents kept in the patient's file.

7.8.3 Direct Access to Source Data

The investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the patients will leave the study site. Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

The FDA or other regulatory authority, the IRB/IEC/REB, and/or the sponsor's Clinical Quality Assurance Group (or designate) may wish to perform source data checks and/or on-site audit inspections. Investigators and their institutions will provide direct access to source data and documents to these authorities. The investigator assures the sponsor of the necessary support at all times.

7.8.4 Archiving Study Records

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Motif Biosciences will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. IRB/IEC/REB approvals for the study protocol and all amendments;
2. All source documents and laboratory records;
3. eCRF copies;
4. Patients' ICFs (with study number and title of study);
5. FDA Form 1572 (as required); and
6. Any other pertinent study document.

7.9 Statistical Methods

The primary efficacy endpoint will be the proportion of 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 among all randomized patients (ITT population).

In general, statistical tests will be two-sided, and at the level of significance alpha = 0.05. The NI assessment will be made with a one-sided test at significance level of 0.025. Confidence intervals will be calculated at a 95% confidence level.

Continuous data will be summarized by treatment group using the number of patients in the analysis population (N), mean, standard deviation (SD), median and range and categorical data will be summarized by treatment group using N and percentage.

7.9.1 Determination of Sample Size

Using Farrington and Manning's method 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% non-inferiority 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% early clinical response rate at TOC in each group and a 10% NI bound delta, a sample size of 300 patients in the ITT population per treatment group is required for 82% power. If the initial endpoint of clinical response at ETP does not achieve statistical significance, no further statistical testing will be done.

A total of 600 patients will be randomized (approximately 300 per treatment group will be randomized).

7.9.2 Patient Populations Analyzed

Intent-to-treat (ITT) population — All randomized patients (primary population for efficacy analyses). Patients will be analyzed in treatment group to which they were randomized.

Microbiological intent-to-treat (mITT) population — All randomized patients who have a Gram-positive baseline bacterial pathogen identified as the cause of ABSSSI.

Modified clinically evaluable (mCE) population consists of all patients excluded from the PP population only because they have received prohibited concomitant or preceding antibiotic therapy active against Gram-positive pathogens.

PP population — ITT patients who receive at least 80% of their planned doses and provide adequate data for assessment for each of the following timepoints: ETP, EOT, and TOC. This excludes patients with Gram-negative bloodstream infections who were discontinued in order to treat the Gram-negative pathogen.

PP microbiologically evaluable population (mPP) — mITT patients who receive at least 80% of their planned doses and provide adequate data for assessment for each of the following timepoints: ETP, EOT, and TOC.

Safety population — All patients who receive any study drug during the trial (primary population for safety analyses). Patients will be analyzed according to the treatment they received.

7.9.3 Efficacy Analysis

7.9.3.1 Primary Efficacy Outcome Measures

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

7.9.3.2 Secondary Efficacy Outcome Measures

The primary NI efficacy analysis will be repeated in the mITT, mCE, the Per Protocol, and the mPP populations as secondary outcomes.

The secondary endpoints are:

1. Resolution or near resolution of ABSSSI (ie, 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, mCE, PP, and mPP populations

2. Resolution or near resolution (≥90%) of ABSSSI at EOT for ITT, mITT, mCE, PP, 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, mCE, PP, 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

7.9.4 Safety Analysis

All patients who received any amount of iclaprim or vancomycin during the trial will be evaluated for safety.

Safety evaluation include incidence of TEAEs, laboratory test results (including liver function tests), vital signs, ECG results, and physical examination findings. All summaries of safety data will be based on the safety population (all treated patients). No formal statistical analysis of the safety data will be performed.

Summary tables will be provided for all AEs by treatment group. The incidence of AEs, related AEs, SAEs, and AEs leading to discontinuation of the study treatment will be presented by Medical Dictionary for Regulatory Activities system organ class (SOC) and preferred term. In addition, the incidence of AEs by severity will be presented by SOC and preferred term.

The AE summary tables will include counts of patients. Therefore, if a patient experiences more than one episode of a particular AE, the patient will be counted only once for that event. If a patient has more than one AE that is coded to the same preferred term, the patient will be counted only once for that preferred term. Similarly, if a patient has more than one AE within a SOC, the patient will be counted only once in that SOC.

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, SD for mean and standard error for mean change, minimum, median, maximum, and number and percent of patients within specified categories). Shift tables (ie, 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. 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.

Descriptive statistics of vital signs and ECG results at each visit will be presented by treatment group. Physical examination findings will be listed for each patient.

7.9.5 Population Pharmacokinetics

Iclaprim plasma concentrations will be used to determine population PK parameters, including C_{max}, AUC to infinity ($AUC_{0-\infty}$), clearance, and volume of distribution. Interindividual variability (IIV) will be determined for PK parameters, as well as residual variability. 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 detailed in a separate population PK analysis plan.

7.9.6 Interim Analysis

When 75% of the randomized patients have undergone the 48- to 72-hour (ETP) response assessment, the sponsor will do a blinded interim analysis to estimate the percentage of patients in the study who classify as having a reduction in the lesion size ≥20% compared to baseline at the 48- to 72-hour visit. Based on the observed overall percentage, 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. RISKS AND BENEFITS

The combined data set from the Phase 3 studies indicated that iclaprim has similar efficacy in the treatment of patients with cSSSI when compared with linezolid. Both iclaprim and linezolid were associated with high clinical cure and bacteriological response rates.

Iclaprim was well tolerated. Results from the Phase 3 clinical studies indicated that administration of iclaprim led to a mean increase of the QTc interval of about 5 to 6 msec more than linezolid, whereas the latter is considered as having no QTc prolonging effect.

The Phase 2 study indicated that iclaprim has similar efficacy in the treatment of patients with cSSSI when compared with vancomycin. The two iclaprim (0.8 and 1.6 mg base per kg body weight) and vancomycin study arms were associated with high clinical cure and bacteriological response rates.

Both doses of iclaprim were well tolerated; however, AEs and shifts from normal baseline in laboratory parameters were recorded somewhat more frequently in the iclaprim 1.6 mg/kg group.

Phase 1 studies to examine the effect of iclaprim on QTc interval have indicated that doses up to 1.6 mg/kg b.i.d. are considered safe for clinical use.

Iclaprim has the potential to be a new antibacterial agent active against Gram-positive drug-resistant strains, with a good safety profile, and therefore should be further studied in larger patient populations.

9. INVESTIGATORS REGULATORY OBLIGATIONS

9.1 Prestudy Documentation

The investigator must provide the sponsor with the following documents BEFORE enrolling any patients:

1. Completed and signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53[c]).
2. All applicable country-specific regulatory forms.
3. Current signed and dated curricula vitae for the investigator, subinvestigators, and all key personnel listed on the clinical study information form.
4. Copy of the IRB/IEC/REB approval letter for the protocol and informed consent. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC/REB must also be provided to the sponsor. Any changes in this study or unanticipated problems involving risks to the patients must be reported promptly to the IRB/IEC/REB. An investigator must not make any changes in the study without IRB/IEC/REB and sponsor approval except when necessary to eliminate apparent immediate hazards to the patients. All protocol amendments must be submitted to the IRB/IEC/REB and approved.
5. Copy of the IRB/IEC/REB-approved informed consent form (ICF) to be used.
6. When applicable, a list of the IRB/IEC/REB members and their qualifications, and a description of the committee's working procedure.
7. Copy of the protocol signature page signed by the investigator.
8. Fully executed clinical study agreement (CSA).
9. A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the Statement of Investigator form. The sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.

9.2 Electronic Data Capture

1. All data will be entered into an electronic data capture (EDC) system or eCRF.
2. Sponsor designees will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the data. The designee will ensure that corrections are made to the eCRFs and that queries are resolved in a timely manner by the study staff.
3. The eCRFs and other pertinent electronic records will be transmitted to the sponsor periodically during and/or at completion or termination of the study.
4. The investigator also must submit all incomplete EDC records that document patient experience with the study drug, including retrievable data on patients who withdraw before completion of the study.

Results of central safety laboratory results will be transmitted monthly to the EDC vendor. At the conclusion of the study all data will be delivered to the sponsor.

9.3 Adverse Event Reporting

The investigator agrees to report all AEs to the sponsor as described in the Adverse Events section (Section 7.6.2.1.2). Furthermore, the investigator is responsible for ensuring that any subinvestigator promptly brings AEs to the attention of the investigator. If applicable, the investigator also is responsible for informing the participating IRB/IEC/REB of any SAEs.

9.4 Review of Source Records

The investigator agrees that qualified representatives of the sponsor and regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Patients will not be identified by name on any of the study documents or samples retained by the sponsor for their analysis, and confidentiality of

information in medical records will be preserved. The confidentiality of the patient will be maintained unless disclosure is required by regulations. Accordingly, the following statement (or similar statement) will be included in the informed consent document:

> "Representatives of regulatory agencies, IRBs/IECs, the sponsor, and your personal physician may review your medical records and all information related to this study as permitted by law."

9.5 Monitoring of the Study

A Study Monitor from Covance Late Stage Development Services will be responsible for monitoring this clinical trial. The Study Monitor will monitor the study conduct, proper eCRFs completion, and source documentation completion and retention, and accurate study drug accountability. To this end, the Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Study Monitor have access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Study Monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The investigator and investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

9.6 Protocol Amendments

There will be no alterations in the protocol without agreement between the sponsor and the investigator. There will be no alterations in the protocol affecting patient safety without the express written approval of the sponsor, investigator, and the IRB/IEC/REB.

A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB/IEC/REB within 5 working days, and submitted to the appropriate regulatory agency in the required time frame.

9.7 Investigator Meeting

Prior to the start of the clinical study, the representative(s) of the sponsor will meet with the investigator(s) and appropriate clinical staff to familiarize the investigator and clinical staff with the materials necessary for conducting the clinical study.

9.8 Change in Investigator

If any investigator retires, relocates, or otherwise withdraws from conducting a study, the responsibility for maintaining records may be transferred to the sponsor, IRB/IEC/REB, or another investigator. The sponsor must be notified of and agree to the change. Regulatory agencies will be notified with the appropriate documentation. An updated Form FDA 1572 will be filed with the sponsor for any changes in the study personnel reported in the current Form FDA 1572.

9.9 Termination of the Study

If the investigator or the CRO Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, he or she must notify the sponsor (or designee) immediately. The sponsor and Medical Monitor will consult to determine whether termination of the study is necessary. The study may also be terminated early at the sponsor's discretion in the absence of such a finding. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the investigator to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements.

- A decision on the part of the sponsor to suspend or discontinue development of iclaprim.

In the case of study termination, all efforts should be made to conduct an Early Termination Assessment and follow-up of AEs as described in Section 7.5.4.

9.10 Final Study Report

A clinical study report will be written to describe the results of this clinical trial. Before any data from this study are published on the initiative of investigator, a manuscript will be sent to the sponsor for review and approval at least 30 days prior to submission to the publisher. The sponsor holds all publication rights to the data obtained from this study.

9.11 Confidentiality

All unpublished information that the sponsor gives to the investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the sponsor.

When the sponsor generates reports for presentations to regulatory agencies, one or more of the investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

The investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the sponsor unless otherwise specified in the CSA.

9.12 Records Retention

All primary data, or copies thereof (eg, laboratory records, eCRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the Covance archives.

The results from screening and data collected during the study will be recorded in the eCRFs and/or source documents, as appropriate, for each patient. To maintain confidentiality, the patients will be identified by numbers and/or initials on the eCRFs.

The completed, signed eCRFs will be transferred to the sponsor or designee. The signature of the investigator (including electronic signature, as appropriate) will designate the investigator's review of the eCRFs. All source documents, records, and reports will be retained by the Covance Late Stage Development Services in accordance with 21 CFR 312.62(c).

9.13 Publications

If on completion of the study the data warrant publication, the investigator may publish the results in recognized (refereed) scientific journals patient to the provisions of the CSA. Unless otherwise specified in the CSA, the following process shall occur:

The institution and investigator shall not publish or present data from an individual study center until the complete multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the investigator expects to participate in the publication of data generated from this site, the institution and investigator shall submit reports, abstracts, manuscripts and/or other presentation materials to the sponsor for review before submission for publication or presentation. The sponsor shall have 60 days to respond with any requested revisions, including without limitation, the deletion of confidential information. The investigator shall act in good faith upon requested revisions, except the investigator shall delete any confidential information from such proposed publications. The investigator shall delay submission of such

publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

9.14 Patient Injury

In general, if a patient is injured as a direct result of the study drug, the sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the patient's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the trial is taking place require additional payment of expenses, the sponsor shall comply with such law or regulation. Where applicable, the sponsor has taken specific national insurance.

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11. APPENDICES

APPENDIX A – CLINICAL LABORATORY EVALUATIONS

The following clinical laboratory evaluations will be performed:

Chemistry [Fasted] (Chem-20):	**Hematology (CBC):**
Albumin	Hematocrit
ALP	Hemoglobin
ALT	MCH
AST	MCHC
BUN	MCV
Chloride	Platelet count
Creatinine	Red blood cell count
GGT	White blood cell count
Glucose	White blood cell differential
LDH	(% & ABS):
Potassium	Basophils
Sodium	Eosinophils
Total Bilirubin	Lymphocytes
Total CO_2 (measured as bicarbonate)	Monocytes
Total Protein	Neutrophils
CPK	CRP
Complete Urinalysis (UA):	**For females of childbearing potential:**
pH and specific gravity	Serum Pregnancy Test
Glucose	Urine Pregnancy Test (alternative until serum pregnancy test results are verified)
Ketones	
Occult blood	
Protein	
Microscopic examination of sediment (including RBCs and WBCs)	
Bilirubin/urobilinogen	

APPENDIX B – DIGITAL PHOTOGRAPHIC PROCEDURES

SERIAL PHOTOGRAPHIC DOCUMENTATION OF INFECTION SITES

Locations:

ID card and color card:	2 each
Anatomical view of the infection site(s):	2 each

Equipment:

Canon EOS D-SLR w/ Ranging Lights

Color Card/Patient ID Holder

Standardized Background Material

Procedures:

In these clinical photographs, for the duration of the study, the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (clothing, jewelry, bandages, etc.) is to be eliminated from the photographic field from the entry visit through the final visit. The necessity of good photos (taken at baseline, ETP, EOT, and TOC) should be stressed to the patients to ensure their cooperation. Lighting, framing, exposure and reproduction ratios must be held constant. In the end, the pictures should read like a time-lapse movie.

1. The supplied equipment is to be used exclusively for this study. No modification, adjustments, or repairs of the camera equipment is to be undertaken without the expressed instruction of Canfield Scientific, Inc.

2. The supplied standardized background material is to be used. Folded or wrinkled material is not allowed.

3. Magnification: the ranging lights on the macro ring flash are set to predefined distance to ensure consistency of reproduction ratio. Once the two lights converge as one, the target image is at the correct distance. If there is any doubt as to the correctness of photographic technique, a re-shoot is encouraged at that time.

4. Each photographic session includes an exposure series of:

    a. Patient ID, which will include the following legible information in black indelible ink. (2 exposures)

        Protocol No.

        Image Date

        Center Number

        Visit Name

        Patient Initials

Patient ID Number

Photographer's Initials

Color Card

b. Anatomical view of the patient's infection site (2 exposures)

5. A secure, validated, and compliant web server set up at Canfield is used for secure transfer of study images by study sites. Images are to be transferred the day recorded. Remote access to all images by the Sponsor is also provided. Only approved individuals by Sponsor have access to the website.

   Canfield is to provide each study site with the necessary hardware, consumables and instructions to acquire consistent serial imaging. Technical support is available as needed.

6. All supplied photographic equipment and photographic originals remain the property of the Sponsor. Any questions or problems regarding the photographic portion of this protocol are to be forwarded to the Project Manager at Canfield Scientific.

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APPENDIX C – TRACING & PLANIMETRY PROCEDURES

The following procedures are to be followed to ensure accurate area measurements are achieved at each visit during the study.

Standard Supplies

Tracing Media:	Sterilized double layer clear plastic acetate tracing film with cardboard backer
Tracing Pens:	Itoya FinePoint, permanent ink, 0.5mm
Tracing Envelope:	Preprinted protective envelope for shipping

1. Tracings of ABSSSI site are conducted at: baseline, ETP, EOT, and TOC.
2. All required patient demographic information is to be recorded on tracing film header. Both films are to be peeled away from the cardboard backer and placed face-up over the patient's infection site. Tracing of the infection site is to be accomplished with the supplied Itoya tracing pen using a continuous stroke.
3. The traced edge must be dark and continuous with no broken ink line.
4. The following ABSSSI demarcations are made:
    a. Erythema (red pen)
    b. Induration (green pen)
    c. Wound (black pen), if necessary
5. The top film is to be peeled from the bottom film and placed back onto the cardboard backer. The bottom film that came into contact with the infection site is to be discarded as biomedical waste at the study site.
6. The top film containing the actual tracing and header information is to be attached to the "waxy" side of the cardboard backer.
7. The tracing is scanned on a supplied flatbed scanner and the scan uploaded to Canfield's secure website for instant image analysis.
8. The Canfield planimetry application automatically detects the outlines of each of the colored demarcations contained on the tracing, and measures each demarcation for area (cm^2).
9. A QC technician performs quality control of the detection and data generated.

APPENDIX D – VANCOMYCIN DOSING NOMOGRAM

Both iclaprim and vancomycin will be diluted in 500 mL of normal saline and infused over 2 hours. Dosing interval for iclaprim will be q12h. Dosing interval for vancomycin will be every q12h, q24h, q48h, or dosed by daily level based on creatinine clearance. Patients randomized to vancomycin who require dosing intervals of q24h, q48h, or dosed by daily level due to renal impairment will receive dummy infusions (normal saline) at 12 hour intervals when they are not to receive vancomycin.

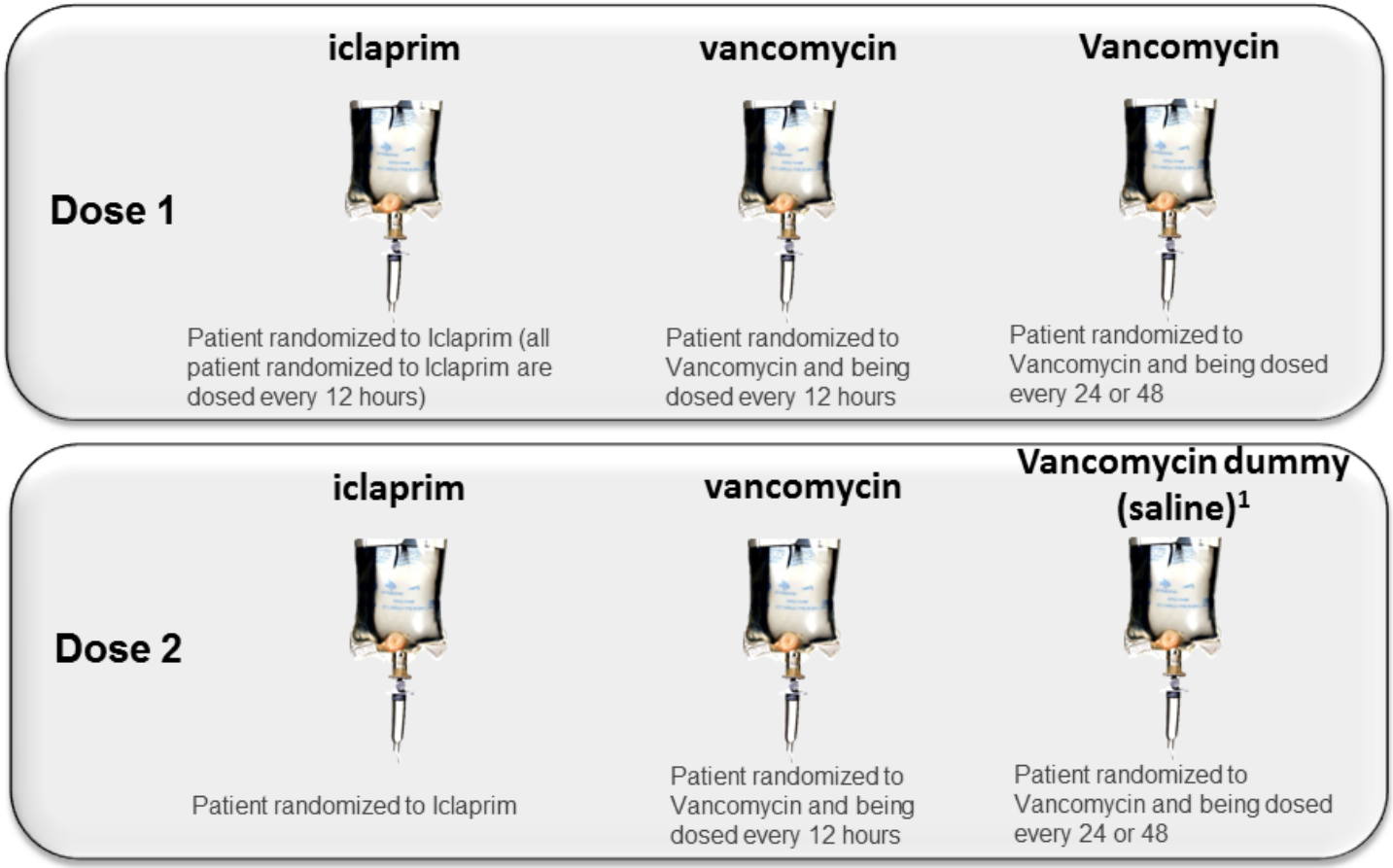
Intervals based on renal clearance [11]:

Creatinine Clearance (mL/min)	Dosing Interval (hours)
≥ 75	Q12H
50-74	Q12H
35-49	Q24H
25-34	Q48H
< 25	Dose by daily level
Intermittent Hemodialysis	Dose after dialysis
CRRT	Q24H
Abbreviations: CRRT = continuous renal replacement therapy; Q*n*H=every *n* hours	

Cockcroft -Gault equation based on actual body weight [17]:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{wt (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} (\times 0.85 \text{ for females})$$

Sample dosing sequence to maintain blind for different dosing intervals



[1] Patients randomized to vancomycin who require dosing intervals of q24h, q48h, or dosed by daily level due to renal impairment will receive dummy infusions (normal saline) at 12 hour intervals when they are not to receive vancomycin.

APPENDIX E – CHILD-PUGH SCORING SYSTEM

Child-Pugh Scoring System [18, 19]:

	Severity Score		
Clinical Marker	**1 point**	**2 points**	**3 points**
Bilirubin (mg/dL)	1-2	2.1-3	≥3.1
Albumin (g/dL)	≥3.5	2.8-3.4	≤2.7
Prothrombin Time *Or* INR	1-4 <1.7	4.1-6 1.7-2.3	≥6.1 >2.3
Ascites	None	Mild	Moderate
Encephalopathy	None	1 or 2	3 or 4
Grade A = 5 to 6 points Grade B = 7 to 9 points Grade C = 10 to 15 points			

APPENDIX F – SHORT-ACTING SYSTEMIC ANTIBIOTICS ACTIVE AGAINST GRAM-POSITIVE PATHOGENS

A short acting systemic antibiotic is defined as an antibiotic dosed q12h or less.

The following is a list of short-acting systemic antibiotics active against Gram-positive pathogens [20,21]:

- Amoxicillin
- Amoxicillin-clavulanate potassium
- Ampicillin
- Ampicillin/sulbactam
- Cefadroxil
- Ceftaroline
- Cefazolin
- Cefepime
- Cefprozil
- Ceftazidime
- Cefuroxime axetil
- Cephalexin
- Ciprofloxacin
- Clarithromycin
- Clindamycin
- Doxycycline
- Linezolid
- Meropenem
- Minocycline
- Nafcillin
- Norfloxacin
- Ofloxacin
- Penicillin
- Piperacillin/ tazobactam
- Trimethorpim-sulfamethoxazole
- Trimethoprim

APPENDIX G – TABLE FOR GRADING THE SEVERITY OF LABORATORY ADVERSE EVENTS

Table for Grading the Severity of Laboratory Adverse Events [22]:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Absolute neutrophil count (ANC)	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin (Hgb)				
(HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *1.32 – 1.55 mmol/L*	7.5 – 8.4 g/dL *1.16 – 1.31 mmol/L*	6.50 – 7.4 g/dL *1.01 – 1.15 mmol/L*	< 6.5 g/dL *< 1.01 mmol/L*
(HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *1.55 – 1.69 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *0.39 – 0.53 mmol/L*	9.0 – 9.9 g/dL *1.40 – 1.54 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *0.54 – 0.68 mmol/L*	7.0 – 8.9 g/dL *1.09 – 1.39 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 0.69 mmol/L*	< 7.0 g/dL *< 1.09 mmol/L*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*
CHEMISTRIES	***Standard International Units are listed in italics***			
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Bicarbonate, serum, low	16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Calcium, serum, high (corrected for albumin)	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low (corrected for albumin)	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	> 6.1 mg/dL *> 1.53 mmol/L*
Cardiac troponin I (cTnI)	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, serum, low	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
LDL cholesterol (fasting)	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Magnesium, serum, low	1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
Potassium, serum, high	5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low	3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high	146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low	130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)	NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid	7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
URINALYSIS	***Standard International Units are listed in italics***			
Hematuria (microscopic)	6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random collection	1 +	2 – 3 +	4 +	NA
Proteinuria, 24 hour collection	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*

† Use age and sex appropriate values (e.g., bilirubin).