CLINICAL STUDY PROTOCOL

BPR-CS-008

Ceftobiprole medocaril

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

Protocol number/Version:	BPR-CS-008 / Version 6.0
Compound:	Ceftobiprole medocaril
Phase of development:	3
EudraCT number:	2017-001605-32
IND number:	64,407
Date:	11 July 2018
Project Physician:	[redacted]
Project Statistician:	[redacted]
Sponsor:	Basilea Pharmaceutica International Ltd Grenzacherstrasse 487 CH-4058 Basel/Switzerland Tel + 41 61 606 1111

SPONSOR SIGNATURES

Protocol Number/Version:	BPR-CS-008 / Version 6.0
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Name/Title	**Date**	**Signature**
[redacted] Project Physician		
[redacted] Project Statistician		

Protocol Synopsis

TITLE	A randomized, double-blind, multicenter study to establish the safety and efficacy of ceftobiprole medocaril compared with vancomycin plus aztreonam in the treatment of acute bacterial skin and skin structure infections
SPONSOR	Basilea Pharmaceutica International Ltd, Switzerland
STUDY PHASE	3
INDICATION	Acute bacterial skin and skin structure infections
U.S. IND NUMBER:	64,407
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OBJECTIVES

Primary objective

To demonstrate the non-inferiority of ceftobiprole to vancomycin plus aztreonam in patients with acute bacterial skin and skin structure infections (ABSSSIs) with respect to early clinical response based on percentage reduction in lesion size at 48–72 hours (h) after first treatment in the Intent-to-Treat (ITT) population.

Main secondary objective

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

Note: The primary and the main secondary objectives will be region-specific. The above primary and main secondary objectives are for submission to the US FDA; in the EU, the above main secondary objective will be the primary objective, and the primary objective listed above will be the main secondary objective. Two separate Statistical Analysis Plans (SAPs) will be prepared for submission to the FDA and the EMA to reflect the different primary and main secondary objectives in each region.

Other secondary objectives

To compare ceftobiprole with vancomycin plus aztreonam with respect to:

1. Early clinical response based on percentage reduction in lesion size at 48–72 h after first treatment (CE population).
2. Clinical response based on percentage reduction in lesion size at the end-of-treatment (EOT) and TOC visits (ITT and CE population).
3. Sustained reduction in lesion size at the EOT and TOC visits (ITT population).
4. Investigator-assessed clinical success evaluated at 48–72 h after first treatment and the EOT visit, and sustained clinical success at the last follow-up (LFU) visit (ITT and CE populations).
5. All-cause mortality through Day 28 (±2 days) (ITT population).
6. Microbiological response at Day 3, Day 5, and the EOT, TOC and LFU visits (mITT and ME populations).

7. Change in patient-reported pain from baseline at all visits except the Day 28 visit (ITT and CE populations).
8. Health economic outcome measures (ITT and CE populations).
9. Safety: incidence, type, severity and relationship to study medication of adverse events and changes in laboratory tests (hematology, biochemistry, and chemistry, including haptoglobin, urinalysis, Coombs test) (Safety population).
10. To assess the pharmacokinetics (PK) of ceftobiprole (PK population).

STUDY DESIGN

Randomized, double-blind, active-controlled, parallel-group, multicenter study in adult hospitalized patients with ABSSSIs. Randomization will be stratified by study site and type of ABSSSI (with major cutaneous abscess comprising ≤ 30% of the ITT population).

PLANNED NUMBER OF PARTICIPANTS

Approximately 674 patients will be randomized in a 1:1 ratio to ceftobiprole or the comparator regimen.

DURATION OF PARTICIPATION

Treatment duration: minimum 5 days, maximum 10 days. (Treatment may be extended up to 14 days if in the investigator's opinion this is required, and the extension is approved by the sponsor's medical monitor).

Study participation: approximately 5–7 weeks.

NUMBER OF CENTERS/LOCATIONS

Approximately 80 centers in North America and Europe.

INCLUSION CRITERIA

Patients meeting <u>all</u> of the following:

1. Male or female, aged ≥18 years.
2. Diagnosis of ABSSSI, meeting at least one of the definitions in (a) to (c) below. Local symptoms must have started within the 7 days prior to the Screening visit.
   (a) Cellulitis/erysipelas, defined as a diffuse skin infection characterized by all of the following within 24 h:
      i. Rapidly spreading areas of erythema, edema, and/or induration with a minimum total lesion surface area of 75 cm^2.
      ii. No collection of pus apparent upon visual examination.
      iii. At least two of the following local signs of infection:
         - erythema
         - induration
         - localized warmth
         - pain or tenderness on palpation
         - swelling/edema

(b) Major cutaneous abscess, defined as infection characterized by a collection of pus within the dermis or deeper that is apparent upon visual examination before or after therapeutic intervention and is accompanied by all of the following within 24 h:

i. Erythema, edema and/or induration with a minimum total lesion surface area of 75 cm^2.

ii. At least two of the following local signs of infection:

- fluctuance
- incision and drainage required
- purulent or seropurulent drainage
- localized warmth
- pain or tenderness on palpation

(c) Wound infection, defined as infection of any apparent break in the skin characterized by at least one of the following:

i. Superficial incision/surgical site infection meeting all of the following criteria:

- involves only the skin or subcutaneous tissue around the incision (does not involve fascia).
- occurs within 30 days of procedure.
- purulent drainage (spontaneous or therapeutic) with surrounding erythema, edema and/ or induration with a minimum total lesion surface area of 75 cm^2.

ii. Post-traumatic wound (including penetrating trauma, e.g., needle, nail, knife, insect and spider bites) meeting the following criterion within 24 h:

- Purulent drainage (spontaneous or therapeutic) with surrounding erythema, edema and/or induration with a minimum total lesion surface area of 75 cm^2.

3. At least one of the following regional or systemic signs of infection at the Screening visit:

(a) Lymph node tenderness and volume increase, or palpable lymph node proximal to the primary ABSSSI.

(b) Fever > 38 °C/100.4 °F measured orally, > 38.5 °C / 101.3 °F measured tympanically, > 37.5 °C / 99.5 °F measured by the axillary method, or > 39 °C / 102.2 °F measured rectally.

(c) White blood cell (WBC) count > 10.0×10^9/L or < 4.0×10^9/L.

(d) > 10% immature neutrophils (band forms).

4. Requirement for intravenous (IV) antibacterial treatment.
5. Willing and able to adhere to study procedures (including prohibitions and restrictions) as specified in this protocol.
6. Willing and able to remain hospitalized (in a hospital or equivalent medical confinement or clinical research unit) until completion of the early-clinical-response assessment for the primary endpoint.
7. Informed consent signed by the patient, or their legally acceptable representative if appropriate, indicating that they understand the purpose of, and procedures required for, the study, and are willing to participate.

EXCLUSION CRITERIA

Patients meeting any one of the following:

1. Use of any systemic antibacterial treatment within 14 days, or topical antibacterial administration on the primary lesion within 96 h, before first infusion of study drug.
   Exception: Receipt of a single dose of a short-acting (half-life ≤ 12 h, see Appendix 1) antibacterial therapy (e.g., for surgical prophylaxis) within > 3 days before randomization (i.e., patients cannot have received any antibacterial treatment within 72 h of randomization).*
2. Contraindication to the administration of either of the study treatments, including known clinically-relevant hypersensitivity to related antibacterial treatments (e.g., beta-lactam and glycopeptide antibiotics), or to metronidazole if required as adjunctive therapy.
3. Participation in any other clinical study within the 30 days prior to randomization, or any prior participation in this study.
4. The primary ABSSSI is an uncomplicated skin and skin structure infection, such as furuncles, minor abscesses (area of suppuration not surrounded by cellulitis/erysipelas), impetiginous lesions, superficial or limited cellulitis/erysipelas, or minor wound infections (e.g., stitch abscesses).
5. The primary ABSSSI is due to, or associated with, any of the following:
   (a) Diabetic foot infection, gangrene, or perianal abscess.
   (b) Concomitant infection at another site (e.g., septic arthritis, endocarditis, osteomyelitis), not including a secondary ABSSSI lesion.
   (c) Infected burns.
   (d) Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease (arterial or venous).
   (e) Any evolving necrotizing process (e.g., necrotizing fasciitis).
   (f) Infections at vascular catheter sites, or involving thrombophlebitis.
6. The primary ABSSSI is associated with, or in close proximity to, a prosthetic device.
7. Patients who are placed in a hyperbaric chamber as adjunctive therapy for the ABSSSI.
8. Patients expected to require more than two surgical interventions in the operating room for the ABSSSI.
9. Severe sepsis or septic shock.
10. Significant or life-threatening condition (e.g., endocarditis, meningitis) that would confound, or interfere with, the assessment of the ABSSSI.
11. Another severe, acute or chronic medical condition, psychiatric condition, or laboratory abnormality that may increase the risks associated with study participation or administration of the investigational product, or may interfere with the interpretation of study results, and which, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
12. Receiving treatment for active tuberculosis.

* The proportion of patients who have received a single dose of a short-acting antibacterial drug within 14 days before randomization will be limited to 25% of the patient population.

13. Absolute neutrophil count < 0.5×10^9/L.
14. Recent history of opportunistic infections (i.e., within 30 days) if the underlying cause of these infections is still active (e.g., leukemia, transplant, acquired immunodeficiency syndrome [AIDS]).
15. Patients receiving systemic steroids (> 40 mg per day prednisolone, or equivalent), or receiving immunosuppressant drugs.
16. Requirement for peritoneal dialysis, plasmapheresis, hemodialysis, venovenous dialysis, or other forms of renal filtration, or expected to require such treatment before the TOC visit.
17. Alanine transaminase (ALT) or aspartate transaminase (AST) levels ≥ 8× the upper limit of normal, OR severe hepatic disease with Child-Pugh class C.
18. Women who are pregnant or nursing.
19. Women who are of childbearing potential and unwilling to use an acceptable method of birth control during the study: female sterilization (bilateral tubal occlusion or oophorectomy, or hysterectomy) or male partner vasectomy; intrauterine device (IUD); combined (estrogen- and progesterone-containing) hormonal contraception (oral, vaginal ring, or transdermal patch) with an ethinylestradiol dose of at least 30 µg, plus use of male condoms (preferably with spermicides), female condoms, a female diaphragm or a cervical cap; or total sexual abstinence.

    Women are not considered to be of childbearing potential if they are either ≥ 1 year post-menopausal (where menopause is defined as at least 12 months of amenorrhea), or have a serum follicle stimulating hormone (FSH) measurement consistent with post-menopausal status according to local laboratory thresholds. An FSH measurement at Screening is to be obtained for post-menopausal females aged < 50 years, or for those aged ≥ 50 years who have been post-menopausal for < 2 years.
20. Inability to start study-drug therapy within 24 h of Screening.
21. Patients with illicit drug use within 12 months of screening, including heroin, other opioids (unless prescribed for medical reasons unrelated to heroin substitution), cocaine / crack cocaine, and amphetamine/methamphetamine.
    Exception: Cannabis use.

STUDY-DRUG ADMINISTRATION

The two intravenous treatment regimens to be administered are:

1. Ceftobiprole 500 mg q8h (with dose adjustment for renal impairment).
2. Vancomycin 1000 mg (or 15 mg/kg) q12h plus aztreonam 1000 mg q12h (both with dose adjustment for renal impairment). Vancomycin dose adjustments for obese and hypermetabolic patients are according to local standards of care (see Section 6.2.2).

    The requirement for aztreonam therapy will be reassessed at the 72-h study visit (Visit 4). Termination of aztreonam is permitted when all of the following criteria are fulfilled:

    - a Gram-positive pathogen has been isolated, and
    - the presence of Gram-negative organisms is highly unlikely based on the investigator's assessment, and
    - Gram-negative coverage is clinically not required based on the investigator's assessment

In cases where (blinded) aztreonam is discontinued after 72 h, re-administration of (blinded) aztreonam is permitted at any point during the study treatment period, at the discretion of the investigator, when there is confirmation or suspicion of a concomitant Gram-negative infection.

Concomitant systemic antibacterials and topical antibacterials (applied to the primary lesion) are prohibited during the study up to the TOC visit, with the following exceptions:

1. Vancomycin PO 125 mg or 250 mg q6h, fidaxomicin PO 200 mg q12h, or metronidazole IV or PO 500 mg q8h, may be used in both treatment groups for the treatment of *Clostridium difficile* infections.
2. Metronidazole IV may also be used as adjunctive therapy in both treatment groups for coverage of anaerobic bacteria.
3. Nitrofurantoin may be used at any time during the study in both treatment groups as it does not achieve therapeutic blood levels.

Study drug will be administered IV in accordance with the following schedule:

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

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

The vancomycin dose may be adjusted according to the local standard of care by the unblinded pharmacist or delegate. Dose adjustment of study drugs is described in detail in the protocol body.

The requirement for aztreonam therapy will be reassessed at the 72-h study visit (Visit 4).

BLINDING

Double-blind with unblinded pharmacist or delegate.

TREATMENT DURATION

Treatment duration: minimum 5 days, maximum 10 days. (Treatment may be extended up to 14 days if in the investigator's opinion this is required, and the extension is approved by the sponsor's medical monitor).

MAIN STUDY ENDPOINTS

The primary and the main secondary endpoints are region-specific. The primary and main secondary endpoints listed below are for submission to the US FDA. In the EU, the main secondary endpoint listed below will be the primary endpoint, and the primary endpoint listed below will be the main secondary endpoint. Two separate SAPs will be prepared for submission to the FDA and the EMA to reflect the different primary and main secondary endpoints in each region.

Primary endpoint

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

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

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

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

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

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

Main secondary endpoint

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

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

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

1. Death from any cause prior to TOC.
2. Additional antibacterial therapy received for treatment of the primary lesion.
3. Initiation of non-study antibacterial treatment of another infection, unless the antibacterial agent lacks efficacy in the treatment of ABSSSI.
4. Requirement for an unplanned surgical procedure for the ABSSSI after start of therapy, (other than debridement at bedside or local bedside wound care), with the exception of cellulitis where there is a conversion into an abscess within 48 h of study treatment initiation, or, for post-surgery patients, when an extension of the original incision is indicated.

5. Indeterminate assessment at TOC for any reason, including but not limited to:
   (a) missing TOC visit
   (b) lost to follow-up
   (c) patient withdrew consent
   (d) missing data in relation to signs and symptoms of the ABSSSI
   (e) discontinuation from the study due to the need for hemodialysis

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

Other secondary endpoints

1. Early clinical response based on percentage reduction in lesion size at 48–72 h after first treatment in the CE population, using the same definition for response as for the primary endpoint.
2. Clinical response defined as ≥ 80% decrease in lesion area at the EOT visit, and ≥ 90% decrease in lesion area at the TOC visit (ITT population), with improvement of local signs of the infection in patients surviving up to the respective visit with no use of any concomitant systemic antibacterial treatment or topical antibacterial administration on the primary lesion, and no unplanned additional surgical procedure (other than debridement at bedside or local bedside wound care), with the exception of cellulitis where there is a conversion into an abscess within 48 h of study treatment initiation, or, for post-surgery patients, when an extension of the original incision is indicated.
3. Sustained reduction in lesion size at the EOT and TOC visits (ITT population).

   Sustained reduction in lesion size is defined as ≥ 20% decrease in lesion area 48–72 h after start of treatment (primary endpoint) that is sustained at the EOT and TOC visits.
4. Investigator-assessed clinical success evaluated at 48–72 h after first treatment and the EOT visit, and sustained clinical success at the LFU visit (ITT and CE populations).

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

   Sustained clinical success requires that all criteria listed for the main secondary endpoint are met and there were no new signs or symptoms of the ABSSSI between the TOC and LFU visits.
5. ACM at Day 28 (±2 days).

   Assessment of survival status at Day 28 (±2 days).
6. Microbiological response at Day 3, Day 5, and the EOT, TOC and LFU visits (mITT and ME populations).

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

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

   Persistence: Evidence of continued growth of the baseline pathogen.

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

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

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

7. Patient-reported pain (ITT and CE populations)

   Time points: all visits, (with exception of Day 28)

   Patient-reported pain, assessed at baseline and throughout the study, using a visual analogue scale (VAS) with a 100 mm line, on which the 0 point indicates 'no pain' and the 100 mm point indicates 'worst pain ever', and a Wong-Baker FACES® Pain Rating Scale.

8. Health economic outcome measures (ITT and CE population)

   Time point: From start of study medication until the LFU visit

   Resource requirements and health economic data will be derived from study-specific data, or collected ancillary to study conduct, to perform health economics analyses. These analyses will aim to enable economic comparisons of ceftobiprole with vancomycin and aztreonam.

9. Safety

   Time point: First dose of study drug until LFU

   Adverse events, laboratory tests (including hematology, biochemistry, and haptoglobin), Coomb's test, vital signs, physical examination, and concomitant medications.

10. Pharmacokinetics

    Time points: Day 4

    Plasma levels of ceftobiprole.

    Sparse PK sampling

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

    Rich PK sampling

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

STATISTICAL ANALYSIS

Sample size justification

The study is designed to determine whether ceftobiprole is non-inferior to vancomycin plus aztreonam for the outcome measure of early clinical response at 48–72 h after start of treatment, defined as a ≥ 20% reduction from baseline in the area (longest length × perpendicular width of erythema, edema, or induration) of the primary lesion, survival for ≥ 72 h from the time of administration of the first dose of study drug, and no use of concomitant systemic antibacterial treatment or topical antibacterial administration on the primary lesion.

A sample size of 674 patients (337 per group) will provide at least 90% power to reject the null hypothesis (H_0) against the alternative hypothesis (H_A) at the one-sided alpha level of 0.025 as follows, using a two-group large-sample normal approximation test of proportions:

H_0: $P_{vancomycin/aztrenonam}$ minus $P_{ceftobiprole} \geq 0.10$ versus

H_A: $P_{vancomycin/aztrenonam}$ minus $P_{ceftobiprole} < 0.10$.

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

The sample size estimate is therefore based on:

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

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

Two separate SAPs will be provided for submission to the FDA and EMA, where the SAP prepared for the FDA will use the protocol-defined primary and secondary objectives, and the SAP prepared for the EMA will use the main secondary objective as the primary objective.

For the EMA primary endpoint, the point estimates of clinical cure at the TOC visit in the co-primary ITT and CE populations are 80% and 90%, respectively, which are supported by previous ABSSSI Phase 3 studies (see Section 8.1).

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

Analysis populations

The following analysis populations are defined for this study:

Intent-to-Treat population (ITT): all randomized patients. Patients will be analyzed according to the study medication assigned at randomization.

Microbiological Intent-to-Treat population (mITT): the subset of patients in the ITT population who have had causative pathogens confirmed from skin lesion or blood cultures.

Clinically Evaluable population (CE): the subset of patients in the ITT population who have complied with important aspects of the study, e.g., no major protocol deviations, a completed response outcome assessment, and no concomitant systemic antibacterial treatment or topical antibacterial applied to the primary lesion.

Microbiologically Evaluable population (ME): the subset of patients in the mITT population who are also in the CE population.

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

Pharmacokinetic population (PK): all patients who receive at least one dose of ceftobiprole and have at least one plasma concentration measurement obtained by the appropriate methodology.

Statistical considerations

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables, will be provided. All comparisons will be for ceftobiprole versus vancomycin plus aztreonam. Exploratory analyses may also be performed.

For between-group comparisons, a two-sided 95% confidence interval (CI) for the difference in outcome rates between the two treatment groups will be derived, unless otherwise specified.

Unless otherwise specified, the latest evaluation prior to the initiation of study drug will be considered the 'baseline' evaluation for statistical analyses.

Demographic and baseline characteristics, prior and concomitant medications, and surgical procedures will be summarized by treatment group. Additional summaries will be provided for prior and concomitant antibacterial treatment use.

Analysis of the primary endpoint

The primary analysis will be based on the ITT population.

The study is designed to determine whether ceftobiprole is non-inferior to vancomycin plus aztreonam for the primary endpoint of early clinical response based on percentage reduction from baseline in lesion size at 48–72 h after first study-drug administration (see Section 3.1.1).

The numbers and percentages of responders and non-responders will be determined in each treatment group. The observed difference in percentage of responders at 48–72 h (ceftobiprole group minus the vancomycin plus aztreonam group) will be determined, and a 95% CI for the observed difference will be computed, with adjustment by geographical region (North America and Europe), and type of ABSSSI.

The non-inferiority hypothesis test is a one-sided hypothesis test performed at the 2.5% level of significance. If the lower limit of the 95% CI for the difference in response rates (ceftobiprole minus vancomycin plus aztreonam) in the ITT population is greater than −10%, the non-inferiority of ceftobiprole to vancomycin plus aztreonam will be concluded. If non-inferiority is declared at the one-sided significance level of 0.025, then superiority will be tested.

The primary efficacy analysis is based on the difference in the early clinical response rates between the two treatment groups. Analyses using risk ratio and odds ratio will also be performed.

Sensitivity analyses and subgroup analyses will be performed for the primary efficacy outcome, as described in protocol Section 8.7.1.

Analysis of the main secondary endpoint

The main secondary endpoint is the investigator-assessed clinical success at the TOC visit according to the following definition: complete or nearly complete resolution of baseline signs and symptoms of the primary infection such that no further antibacterial treatment is needed (see Section 3.1.2).

This main secondary endpoint will be specified in a separate SAP as the primary endpoint for the EMA, with non-inferiority assessed by the two-sided 95% CI of the between-group difference (ceftobiprole minus vancomycin plus aztreonam) using a 10% non-inferiority margin in the co-primary ITT and CE populations.

Sensitivity analyses and subgroup analyses will be performed for the main secondary efficacy outcome, as described in Section 0.

Analysis of other secondary endpoints

The following additional secondary endpoints will be analyzed using the same statistical methods as for the primary endpoint:

1. Early clinical response based on percentage reduction in lesion size at 48–72 h after first treatment (CE population).
2. Clinical response defined as ≥ 80% decrease in lesion area at the EOT visit, and ≥ 90% decrease in lesion area at the TOC visit (ITT population), with improvement of local signs of the infection in patients surviving up to the respective visit with no use of any concomitant systemic antibacterial treatment or topical antibacterial administration on the primary lesion, and no unplanned additional surgical procedure (other than debridement at bedside or local bedside wound care), with the exception of cellulitis where there is a conversion into an abscess within 48 h of study treatment initiation, or, for post-surgery patients, when an extension of the original incision is indicated.
3. Sustained reduction in lesion size, defined as ≥ 20% decrease in lesion area 48–72 h after start of treatment (primary endpoint), that is sustained at the EOT and TOC visits (ITT population).
4. Investigator-assessed clinical success evaluated at 48–72 h after first treatment and the EOT visit, and sustained clinical success at the LFU visit (ITT and CE populations).

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

   Sustained clinical success requires that all criteria listed for the main secondary endpoint are met and there were no new signs or symptoms of the ABSSSI between the TOC and LFU visits.
5. All-cause mortality through Day 28 (±2 days) (ITT population).

   A time to event analysis using the Kaplan-Meier method will also be performed for all-cause mortality.
6. Microbiological response at Day 3, Day 5, and the EOT, TOC and LFU visits in the mITT and ME populations, based on post-therapy cultures obtained from the primary infection site at the respective time points, using the definitions in Section 3.1.3.

Additional analyses of secondary endpoints are described in Section 0.

Additional analyses may be conducted at the sponsor's discretion; the details of such analyses will be described in the SAPs.

Safety analyses

Safety will be assessed through summaries of adverse events (AEs), safety laboratory evaluations, physical examinations, and vital signs. Analyses will be based on the Safety population and presented by treatment group, as described in Section 8.8.

Pharmacokinetics

Plasma concentration data will be analyzed at each time point as described in Section 5.3.12, and will be presented with descriptive statistics (mean, SD, CV%, min, median, max).

Blinded interim analysis

One blinded interim analysis for sample size re-estimation will be conducted based solely on pooled information across the two treatment arms when early clinical response data are available for 60% of the patients planned to be randomized (approximately 404 patients). No statistical adjustment is required. The interim analysis will involve a sample size re-estimation to assess whether the initial sample size estimate is adequate for evaluating the primary endpoint of the study.

Details will be provided in the Data and Safety Monitoring Board (DSMB) charter.

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

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

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LIST OF ABBREVIATIONS

ABSSSI	Acute bacterial skin and skin structure infection
ACM	All-cause mortality
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
AST	Aspartate transaminase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
CAP	Community-acquired pneumonia
CE	Clinically evaluable
CI	Confidence interval
CL_{CR}	Creatinine clearance
CLSI	Clinical and Laboratory Standards Institute
CRP	C-reactive protein
CRF	Case report form
cSSTI	Complicated skin and soft tissue infection
DSMB	Data and Safety Monitoring Board
EOT	End-of-treatment
EMA	European Medicines Agency
ESBLs	Extended-spectrum beta-lactamases
ESRD	End-stage renal disease
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	United States Food and Drug Administration
FSH	Serum follicle stimulating hormone
GGT	Gamma-glutamyl transferase
GISA	Glycopeptide-intermediate *Staphylococcus aureus*
HAP	Hospital-acquired pneumonia
HCT	Hematocrit
HGB	Hemoglobin
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IDSA	Infectious Diseases Society of America
ISF	Investigator Site File

ITT	Intent-to-Treat
IUD	Intrauterine device
IV	Intravenous(ly)
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LFU	Last follow-up (visit)
LPLV	Last Patient Last Visit
MHRA	UK Medicines & Healthcare products Regulatory Agency
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NOAEL	No-observed-adverse-effect level
NSAID	Nonsteroidal anti-inflammatory drug
PBPs	Penicillin-binding proteins
PD	Pharmacodynamics
PK	Pharmacokinetics
PO	Oral(ly)
PT	Preferred Term
PT	Prothrombrin time
RBC	Red blood cell
RSI	Reference safety information
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SPA	Special protocol assessment
SUSAR	Suspected unexpected serious adverse reaction
T>MIC	Time drug concentration is above the MIC
$t_{1/2}$	Elimination half-life
TOC	Test-of-cure
VAP	Ventilator-associated pneumonia
VAS	visual analogue scale
VISA	Vancomycin-intermediate *Staphylococcus aureus*
VRSA	Vancomycin-resistant *Staphylococcus aureus*
V_{ss}	Volume of distribution at steady state
WBC	White blood cell

1 BACKGROUND AND RATIONALE

1.1 Disease characteristics and treatment

Acute bacterial skin and skin structure infections (ABSSSIs), previously referred to as complicated skin and soft tissue infections (cSSTIs), are among the most common infections encountered in both community and hospital settings, and include infections with resistance to previously effective antibacterial treatments (Dryden 2010). Increasing in incidence, they have become a challenging medical problem associated with high direct and indirect costs to both the medical system and society (Pollack 2015). Infections due to bacteria with resistance to previously effective antibacterial treatments, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are increasing in incidence and have led to higher rates of complications and hospitalization. MRSA has emerged as the most common cause of purulent infections in the United States and many other areas.

In 2013, the United States Food and Drug Administration (FDA) issued the *Guidance for Industry, Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment*, standardizing the nomenclature to be used in the evaluation of new antibacterial treatments for complicated skin and skin structure infections, which are now referred to as ABSSSIs:

> *ABSSSIs include cellulitis/erysipelas, wound infection, and major cutaneous abscess with a minimum lesion surface area of 75 cm^2. Diabetic foot ulcers and burn wound infections are excluded. Bacterial pathogens that commonly cause ABSSSI include Streptococcus pyogenes and Staphylococcus aureus, including MRSA strains. Less commonly identified bacteria include other Streptococcus species, Enterococcus faecalis, and Gram-negative bacteria.*

Considerations in selection of an empiric antibacterial for the treatment of ABSSSIs include suspected bacteriologic etiology, susceptibility, spectrum, host status (e.g., neutropenia, immunocompromised, diabetes), compliance, allergies, and location.

Current Infectious Diseases Society of America (IDSA) recommendations (with dose recommendations for non-pregnant adult patients with normal hepatic and renal function) for the treatment of ABSSSIs when MRSA is suspected or identified are shown below (IDSA 2014, Pollack 2015).

- Vancomycin, 15–20 mg/kg/dose intravenously (IV) every 8–12 hours (q8–12h)
- Linezolid, 600 mg PO/IV q12 h
- Daptomycin, 4 mg/kg/dose IV q24 h
- Telavancin, 10 mg/kg/dose IV q24 h
- Clindamycin, 600 mg PO/IV q8h
- Tedizolid, 200 mg PO/IV q24 h
- Dalbavancin, 1000 mg IV on Day 1, then 500 mg IV on Day 8
- Oritavancin, 1200 mg IV single dose

1.2 Investigational medicinal products

- Ceftobiprole 500 mg q8h (with dose adjustment for renal impairment).
- Vancomycin 1000 mg or 15 mg/kg q12h plus aztreonam 1000 mg q12h (both with dose adjustment for renal impairment)

  The requirement for aztreonam therapy will be reassessed at the 72-h study visit (see Section 6.1).

Ceftobiprole medocaril plus placebo is the test product; vancomycin plus aztreonam is the comparator regimen.

1.3 Nonclinical studies with ceftobiprole

1.3.1 Microbiology

Ceftobiprole has a strong affinity for several penicillin-binding proteins (PBPs), including PBP2a and PBP2x, which mediate resistance to other beta-lactams in staphylococci and pneumococci, respectively (Hebeisen 2001, Lovering 2012, Davies 2007, Davies 2010, Henry 2013, Entenza 2002). In contrast to earlier generation cephalosporins, ceftobiprole effectively prevents the intracellular growth of both methicillin-susceptible *S. aureus* (MSSA) and MRSA strains in macrophages and keratinocytes, due in part to its ability to better bind PBP2a under both neutral and acidic pH conditions (Lemaire 2009). Ceftobiprole also binds to and saturates several other essential PBPs (Davies 2010, Henry 2013), distinguishing it from other available beta-lactams, and is stable to hydrolysis by the *S. aureus* PC1 Class A beta-lactamase, conserving its activity against staphylococci (Queenan 2007).

Ceftobiprole is also relatively stable against AmpC cephalosporinases and common class A beta-lactamases produced by Gram-negative bacteria, but not to extended-spectrum beta-lactamases (ESBLs), carbapenemases, or OXA beta-lactamases (Queenan 2007).

In vitro single- and multiple-passage selection studies performed with several Gram-positive pathogens, including MRSA, demonstrated a very low propensity for resistance after exposure to ceftobiprole (Queenan 2007, Bogdanovich 2006, Queenan 2005, Kosowska 2005, Bogdanovich 2005, Queenan 2010), which is due to ceftobiprole's unique ability to bind to multiple target sites.

No emergence of resistance was seen throughout the extensive clinical development program and no MIC shifts were seen in surveillance studies.

In vitro, ceftobiprole has shown a bactericidal mode of action against MSSA, MRSA and many other resistant *S. aureus* strains, including glycopeptide-intermediate (GISA), vancomycin-intermediate (VISA), vancomycin-resistant (VRSA), daptomycin non-susceptible, and linezolid non-susceptible strains, using both broth microdilution and time-kill methods (Borbone 2010, Leonard 2008, Rouse 2007, Deshpande 2013, Farrell 2014).

Ceftobiprole also effectively reduced the colony-counts of MSSA and MRSA strains tested in an *in vitro* biofilm model, none of which were affected by daptomycin, vancomycin or rifampicin (Abbanat 2014).

Further details on the microbiology of ceftobiprole medocaril are provided in the Investigator's Brochure (IB).

1.3.2 Pharmacokinetics and product metabolism in animals

In animals after single IV dose pharmacokinetic (PK) studies, ceftobiprole medocaril was rapidly metabolized via non-specific esterases to ceftobiprole. The volume of distribution of ceftobiprole was restricted to the extracellular compartment and its elimination occurred predominantly by passive glomerular filtration of unchanged ceftobiprole. The *in vitro* and *in vivo* metabolic patterns of ceftobiprole in rats, dogs, mice, marmosets, and humans were similar, with the ring-open product BAL1029 as the main metabolite. After multiple doses to rats, rabbits, marmosets, cynomolgus monkeys, and dogs, high and dose-proportional exposures to ceftobiprole in all species were achieved, exceeding the expected human therapeutic exposure at the no-observed-adverse-effect level (NOAEL). There were no relevant indications of accumulation, differences related to sex, or time-dependent PK.

Whole-body autoradiography in animals demonstrated rapid and large distribution of ceftobiprole in all organs without specific accumulation in any organs, with the exception of the kidney as excretory organ. Results from a reproductive toxicology study in rats indicated that nursing pups were not systemically exposed to ceftobiprole. Protein binding of ceftobiprole in plasma in all species was low, and concentration-independent. Mean plasma protein binding in humans was 16%. In rats, excretion was almost complete (> 94%) within 4 days after IV administration of the prodrug.

Based on *in vitro* cytochrome P450 inhibition and induction data, the lack of a specific enzyme involved in the cleavage of the prodrug, and ceftobiprole distribution being restricted to the extracellular compartment, the potential of ceftobiprole to exhibit clinically-relevant enzyme-related drug-drug interactions is small.

Further details on the nonclinical pharmacology, PK and pharmacodynamics (PD) of ceftobiprole medocaril are provided in the IB.

1.3.3 Toxicology

The primary targets of toxicity after IV administration in animals were the kidneys and the infusion site.

- **Renal toxicity** was attributable to the high rate of glomerular filtration leading to high concentrations of ceftobiprole in urine, precipitation of ceftobiprole in distal parts of the nephron, and resultant renal tissue damage. This effect is not thought to apply to humans because glomerular filtration of ceftobiprole in humans is much slower, and urinary concentrations of ceftobiprole do not approach the limit of solubility.
- **Local tolerance**: In 4- and 13-week studies in rats and marmosets, concentration-dependent slight to moderate local endothelial irritation was observed when ceftobiprole medocaril was administered over 4–8 h into the *vena cava* at concentrations up to 62 mg/mL.

In a local tolerability study in rabbits, repeated IV administration of ceftobiprole into the auricular vein (8 consecutive days with a 3-minute endothelial contact period per day) caused no irritation at ceftobiprole concentrations of 2 and 10 mg/mL (nominal ceftobiprole medocaril concentrations of 2.66 and 13.3 mg/mL).

Hemolysis, plasma turbidity and precipitation were observed in human, dog, rat and marmoset blood at concentrations ≥ 12.5 mg/mL.

Ceftobiprole medocaril was neither teratogenic nor embryotoxic in rats and cynomolgus monkeys, and had no effects on fertility and early embryonic development in rats. No effects on behavioral or developmental parameters were noted in pups. No signs of skin sensitization, irritation, or phototoxicity were seen. The antigenic potential of ceftobiprole medocaril is low.

The convulsive potential after intracerebroventricular administration to mice was comparable to that of imipenem.

No cardiac or pulmonary toxicity was observed.

Further details on the non-clinical toxicology of ceftobiprole medocaril are provided in the IB.

1.4 Clinical studies with ceftobiprole

1.4.1 Pharmacokinetics, product metabolism, and tissue distribution in humans

The PK of ceftobiprole in adults are predictable, linear and time-independent across the dose range of 125–1000 mg, and variability is low (< 30%). Steady-state drug concentrations are attained on the first day of dosing (q8h), and no appreciable accumulation is observed in adults with normal renal function. The volume of distribution at steady state (V_{ss}) of ceftobiprole is 18 L, suggesting that distribution is restricted to the extracellular water compartment. The total body clearance of ceftobiprole is approximately 5 L/h, and the apparent half-life ($t_{1/2}$) is 3–4 hours.

Ceftobiprole is eliminated primarily unchanged by renal excretion, with minimal metabolism to an open-ring metabolite, which accounts for approximately 4% of total exposure. The predominant mechanism responsible for elimination is glomerular filtration. As the systemic clearance of ceftobiprole correlates with creatinine clearance (CL_{CR}), dose regimen adjustments are recommended in patients with moderate or severe renal impairment, patients with end-stage renal disease (ESRD), and patients with CL_{CR} > 150 mL/min. At comparable CL_{CR}, the PK of ceftobiprole in patients in an intensive-care unit setting, and in patients from studies in hospital-acquired pneumonia (HAP) Awad 2014 and community-acquired pneumonia (CAP) Nicholson 2012, were similar to the PK in healthy subjects. Given no underlying renal impairment, the primary PK/PD driver of ceftobiprole (time that drug concentration exceeds the minimum inhibitory concentration [MIC], T>MIC) is unaffected by gender, obesity, age, or race, and no dose adjustment is required in these sub-populations.

The distribution of ceftobiprole in lung epithelial lining fluid, bone, muscle and adipose tissue is similar to that of other cephalosporins.

Following administration of 500 mg ceftobiprole q8h for 7 days, ceftobiprole could not be detected in the feces of healthy subjects, there were no significant changes in the aerobic or anaerobic intestinal microflora, and no new colonizing aerobic or anaerobic bacteria resistant to ceftobiprole were observed.

1.4.2 Pharmacodynamics

In animal models, for efficacy (bacteriostasis) the plasma concentrations of ceftobiprole must remain above the target MIC (T>MIC) of 4 µg/mL for > 30% of the dosing interval for susceptible Gram-positive pathogens, and > 50% for susceptible Gram-negative pathogens. For 1 log-kill in colony-forming units (bactericidal effect) in animal pneumonia and thigh models, the target T>MIC of 4 µg/mL remains > 30% of the dosing interval for susceptible Gram-positive pathogens, and is > 60% for susceptible Gram-negative pathogens. A retrospective population PK analysis of subjects in the Phase 3 HAP study demonstrated the probability of target attainment to be 100% for Gram-positive pathogens and > 96% for Gram-negative pathogens with the recommended clinical dose regimen for ceftobiprole (i.e. 500 mg administered q8h as a 120-minute IV infusion).

1.4.3 Susceptibility testing breakpoints

Minimum inhibitory concentration breakpoints for ceftobiprole established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are shown in Table 1.

Table 1 Ceftobiprole MICs established by EUCAST

Organisms	MIC breakpoints (mg/L)	
	Susceptible (≤ S)	Resistant (R >)
Staphylococcus aureus (including MRSA)	2	2
Streptococcus pneumoniae	0.5	0.5
Enterobacteriaceae	0.25	0.25
Pseudomonas aeruginosa	IE [a]	IE [a]
Non-species specific breakpoint [b]	4	4

[a] Insufficient evidence.
[b] Based on the PK/PD target for Gram-negative organisms.

1.4.4 Efficacy in ABSSSIs/cSSTIs

Two Phase 3 studies have previously been completed with ceftobiprole in ABSSSIs/cSSTIs. Study BAP00414 compared ceftobiprole 500 mg q8h (N=547) with vancomycin 1 g q12h plus ceftazidime 1 g q8h (N=281) in patients with Gram-positive or Gram-negative ABSSSIs/cSSTIs including patients with diabetic foot infections (Noel 2008a). Study BAP00154 compared ceftobiprole 500 mg q12h (N=397) with vancomycin 1 g q12h (N=387) in patients with Gram-positive ABSSSIs/cSSTIs (Noel 2008b).

Clinical cure at the test-of-cure (TOC) visit was the primary endpoint in both studies. Clinical cure rates in study BAP00414 were 81.9% (ceftobiprole) vs 80.8%

(vancomycin/ceftazidime) in the Intent-to-Treat (ITT) analysis set (95% confidence interval [CI] of the between-group difference ceftobiprole minus comparator: −4.5 to 6.7), and 90.5% (ceftobiprole) vs 90.2% (vancomycin/ceftazidime) in the Clinically Evaluable (CE) analysis set (95% CI of between-group difference: −4.2 to 4.9)

Clinical cure rates in study BAP00154 were 77.8% (ceftobiprole) vs 77.5% (vancomycin) in the ITT analysis set (95% CI of between-group difference: −5.5 to 6.1), and 93.3% (ceftobiprole) vs 93.5% (vancomycin) in the CE analysis set (95% CI of between-group difference: −4.4 to 3.9).

1.4.5 Efficacy in community-acquired pneumonia

The results of the Phase 3 CAP-3001 study (Nicholson 2012) demonstrated the non-inferiority of ceftobiprole 500 mg administered every 8 hours as a 2-hour infusion to treatment with ceftriaxone with or without linezolid for patients hospitalized with CAP within a pre-specified margin of 10% for the primary efficacy endpoint of clinical cure rate at the TOC visit. The ITT analysis set included 314 patients in the ceftobiprole group and 324 patients in the comparator group.

The clinical cure rates at the TOC visit were 86.6% and 87.4% in the ceftobiprole and ceftriaxone with or without linezolid groups, respectively, in the CE analysis set, and 76.4% and 79.3% in the ITT analysis set. The respective clinical cure rates in patients in PORT Risk Classes ≥ III (PSI score ≥ 71) were 86.5% and 86.3% (ITT), and 79.1% and 78.5% (CE).

1.4.6 Efficacy in hospital-acquired pneumonia

In the Phase 3 HAP study BAP248/307 (Awad 2014), the non-inferiority of ceftobiprole to ceftazidime plus linezolid was demonstrated within the pre-specified 15% margin for the primary efficacy endpoint of clinical cure rate at the TOC visit for all patients in the CE and ITT analysis sets. The ITT analysis set included 391 patients in the ceftobiprole group and 390 patients in the comparator group.

The clinical cure rates at the TOC visit were 69.3% and 71.3% (CE), and 49.9% and 52.8% (ITT) in the ceftobiprole and linezolid/ceftazidime groups, respectively.

Non-inferiority of ceftobiprole to linezolid/ceftazidime was also demonstrated in the pre-specified subgroup of patients with HAP (excluding ventilator-associated pneumonia [VAP]) subjects (N=571). Non-inferiority of ceftobiprole was not demonstrated in the smaller subset of VAP patients (N=210).

1.4.7 Safety

The current safety experience from clinical studies of ceftobiprole comprises 3037 subjects (1404 from Phase 3 pneumonia studies, 1633 from Phase 2 and Phase 3 cSSTI studies, and 511 subjects from Phase 1 studies). The observed safety profile is consistent with that of the cephalosporin class as a whole.

The most common adverse reactions, occurring in ≥3% of subjects treated with ceftobiprole, were nausea, vomiting, diarrhea, infusion site reactions, hypersensitivity (including urticaria, pruritic rash and drug hypersensitivity), and dysgeusia.

Less frequently reported, but more serious, adverse reactions include thrombocytopenia, agranulocytosis, anaphylaxis, *Clostridium difficile* colitis, convulsion, agitation (including anxiety, panic attacks and nightmares), and renal failure.

The development of a positive direct-antiglobulin test may occur during treatment with a cephalosporin. In clinical studies with ceftobiprole there was no evidence of hemolytic anemia. However, the possibility that hemolytic anemia may occur in association with ceftobiprole treatment cannot be ruled out. Patients experiencing anemia during or after treatment with ceftobiprole should be investigated for this possibility.

It is not known whether ceftobiprole, like some other cephalosporins, interferes with the alkaline picrate assay to measure serum creatinine (Jaffé reaction), which may lead to erroneously high creatinine measurements. During treatment with ceftobiprole it is recommended that an enzymatic method of measuring serum creatinine be used.

During treatment with ceftobiprole it is recommended that an enzymatic method to detect glucosuria be used, because of potential interference with tests using the copper reduction technique.

Further details can be found in the IB.

1.5 Rationale for study BPR-CS-008

Ceftobiprole, a novel cephalosporin is potentially an important addition to ABSSSI treatment options. Ceftobiprole has broad *in vitro* activity against Gram-positive pathogens, including MSSA/MRSA, and against *P. aeruginosa* and other Gram-negative organisms.

Therefore, due to the beneficial profile of this compound as well as the need for additional agents to treat ABSSSIs, including those caused by MRSA, this Phase 3 study will evaluate ceftobiprole therapy against standard therapy in terms of safety, efficacy and resource utilization.

1.5.1 Summary of study design

This is a randomized, double-blind, active-controlled, parallel-group, multicenter study in adult hospitalized patients to establish the safety and efficacy of ceftobiprole medocaril compared with vancomycin plus aztreonam in the treatment of ABSSSIs.

1.5.2 Study design rationale

The study design is in accordance with the current FDA *Guidance for Industry, Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (October 2013)*. In parallel, in 2014 the European Medicines Agency (EMA) published the *Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections*. Whereas the disease description and patient selection appear to be quite similar between both guidance documents, the recommended primary endpoints to evaluate treatment success are different.

For the primary analysis, the FDA recommends an early clinical success endpoint:

> *Clinical response should be based on the percent reduction in the lesion size at 48 to 72 hours compared to baseline, measured in patients who did not receive rescue therapy and are alive. A clinical response in a patient generally is defined as a percent reduction in lesion size greater than or equal to 20 percent compared to baseline.*

The EMA recommends the assessment of clinical outcome at a later timepoint, approximately 7–14 days after the end of therapy:

> *Clinical outcome documented at a test of cure (TOC) visit timed from randomization so that it occurs within a window of approximately 7–14 days after the last day of treatment would be an acceptable primary endpoint.*

The data obtained during course of the study will be analyzed and presented using similar timeframes; however the TOC visit will be linked to the time of randomization, rather than to the EOT. Separate statistical analysis plans (SAPs) will be prepared for the FDA and EMA.

1.5.3 Study drug and dose

1.5.3.1 Ceftobiprole medocaril

Ceftobiprole medocaril is the water-soluble prodrug of ceftobiprole, a novel cephalosporin which has been developed for IV administration. Ceftobiprole is characterized by potent, broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative pathogens, including those that have developed various forms of antibacterial resistance.

Ceftobiprole medocaril is a powder for concentrate for solution for infusion. The volume of distribution at steady state of ceftobiprole is 18 L, suggesting that distribution is restricted to the extracellular water compartment, which is comparable to other beta-lactam antibiotics.

The total body clearance of ceftobiprole is approximately 5 L/h. The mean apparent half-life of ceftobiprole approximately 3 to 4 hours. Protein binding in human is low and concentration independent, with a mean plasma protein binding value of 16% Ceftobiprole is eliminated primarily unchanged by renal excretion, where renal clearance is approximately 4 L/h; the predominant mechanism responsible for elimination is glomerular filtration.

The recommended dose of ceftobiprole is 500 mg administered as a 2-hour IV infusion q8h.

1.5.3.2 Vancomycin

Vancomycin is an antibacterial agent inhibiting bacterial cell wall synthesis and altering cell-membrane permeability and RNA synthesis, which can be administered either orally or parenterally, with a mean half-life of 4–6 hours. Vancomycin is not metabolized, and about 75% is excreted in the urine by glomerular filtration. Administered IV, vancomycin

is 55% protein-bound and distributes in pleural, pericardial, ascitic, and synovial fluids, in urine, in peritoneal dialysis fluid, and in atrial appendage tissue.

Vancomycin is administered IV for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (beta-lactam-resistant) staphylococci, and the treatment of staphylococcal, streptococcal, enterococcal, or diphtheroid endocarditis. Oral absorption of vancomycin is poor, and is limited to the treatment of *C. difficile*-associated diarrhea or staphylococcal enterocolitis.

The usual daily IV dose of vancomycin is 2000 mg, either as 500 mg every q6h or 1000 mg q12h. Patient factors, such as age, obesity, or renal function, may require modification of the daily IV dose.

Vancomycin steady state trough levels measured immediately prior to the next dose should be 10–15 mg/L. Ototoxicity has been associated with serum drug levels of 80–100 mg/L, but this is rarely seen when serum levels are kept at or below 30 mg/L.

1.5.3.3 Aztreonam

Aztreonam is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis. It confers selective activity against Gram-negative aerobic bacteria, and is not efficacious against Gram-positive bacteria. Aztreonam is 56% protein-bound. Hepatic metabolism is minor, and aztreonam is renally excreted. Mean half-life is 1.7 hours. Aztreonam has been used in previous Phase 3 ABSSSI studies with a dose regimen of 1000 mg q12h (Corey 2010) in combination with vancomycin, which lacks efficacy against Gram-negative bacteria.

The requirement for aztreonam therapy will be reassessed at the 72-h study visit (see Section 6.1).

2 OBJECTIVES OF THE STUDY

2.1 Primary objective

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

2.2 Secondary objectives

2.2.1 Main secondary objective

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

Note: The primary and the main secondary objectives will be region-specific. The above primary and main secondary objectives are for submission to the US FDA; in the EU, the above main secondary objective will be the primary objective, and the primary objective listed above will be the main secondary objective. Two separate Statistical Analysis Plans (SAPs) will be prepared for submission to the FDA and the EMA to reflect the different primary and main secondary objectives in each region.

2.2.2 Other secondary objectives

To compare ceftobiprole with vancomycin plus aztreonam with respect to:

1. Early clinical response based on percentage reduction in lesion size at 48–72 h after first treatment (CE population).
2. Clinical response based on percentage reduction in lesion size at the end-of-treatment (EOT) and TOC visits (ITT and CE population).
3. Sustained reduction in lesion size at the end-of-treatment (EOT) and TOC visits (ITT population).
4. Investigator-assessed clinical success evaluated at 48–72 h after first treatment and the EOT visit, and sustained clinical success at the last follow-up (LFU) visit (ITT and CE populations).
5. All-cause mortality (ACM) through Day 28 (±2 days) (ITT population).
6. Microbiological response at Day 3, Day 5, and the EOT, TOC and LFU visits (Microbiological Intent-to-Treat population [mITT] and Microbiologically Evaluable [ME] populations).
7. Change in patient-reported pain from baseline at all visits except the Day 28 visit (ITT and CE populations).
8. Health economic outcome measures (ITT and CE populations).
9. Safety: incidence, type, severity and relationship to study medication of adverse events (AEs) and changes in laboratory tests (hematology, biochemistry, and chemistry, including haptoglobin, urinalysis, Coombs test) (Safety population).
10. To assess the PK of ceftobiprole (PK population).

3 STUDY DESIGN

3.1 Overview of study design and dosing regimen

This is a randomized, double-blind, active-controlled, parallel-group, multicenter study in adult hospitalized patients to establish the safety and efficacy of ceftobiprole medocaril compared with vancomycin plus aztreonam in the treatment of ABSSSIs.

Table 2 Summary of treatment and follow-up schedule

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

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

The study comprises three phases:

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

In addition, at 28 days after randomization, survival status is to be verified for evaluation of ACM.

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

Study assessments are shown in Table 4 and outlined in more detail in Section 5. After randomization and during active treatment, patients will receive ceftobiprole and placebo or vancomycin and aztreonam according to the schedule outlined in Table 3.

Table 3 Study-drug administration

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

* Or 15 mg/kg vancomycin: the decision to use vancomycin at a fixed or weight-based dose is to be made by the investigator on the basis of the site's standard of care, and needs to be communicated prior to randomization to the unblinded pharmacist or delegate. If VTT is performed, the vancomycin dose may be adjusted according to trough levels.
** The requirement for aztreonam therapy will be reassessed at the 72-h study visit (see Section 6.1).
NA, not applicable.

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

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

Dose adjustment of study drugs according to renal function is described in detail in Section 6.2.

The primary and the main secondary endpoints are region-specific. The primary and main secondary endpoints listed below are for submission to the US FDA. In the EU, the main secondary endpoint listed below will be the primary endpoint, and the primary endpoint listed below will be the main secondary endpoint. Two separate SAPs will be prepared for submission to the FDA and the EMA to reflect the different primary and main secondary endpoints in each region.

3.1.1 Primary endpoint

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

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

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

Standardized measurement of the lesion area (i.e., erythema, edema, or induration, whichever is largest) is to be performed with a flexible plastic ruler or tape measure, by multiplying the longest length of the lesion by the widest width perpendicular to that length. In addition, a measurement of the maximum width of erythema or edema/induration from the edge of the wound (surgical or traumatic) or abscess will be recorded. If abscess, the measurement should be taken from the end of the fluctuance before drainage or from the edge of the drainage site after drainage.

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

3.1.2 Main secondary endpoint

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

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

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

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

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

3.1.3 Other secondary endpoints

1. Early clinical response based on percentage reduction in lesion size at 48–72 h after first treatment in the CE population, using the same definition for response as for the primary endpoint.
2. Clinical response defined as ≥ 80% decrease in lesion area at the EOT visit, and ≥ 90% decrease in lesion area at the TOC visit (ITT population), with improvement of local signs of the infection in patients surviving up to the respective visit with no use of any concomitant systemic antibacterial treatment or topical antibacterial administration on the primary lesion, and no unplanned additional surgical procedure (other than debridement at bedside or local bedside wound care), with the exception of cellulitis where there is a conversion into an abscess within 48 h of study treatment initiation, or, for post-surgery patients, when an extension of the original incision is indicated.
3. Sustained reduction in lesion size at the EOT and TOC visits (ITT population).
   Sustained reduction in lesion size is defined as ≥ 20% decrease in lesion area 48–72 h after start of treatment (primary endpoint) that is sustained at the EOT and TOC visits.
4. Investigator-assessed clinical success evaluated at 48–72 h after first treatment and the EOT visit, and sustained clinical success at the LFU visit (ITT and CE populations).
   Clinical success at the EOT visit is defined by the same criteria as for the main secondary endpoint, with an indeterminate assessment to include a missing EOT visit.
   Sustained clinical success requires that all criteria listed for the main secondary endpoint are met and there were no new signs or symptoms of the ABSSSI between the TOC and LFU visits.
5. ACM at Day 28 (±2 days).
   Assessment of survival status at Day 28 (±2 days).
6. Microbiological response at Day 3, Day 5, and the EOT, TOC and LFU visits (mITT and ME populations)
   Eradication: No growth of the baseline pathogen(s) based on post-therapy cultures obtained from the primary infection site at the respective time points.
   Presumed eradication: No post-therapy culture due to lack of culturable material, accompanied by investigator-assessed clinical success.
   Persistence: Evidence of continued growth of the baseline pathogen.
   Presumed persistence: No post-therapy culture due to lack of culturable material, accompanied by the absence of investigator-assessed clinical success.
   Superinfection: Emergence of a new pathogen(s) at the primary site of infection, accompanied by the absence of an investigator-assessed clinical success.
   Relapse or recurrence: Pre-therapy pathogen isolated between the EOT and TOC visits, or between the TOC and LFU visits, after a pathogen response of ‘eradication’ or ‘presumed eradication’ at the EOT or TOC visits.

7. Patient-reported pain (ITT and CE populations)
   Time points: all visits, (with exception of Day 28)
   Patient-reported pain, assessed at baseline and throughout the study, using a visual analogue scale (VAS) with a 100 mm line, on which the 0 point indicates 'no pain' and the 100 mm point indicates 'worst pain ever', and a Wong-Baker FACES® Pain Rating Scale.
8. Health economic outcome measures (ITT and CE population)
   Time point: From start of study medication until the LFU visit
   Resource requirements and health economic data will be derived from study-specific data, or collected ancillary to study conduct, to perform health economics analyses. These analyses will aim to enable economic comparisons of ceftobiprole with vancomycin and aztreonam.
9. Safety
   Time point: First dose of study drug until LFU
   Adverse events, laboratory tests (including hematology, biochemistry, and haptoglobin), Coomb's test, vital signs, physical examination, and concomitant medications.
10. Pharmacokinetics
    Time points: Day 4
    Plasma levels of ceftobiprole.
    Sparse PK sampling
    - Day 4: predose, 2 h (end of infusion), 4 to 6 h

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

3.2 Treatment plan

3.2.1 Duration of treatment

Treatment duration will be for at least 5 days and up to 10 days. The required treatment duration within the 5–10 day window will be determined for each patient by the treating investigator. Study treatment may be extended up to 14 days if in the investigator's opinion this is required, and the extension is approved by the sponsor's medical monitor.

3.2.2 Missed-dose management

If one or more doses are missed due to administrative reasons, no doses are to be administered other than in accordance with the schedule provided in Table 3. In such cases, the investigator may consider exclusion of the patient from the study after discussion with the sponsor's medical monitor.

3.2.3 Overdose

Ceftobiprole: There is no available information on overdoses with ceftobiprole in humans. The highest daily dose administered in Phase 1 clinical studies was 3 g (1 g every 8 hours). If an overdose occurs, it should be treated symptomatically. Ceftobiprole plasma concentrations can be reduced by hemodialysis.

Vancomycin: Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance. The median non-clinical lethal IV dose was 319 mg/kg in rats, and 400 mg/kg in mice.

Aztreonam: There have been no reported cases of overdoses of aztreonam. If necessary, aztreonam may be cleared from the serum by hemodialysis and/or peritoneal dialysis. Aztreonam has been shown to be cleared from the serum by continuous arteriovenous hemofiltration.

3.3 Definition of end of study

The end of the study is defined as the completion of the last study-related contact with any patient, referred to as the date of 'Last Patient Last Visit' (LPLV).

3.4 Data and Safety Monitoring Board

For safety monitoring, a Data and Safety Monitoring Board (DSMB) will be utilised periodically throughout the study. Additional blinded interim safety assessments will be performed twice in each year after enrollment of the first patient. Details are provided in the DSMB Charter.

4 STUDY POPULATION

4.1 Target population

Adult male or female patients with an ABSSSI meeting all of the inclusion criteria and none of the exclusion criteria are eligible for enrollment in this study.

4.2 Inclusion criteria

Patients meeting all of the following:

1. Male or female, aged ≥ 18 years.
2. Diagnosis of ABSSSI, meeting at least one of the definitions in (a) to (c) below. Local symptoms must have started within the 7 days prior to the Screening visit.
   (a) Cellulitis/erysipelas, defined as a diffuse skin infection characterized by all of the following within 24 h:
      i. Rapidly spreading areas of erythema, edema, and/or induration with a minimum total lesion surface area of 75 cm^2.
      ii. No collection of pus apparent upon visual examination.
      iii. At least two of the following local signs of infection:
         - erythema
         - induration
         - localized warmth
         - pain or tenderness on palpation
         - swelling/edema

   (b) Major cutaneous abscess, defined as infection characterized by a collection of pus within the dermis or deeper that is apparent upon visual examination before or after therapeutic intervention and is accompanied by all of the following within 24 h:
      i. Erythema, edema and/or induration with a minimum total lesion surface area of 75 cm^2.
      ii. At least two of the following local signs of infection:
         - fluctuance
         - incision and drainage required
         - purulent or seropurulent drainage
         - localized warmth
         - pain or tenderness on palpation

   (c) Wound infection, defined as infection of any apparent break in the skin characterized by at least one of the following:
      i. Superficial incision/surgical site infection meeting all of the following criteria:
         - involves only the skin or subcutaneous tissue around the incision (does not involve fascia).
         - occurs within 30 days of procedure.
         - purulent drainage (spontaneous or therapeutic) with surrounding erythema, edema and/or induration with a minimum total lesion surface area of 75 cm^2.

ii. Post-traumatic wound (including penetrating trauma, e.g., needle, nail, knife, insect and spider bites) meeting the following criterion within 24 h:
   - Purulent drainage (spontaneous or therapeutic) with surrounding erythema, edema and/or induration with a minimum total lesion surface area of 75 cm^2.

3. At least one of the following regional or systemic signs of infection at the Screening visit:
   (a) Lymph node tenderness and volume increase, or palpable lymph node proximal to the primary ABSSSI.
   (b) Fever > 38 °C / 100.4 °F measured orally, > 38.5 °C / 101.3 °F measured tympanically, > 37.5 °C / 99.5 °F measured by the axillary method, or > 39 °C / 102.2 °F measured rectally.
   (c) White blood cell (WBC) count > 10.0×10^9/L or < 4.0×10^9/L.
   (d) > 10% immature neutrophils (band forms).
4. Requirement for intravenous (IV) antibacterial treatment.
5. Willing and able to adhere to study procedures (including prohibitions and restrictions) as specified in this protocol.
6. Willing and able to remain hospitalized (in a hospital or equivalent medical confinement or clinical research unit) until completion of the early-clinical-response assessment for the primary endpoint.
7. Informed consent signed by the patient, or their legally acceptable representative if appropriate, indicating that they understand the purpose of, and procedures required for, the study, and are willing to participate.

4.3 Exclusion criteria

Patients meeting any one of the following:

1. Use of any systemic antibacterial treatment within 14 days, or topical antibacterial administration on the primary lesion within 96 h, before first infusion of study drug.

   Exception: Receipt of a single dose of a short-acting (half-life ≤ 12 h, see Appendix 1) antibacterial therapy (e.g., for surgical prophylaxis) within > 3 days before randomization (i.e., patients cannot have received any antibacterial treatment within 72 h of randomization).*
2. Contraindication to the administration of either of the study treatments, including known clinically-relevant hypersensitivity to related antibacterial treatments (e.g., beta-lactam and glycopeptide antibiotics), or to metronidazole if required as adjunctive therapy.

* The number of patients who have received a single dose of a short-acting antibacterial drug within 14 days before randomization will be limited to 25% of the patient population.

3. Participation in any other clinical study within the 30 days prior to randomization, or any prior participation in this study.
4. The primary ABSSSI is an uncomplicated skin and skin structure infection, such as furuncles, minor abscesses (area of suppuration not surrounded by cellulitis/erysipelas), impetiginous lesions, superficial or limited cellulitis/erysipelas, or minor wound infections (e.g., stitch abscesses).
5. The primary ABSSSI is due to, or associated with, any of the following:
   (a) Diabetic foot infection, gangrene, or perianal abscess.
   (b) Concomitant infection at another site (e.g., septic arthritis, endocarditis, osteomyelitis), not including a secondary ABSSSI lesion.
   (c) Infected burns.
   (d) Decubitus or chronic skin ulcer, or ischemic ulcer due to peripheral vascular disease (arterial or venous).
   (e) Any evolving necrotizing process (e.g., necrotizing fasciitis).
   (f) Infections at vascular catheter sites, or involving thrombophlebitis.
6. The primary ABSSSI is associated with, or in close proximity to, a prosthetic device.
7. Patients who are placed in a hyperbaric chamber as adjunctive therapy for the ABSSSI.
8. Patients expected to require more than two surgical interventions in the operating room for the ABSSSI.
9. Severe sepsis or septic shock.
10. Significant or life-threatening condition (e.g., endocarditis, meningitis) that would confound, or interfere with, the assessment of the ABSSSI.
11. Another severe, acute or chronic medical condition, psychiatric condition, or laboratory abnormality that may increase the risks associated with study participation or administration of the investigational product, or may interfere with the interpretation of study results, and which, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
12. Receiving treatment for active tuberculosis.
13. Absolute neutrophil count $< 0.5 \times 10^9$/L.
14. Recent history of opportunistic infections (i.e., within 30 days) if the underlying cause of these infections is still active (e.g., leukemia, transplant, acquired immunodeficiency syndrome [AIDS]).
15. Patients receiving systemic steroids (> 40 mg per day prednisolone, or equivalent), or receiving immunosuppressant drugs.
16. Requirement for peritoneal dialysis, plasmapheresis, hemodialysis, venovenous dialysis, or other forms of renal filtration, or expected to require such treatment before the TOC visit.

17. Alanine transaminase (ALT) or aspartate transaminase (AST) levels ≥ 8× the upper limit of normal, OR severe hepatic disease with Child-Pugh class C.
18. Women who are pregnant or nursing.
19. Women who are of childbearing potential and unwilling to use an acceptable method of birth control during the study: female sterilization (bilateral tubal occlusion or oophorectomy, or hysterectomy) or male partner vasectomy; intrauterine device (IUD); combined (estrogen- and progesterone-containing) hormonal contraception (oral, vaginal ring, or transdermal patch) with an ethinylestradiol dose of at least 30 µg, plus use of male condoms (preferably with spermicides), female condoms, a female diaphragm or a cervical cap; or total sexual abstinence.

    Women are not considered to be of childbearing potential if they are either ≥ 1 year post-menopausal (where menopause is defined as at least 12 months of amenorrhea), or have a serum follicle stimulating hormone (FSH) measurement consistent with post-menopausal status according to local laboratory thresholds. An FSH measurement at Screening is to be obtained for post-menopausal females aged < 50 years, or for those aged ≥ 50 years who have been post-menopausal for < 2 years.
20. Inability to start study-drug therapy within 24 h of Screening.
21. Patients with illicit drug use within 12 months of screening, including heroin, other opioids (unless prescribed for medical reasons unrelated to heroin substitution), cocaine / crack cocaine, and amphetamine/methamphetamine.
    Exception: Cannabis use.

4.4 Patient withdrawal

Patients may voluntarily withdraw from the study at any time for any reason. The investigator may also withdraw a patient from the study.

The investigator should discuss all study withdrawals with the medical monitor.

4.5 Criteria for discontinuation of treatment

Patients may continue to receive treatment for up to 14 days unless disease progression (lack of efficacy) or unacceptable toxicity occurs. Reasons for discontinuation of treatment must be recorded.

Reasons for premature discontinuation of treatment may include:

- AE
- abnormal laboratory value
- abnormal test procedure result
- intercurrent illness that prevents or interfere with further administration of treatment
- death
- protocol deviation
- lost to follow-up
- administrative/ logistical reasons

A patient must be discontinued from study treatment if any of the following events occur:

- need for the use of systemic non-study antibacterial therapy to treat ABSSSI (e.g., due to lack of efficacy)
- hemodialysis
- pregnancy

All patients must have an LFU visit at 28–35 days after last study-drug administration.

If a patient who has received at least one dose of study drug discontinues from the study at any time, every effort must be made to obtain the patient's consent to the use of the data generated so far, and to have the patient complete the post-treatment EOT, TOC and LFU visits.

For patients who fail to return for EOT, TOC, or LFU visits, the investigator must make every effort to contact the patient (by telephone or mail correspondence). The outcome of this contact must be documented by the investigator and filed in the source data. The reasons for this must be recorded in the case report form (CRF).

4.6 Replacement of patients

Patients failing Screening procedures are to be replaced.

Patients who discontinue participation in the study for any reason after receiving the first dose of study drug are not to be replaced.

Any patient withdrawn from the study or patients failing Screening procedures may not re-enter the study.

Any patient having completed the study is not allowed to re-enroll into the study again.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Summary of schedule of assessments

Table 4 presents a summary of the schedule of assessments to be performed from Screening to the LFU visit.

Study days, as outlined in the schedule of assessments and study visits, are calendar days.

Day 1 is defined as the day on which first study drug administration occurs. However, some study procedures that belong to the Day 1 visit may occur on the previous calendar day, e.g., if randomization occurs on the calendar day prior to first study drug administration, randomization will nevertheless be considered to belong to the Day 1 visit. Actual elapsed time (rather than calendar days) will be used to measure the time:

- from first dose of study drug to the 48–72 h early-response assessment
- from randomization to the TOC visit (15–22 days)
- from last dose of study drug to the LFU visit (28–35 days)
- from randomization to recording of survival status (28 days)

Table 4 Schedule of assessments

	Screening Pre-treatment	Active treatment[1]							Post-treatment			
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12
Time	**Within 24 h before first dose**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 14**	**EOT***	**TOC***	**Day 28**	**LFU***
Screening/baseline/informed consent/subject number	X											
Medical history/demographics/ prior (within 30 days) antibacterial and other pre-study drug/non-drug therapy, Inclusion/exclusion criteria	X											
Documentation of any ABSSSI surgical procedures anticipated during the course of the study and planned at baseline	X											
Complete physical examination[2]	X											
Randomization by IWRS		X										
Brief physical examination[3]				X					X	X		X
Body temperature[4]	X	<----------2X---------->						X	X	X		X
Vital signs[5]	X	<----------X---------->						X	X	X		X
Pregnancy test[6]	X											X
Safety laboratory (local lab)[7]	X											
Safety laboratory (central lab)	X			X		X			X			X
Haptoglobin and Coombs test (central lab)	X								X			
Reticulocytes (central lab)	X								X			
WBC count and CRP (central lab)	X	X	X	X	X	X			X	X		
Infection-site specimen collection[8]	X			X		X			X	X		X
Blood culture [8, 9]	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		(X)
PK blood sample collection[10]					X							
Patient-reported pain assessment[11]	X	X	X	X	X	X	X	X	X	X		X

	Screening Pre-treatment	Active treatment[1]							Post-treatment			
Visit No.	1	2	3	4	5	6	7	8	9	10	11	12
Time	**Within 24 h before first dose**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 8**	**Day 14**	**EOT***	**TOC***	**Day 28**	**LFU***
Study-drug administration		<----------X[1]---------->										
Drug accountability		<----------X---------->										
Investigator infection-site assessment[12]	X		2X	2X	2X		X		X	X		X
Digital photography[13]	X			X					X	X		
Investigator assessment of clinical success[14]			X	X	X	X	X		X	X		X
Concomitant antibacterial and other therapies[15]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant non-drug procedures[15]	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine clearance[16]	X	X	X	X	X	X	X					
Vancomycin trough level (central laboratory) [17]			(X)		(X)							
Vancomycin trough levels (local laboratory) [18]		<----------X---------->										
Health economics outcome measures[19]												X
Adverse events		<----------X---------->							X	X	X	X
Survival status[20]											X	

* EOT: ≤ 24 h after last treatment. TOC: 15–22 days after randomization. LFU: 28–35 days after last treatment.

1. Patients will receive IV study-drug therapy for a minimum of 5 days and a maximum of 14 days.
2. Physical examination includes general appearance, skin, neck inclusive thyroids, eyes, nose, throat, cardiovascular system, thorax/lungs, abdomen, lymph nodes, extremities, nervous system, and mental status.
3. Physical examination is to be focused on any changes from baseline.
4. Measured twice daily (morning and evening) during the visits on the first 8 days of treatment. Afterwards temperature measurements are to be taken once on each scheduled study-visit day except Day 28. The same method of measuring temperature should be chosen within a site for all patients during course of the study.
5. Vital signs include height, weight, blood pressure, respiratory rate, pulse rate; to be taken once at each study visit at a time point when temperature assessment is performed (see Note 4). A patient's height must only be assessed during the Screening visit.

6. Pregnancy testing is to be performed for women of childbearing potential; at Screening a serum pregnancy test is to be obtained; at the LFU visit it is at the discretion of the investigator whether a serum or urine pregnancy test is obtained, and subject to local regulations. The investigator may conduct additional (serum or urine) pregnancy tests to confirm the absence of pregnancy at any time during the study (Section 5.3.6). If a pregnancy test result is positive, study drug must be discontinued, and the patient followed for safety, and assessment of the pregnancy outcome (Section 7.4.2).
7. Local safety laboratory includes hematology, biochemistry, glucose levels, coagulation and urinalysis. At Screening, an FSH measurement is to be obtained for post-menopausal (where menopause is defined as at least 12 months of amenorrhea) females aged < 50 years, or for those aged ≥ 50 years who have been post-menopausal for < 2 years. Local laboratory tests will be used to assess patient eligibility, and additional local laboratory tests may be performed at any time during the study as clinically indicated; results of additional tests should not be entered in the CRF laboratory results page, but if constituting an AE should be entered in the CRF AE page. Creatinine clearance is to be calculated using the Cockcroft-Gault formula.
8. ABSSSI site specimens (obtained surgically or by aspiration, biopsy or deep swab) and blood specimens for culture are to be obtained from each patient during Screening, but results are not required to be available prior to randomization. If the specimen obtained during Screening was inadequate or was not available for testing, additional blood and ABSSSI site specimens are to be obtained within 24 h of study-drug administration. During the treatment period, additional ABSSSI site specimens (if material is available) are to be obtained at Day 3, Day 5, the EOT, TOC and LFU visits, and at any other time if clinically indicated, e.g., in the event of failure, or when no improvement in lesion(s), or deterioration of lesion(s), is observed and if easily accessible. Specimens are to be cultured by the local laboratory using standard microbiological procedures. All unique organisms from blood and the ABSSSI site are to be sent to the central microbiology laboratory for identification, and for susceptibility testing with all study drugs.
9. Two blood samples are to be collected for cultures from all patients within the 6 h before randomization. If the result of the blood culture is positive, additional blood cultures should be collected at each visit, or more frequently if clinically indicated, until two consecutive negative results are obtained on separate days.
10. For the determination of plasma ceftobiprole levels, sparse PK sampling will be collected on Day 4 predose, 2 h (end of infusion), and 4 to 6 h after the start of infusion. Rich PK sampling will be collected on Day 4: predose, 2 h (end of infusion), 3 h, 4 h, 6 h, and 8 h after the start of infusion.
11. Patient-reported pain using a VAS with a 100 mm line; 0 point = “no pain”, 100 mm point = “worst pain ever”, and a Wong-Baker FACES® Pain Rating Scale.
12. Primary measurement of the target lesion size is to be performed using a flexible ruler, measuring longest length, and maximum width perpendicular to the length. Measurements are to be performed at Screening (prior to randomization and within the 6 h prior to first dose of study drug), twice on Day 2, Day 3, and Day 4, and once on Day 8, and the EOT, TOC and LFU visits. On days when two measurements are obtained, the measurements are to be taken at least 8 h apart. Infection-site assessment includes incision/drainage, erythema, heat/localized warmth, pain/tenderness to palpation, fluctuance, swelling/induration.
13. A digital photograph will be obtained at Screening, at the early clinical response assessment (48–72 h after first treatment), and at the EOT and TOC visit, for each patient (primary ABSSSI lesion), and will be used for documentation purposes and as source data. Digital photography will not be used for the measurement of the ABSSSI lesion size area; the determination of the ABSSSI lesion size area will be solely based on the ruler measurements.
14. Clinical success will be assessed by the investigator using a four-point scale relative to the baseline assessment: cured, improved, stable, or worsened. In case of worsened (e.g., bacteremia, osteomyelitis, amputation), signs and symptoms need to be documented as AEs.

15. Concomitant antibacterial therapies, other drug therapies, and non-drug procedures will be assessed at all scheduled study visits.
16. Creatinine clearance: CL_{CR} should be calculated using the Cockcroft-Gault formula based on local laboratory results, and should be performed at Screening, and at a minimum on study Days 1, 2, 3, 4, 5, and 8. The actual age, weight and serum creatinine level on the day of CL_{CR} calculation should be used. Additional CL_{CR} calculations may be performed as clinically indicated. All CL_{CR} results obtained during the active treatment period (i.e., when the patient is receiving study medication) need to be reviewed by the unblinded pharmacist (or delegate) on the day when local laboratory serum-creatinine results are obtained and the doses of vancomycin and ceftobiprole are adjusted in accordance with Table 8.
17. Vancomycin trough level (central laboratory assessment): a vancomycin trough level for central laboratory assessment is to be obtained approximately 30 minutes before administration of the fourth dose of vancomycin (i.e., on Day 2 for patients who receive vancomycin on a q12h schedule, and on Day 4 for patients who receive vancomycin on a q24h schedule). The central laboratory result will not be communicated to the study site.
18. Vancomycin trough levels (local laboratory assessment): in study sites which use vancomycin trough level monitoring to guide vancomycin dosing and which perform vancomycin trough level testing using a local laboratory, an additional blood sample for local laboratory testing of the vancomycin trough level should also be obtained before administration of the fourth dose of vancomycin on Day 2 (vancomycin q12h schedule) or Day 4 (vancomycin q24 h schedule). Additional local laboratory testing of vancomycin trough levels should be obtained according to institutional practices at the respective study site.
19. Information on health economics outcome measures from baseline to the LFU visit will be collected at the LFU visit, including study treatment duration, total length of stay in hospital, location of treatment within the healthcare system (e.g., Emergency Department), concomitant medications, post-study drug procedures and interventions including AEs and any treatment required by these events, re-admission rates, outpatient healthcare encounters, Emergency Department visits, antibacterial use, and surgical and non-surgical procedures, e.g., debridement, grafts, amputation, prostheses.
20. Survival status (by telephone or visit) must be obtained at Day 28 (±2 days).

5.2 Study visits

5.2.1 Visit 1: Screening (Day −1; within 24 h before first dose)

The following assessments and procedures must be performed at the Screening visit:

- Screening/baseline/informed consent
- Assign Subject number and Interactive Web Response System (IWRS) registration
- Inclusion/exclusion criteria
- Medical history/demographics/ prior (within 30 days) antibacterial and other pre-study drug/non-drug therapy
- Complete physical examination
- Body temperature
- Vital signs
- Pregnancy test (serum)
- Safety laboratory (local lab)
- Safety laboratory (central lab)
- Haptoglobin and Coombs test (central lab)
- Reticulocytes (central lab)
- WBC count and C-reactive protein (CRP) (central lab)
- Infection-site specimen collection
- Blood culture
- Patient-reported pain assessment
- Investigator infection-site assessment
- Digital photography
- Concomitant antibacterial and other therapies
- Concomitant non-drug procedures
- CL_{CR} should be calculated using the Cockcroft-Gault formula
- Documentation of any ABSSSI surgical procedures anticipated during the course of the study and planned at baseline

The infection site assessment should occur before randomization, and within the 6 hours prior to the first dose of study drug. Infection-site specimens must be obtained from each patient during Screening (i.e., within 24 h prior to first dose of study treatment). Gram stain, culture, and susceptibility testing must be performed from the infection site specimens, but results are not required to be available prior to randomization.

5.2.2 Visit 2: Active treatment Day 1

The following assessments and procedures are to be performed at Visit 2:

- Randomization
- Body temperature (twice daily)
- Vital signs
- WBC count and CRP (central lab)
- Blood culture (if positive result was obtained at baseline)
- Patient-reported pain assessment
- Study-drug administration
- Drug accountability
- Concomitant antibacterial and other therapies
- Concomitant non-drug procedures
- Serum creatinine (local laboratory) and CL_{CR} (calculated using the Cockcroft-Gault formula)
- AEs

Intravenous study treatment is to be administered within 6 hours of randomization.

5.2.3 Visit 3: Active treatment Day 2

The following assessments and procedures are to be performed at Visit 3:

- Body temperature (twice daily)
- Vital signs
- WBC count and CRP (central lab)
- Vancomycin trough level (central laboratory) to be obtained 30 min prior to the fourth dose of vancomycin for patients on a q12h vancomycin schedule
- Vancomycin trough level (local laboratory) in study sites which use vancomycin trough level monitoring to guide vancomycin dosing using a local laboratory; to be obtained 30 min prior to the fourth dose of vancomycin for patients on a q12h vancomycin schedule
- Blood culture (if positive result was obtained at baseline)
- Patient-reported pain assessment
- Study-drug administration
- Drug accountability
- Investigator infection-site assessment (twice daily)
- Investigator assessment of clinical success
- Concomitant antibacterial and other therapies
- Concomitant non-drug procedures
- Serum creatinine (local laboratory) and CL_{CR} (calculated using the Cockcroft-Gault formula)
- AEs

5.2.4 Visit 4: Active treatment Day 3

The following assessments and procedures are to be performed at Visit 4:

- Brief physical examination
- Body temperature (twice daily)
- Vital signs
- Safety laboratory (central lab)
- WBC count and CRP (central lab)
- Serum creatinine (local laboratory) and CL_{CR} (calculated using the Cockcroft-Gault formula)
- Infection-site specimen collection
- Blood culture (if positive result was obtained at baseline and two consecutive negative results have not been obtained on separate days)
- Patient-reported pain assessment
- Study-drug administration
- Drug accountability
- Investigator infection-site assessment (twice daily)
- Investigator assessment of clinical success
- Digital photography
- Concomitant antibacterial and other therapies
- Concomitant non-drug procedures
- AEs

5.2.5 Visit 5: Active treatment Day 4

The following assessments and procedures are to be performed at Visit 5:

- Body temperature (twice daily)
- Vital signs
- WBC count and CRP (central lab)
- Vancomycin trough level (central laboratory) to be obtained 30 min prior to the fourth dose of vancomycin for patients on a q24h vancomycin schedule
- Vancomycin trough level (local laboratory) in study sites which use vancomycin trough level monitoring to guide vancomycin dosing using a local laboratory; to be obtained 30 min prior to the fourth dose of vancomycin for patients on a q24h vancomycin schedule
- PK blood sample collection
- Patient-reported pain assessment
- Blood culture (if positive result was obtained at baseline and two consecutive negative results have not been obtained on separate days)
- Study-drug administration

- Drug accountability
- Investigator infection-site assessment (twice daily)
- Investigator assessment of clinical success
- Concomitant antibacterial and other therapies
- Concomitant non-drug procedures
- Serum creatinine (local laboratory) and CL_{CR} (calculated using the Cockcroft-Gault formula)
- AEs

5.2.6 Visit 6: Active treatment Day 5

The following assessments and procedures are to be performed at Visit 6:

- Body temperature (twice daily)
- Vital signs
- Safety laboratory (central lab)
- WBC count and CRP (central lab)
- Infection-site specimen collection
- Blood culture (if positive result was obtained at baseline and two consecutive negative results have not been obtained on separate days)
- Patient-reported pain assessment
- Study-drug administration
- Drug accountability
- Investigator assessment of clinical success
- Concomitant antibacterial and other therapies
- Concomitant non-drug procedures
- Serum creatinine (local laboratory) and CL_{CR} (calculated using the Cockcroft-Gault formula)
- AEs

5.2.7 Visit 7: Active treatment Day 8

The following assessments and procedures are to be performed at Visit 7:

- Body temperature (twice daily)
- Vital signs
- Blood culture (if positive result was obtained at baseline and two consecutive negative results have not been obtained on separate days)
- Patient-reported pain assessment
- Study-drug administration
- Drug accountability
- Investigator infection-site assessment

- Investigator assessment of clinical success
- Concomitant antibacterial and other therapies
- Concomitant non-drug procedures
- Serum creatinine (local laboratory) and CL_{CR} (calculated using the Cockcroft-Gault formula)
- AEs

5.2.8 Visit 8: Active treatment Day 14

The following assessments and procedures are to be performed at Visit 8:

- Body temperature
- Vital signs
- Blood culture (if positive result was obtained at baseline and two consecutive negative results have not been obtained on separate days)
- Patient-reported pain assessment
- Study-drug administration
- Drug accountability
- Concomitant antibacterial and other therapies
- Concomitant non-drug procedures
- AEs

5.2.9 Visit 9: Post-treatment EOT visit

The EOT visit is to take place within 24 h after last study-drug administration.

For patients who terminate study-drug treatment early, the EOT visit should take place within 72 h of the discontinuation.

The following assessments and procedures are to be performed at the EOT visit:

- Brief physical examination
- Body temperature
- Vital signs
- Haptoglobin and Coombs test (central lab)
- Safety laboratory (central lab)
- Reticulocytes (central lab)
- WBC count and CRP (central lab)
- Infection-site specimen collection
- Blood culture (if positive result was obtained at baseline and two consecutive negative results have not been obtained on separate days)
- Patient reported pain assessment
- Investigator infection-site assessment

- Investigator assessment of clinical success
- Digital photography
- Concomitant antibacterial and other therapies
- Concomitant non-drug procedures
- AEs

5.2.10 Visit 10: Post-treatment TOC visit

The TOC visit is to take place 15–22 days after randomization. The TOC visit should be performed at least 5 days after EOT.

The following assessments and procedures are to be performed at the TOC visit:

- Brief physical examination
- Body temperature
- Vital signs
- WBC count and CRP (central lab)
- Infection-site specimen collection
- Blood culture (if positive result was obtained at baseline and two consecutive negative results have not been obtained on separate days)
- Patient-reported pain assessment
- Investigator infection-site assessment
- Investigator assessment of clinical success
- Digital photography
- Concomitant antibacterial and other therapies
- Concomitant non-drug procedures
- AEs

5.2.11 Visit 11: Post-treatment Day 28 (survival status via phone or visit)

The following assessments and procedures are to be performed at the Day 28 visit (±2 days):

- Concomitant antibacterial and other therapy
- Concomitant non-drug procedures
- AEs
- Survival status

5.2.12 Visit 12: Post-treatment LFU visit

The LFU visit is to take place 28–35 days after last treatment.

The following assessments and procedures are to be performed at the LFU visit:

- Brief physical examination
- Body temperature
- Vital signs
- Pregnancy test (serum or urine)
- Safety laboratory (central lab)
- Infection-site specimen collection
- Blood culture (if positive result was obtained at baseline and two consecutive negative results have not been obtained on separate days)
- Patient-reported pain assessment
- Investigator infection-site assessment
- Investigator assessment of clinical success
- Concomitant antibacterial and other therapies
- Concomitant non-drug procedures
- Health economics outcome measures
- AEs

5.3 Study procedures

5.3.1 Screening/baseline/informed consent

The investigator must obtain the patient's informed consent to participation in the study before carrying out any study procedures during Screening. At the Screening visit, the investigator must obtain the patient's medical history/demographics/prior (within 30 days) antibacterial and other pre-study drug/non-drug therapy, and review the inclusion/exclusion criteria.

The investigator is to assign a Subject number (Country code-Site ID-Subject ID) at Screening.

5.3.2 Patient registration and Interactive Voice/Web Response System

An IWRS will be used for this study.

The investigator will register eligible patients in the IWRS. Randomization, further registrations and events will be handled according to the IWRS manual.

Detailed handling instructions are provided in the IWRS manual.

5.3.3 Physical examination

A complete physical examination must be performed in accordance with the schedule of assessments (see Table 4). Physical examination includes general appearance, skin, neck inclusive thyroids, eyes, nose, throat, cardiovascular system, thorax/lungs, abdomen, lymph nodes, extremities, nervous system, and mental status.

A brief physical examination must be performed in accordance with the schedule of assessments (see Table 4). Brief physical examination is to be focused on any changes from baseline.

5.3.4 Body temperature measurement

Body temperature is to be measured twice daily (morning and evening) during the visits on the first 8 days of treatment, after which temperature measurements are to be taken once on each scheduled study visit day except Day 28. The same method of measuring temperature should be chosen within a site for all patients during the course of the study.

5.3.5 Vital signs

Vital signs must be assessed in accordance with the schedule of assessments (see Table 4), at the same time as the temperature assessment is performed.

Vital signs include height, weight, respiratory rate, radial pulse rate, systolic blood pressure and diastolic blood pressure. Pulse rates and blood pressures must be obtained in the same position throughout a visit, i.e., either sitting or supine as appropriate, after the patient has been at rest for at least 5 min.

A patient's height must only be assessed during the Screening visit.

5.3.6 Pregnancy testing

Women of childbearing potential must have a negative serum pregnancy test result during Screening.

At the LFU visit it is at the discretion of the investigator whether a serum or urine pregnancy test is obtained, and subject to local regulations.

The investigator may conduct additional pregnancy tests (serum or urine) to confirm the absence of pregnancy at any time during the study. If a pregnancy test result is positive, study drug must be discontinued, and the patient followed for safety, and assessment of the pregnancy outcome.

Further details regarding pregnancy are provided in Section 7.4.

5.3.7 Safety laboratory parameters

Local safety laboratory parameters to be used to assess patient eligibility at Screening include hematology, biochemistry, coagulation, blood glucose, and urinalysis.

At Screening, a FSH measurement is to be obtained for post-menopausal (where menopause is defined as at least 12 months of amenorrhea) females aged < 50 years, or for those aged ≥ 50 years who have been post-menopausal for < 2 years. CL_{CR} for dose determination is to be calculated using the Cockcroft-Gault formula.

Additional local laboratory tests may be performed at any time during the study as clinically indicated. The results of such additional tests should not be entered in the

laboratory results page of the CRF; if the results constitute an AE they should be entered in the CRF AE page.

Central laboratory safety parameters will be carried out in accordance with the schedule of assessments (see Table 4). Additional central testing may be performed at the discretion of the investigator whenever clinically indicated. All samples for a given study center must be analyzed by the same central laboratory throughout the study, as designated by the sponsor. The results are to be printed, signed and dated by the investigator/designee.

Table 5 Local laboratory safety parameters mandatory (for patient eligibility) at Screening

Hematology	Clinical chemistry	Coagulation	Urine (dipstick analysis)
HGB	Albumin	PT	Blood
HCT	ALT		Glucose
RBC count	AST		Ketones
WBC count	Bilirubin (total)		Leukocytes
Platelets	Potassium		Nitrite
(Abs. neutrophils and % immature neutrophils [bands] are to be obtained if required for patient eligibility)	Sodium		pH
	Creatinine		Protein
	Urea or BUN		Specific gravity
	Glucose		Bilirubin
	Serum-pregnancy test		Urobilinogen
	FSH*		

ALT=alanine transaminase; AST=aspartate transaminase; FSH=serum follicle stimulating hormone; HCT=hematocrit; HGB=hemoglobin; PT=prothrombin time; RBC=red blood cell; WBC=white blood cell.
*for post menopausal females aged < 50 years, or for those aged ≥ 50 years who have been post-menopausal for < 2 years.

Table 6 Central laboratory safety parameters

Hematology	Clinical chemistry	Coagulation
HGB	Albumin	PT
HCT	Total Protein	INR
RBC count	AP	aPTT
WBC count	ALT	
Platelets	AST	
% Basophils	GGT	
% Eosinophils	LDH	
% Lymphocytes	Bilirubin (direct & indirect)	
Monocytes	Potassium	
Neutrophils	Sodium	
Abs. basophils	Chloride	
Abs. eosinophils	Creatinine	
Abs. lymphocytes	Urea	
Abs. monocytes	Uric acid	
Abs. neutrophils	Glucose	
	CRP	

ALT=alanine transaminase; AST=aspartate transaminase; AP=alkaline phosphatase; aPTT= activated partial thromboplastin time; CRP=C-reactive protein; GGT=gamma-glutamyl transferase; HCT=hematocrit; HGB=hemoglobin; INR=International Normalized Ratio; LDH=lactate dehydrogenase; PT=prothrombin time; RBC=red blood cell; WBC=white blood cell.

In the event of unexplained abnormal laboratory test values, the tests might be repeated immediately and followed-up until the results return to the normal range, stabilization, and/or until an adequate explanation of the abnormality has been determined. If a clear explanation is established, this must be recorded in the CRF. Abnormal laboratory results should not be recorded as an AE unless the abnormality is associated with a clinically relevant condition.

Detailed handling instructions are provided in the Laboratory manual.

5.3.8 Reticulocytes, haptoglobin and Coombs test

Reticulocytes, haptoglobin and Coombs test will be assessed by central laboratory according to the schedule shown in Table 4.

5.3.9 WBC count and CRP testing

WBC counts and CRP levels will be assessed by central laboratory according to the schedule shown in Table 4.

5.3.10 Creatinine clearance

Creatinine clearance (CL_{CR}): CL_{CR} should be calculated using the Cockcroft-Gault formula based on local laboratory results, and should be performed at Screening, and at a minimum on study Days 1, 2, 3, 4, 5, and 8. The actual age, weight, and serum creatinine level on the day of CL_{CR} calculation should be used. Additional CL_{CR} calculations may be performed as clinically indicated. All CL_{CR} results obtained during the active treatment period (i.e., when the patient is receiving study medication) need to be reviewed by the unblinded pharmacist (or delegate) on the day when local laboratory serum-creatinine results are obtained and the doses of vancomycin and ceftobiprole are adjusted in accordance with Table 8.

5.3.11 Microbiological assessments

A laboratory manual will be provided to each site which will provide guidance on the microbiological sampling, and processing and shipments of microbiological samples.

5.3.11.1 ABSSSI site specimen

An ABSSSI site specimen for Gram stain, culture, and susceptibility testing must be obtained from each patient within the 24 h prior to study-drug administration. The specimen must be maintained at room temperature and processed for Gram stain and culture as soon as possible (maximum 2 hours), unless using an appropriate transport medium. If the Screening-visit sample was inadequate or not available for testing, additional samples may be obtained if accessible on Day 1. During the Treatment Period, additional ABSSSI site specimens (if material is available) are to be obtained at Day 3, Day 5, at the EOT, TOC and LFU visits, and at any other time if clinically indicated, e.g., in the event of failure, or when no improvement in lesion(s), or deterioration of lesion(s), is observed and if easily accessible.

Samples will be obtained using sterile techniques for the methods outlined in Table 7. A superficial swab of the ABSSSI site is not acceptable.

Table 7 Acceptable methods for ABSSSI specimen collection

Type of ABSSSI	Source of material	Method of collection*
Abscess	• Purulent fluid	• Aseptic aspiration of purulent fluid
	• Biopsy material	• Biopsy material obtained from incision and drainage under sterile conditions
Cellulitis	• Aspirate • Punch biopsy	• After cleansing the skin at the leading edge of erythema, inject and aspirate saline, or perform a punch biopsy, as medically appropriate
Traumatic wound	• Scrapings from wound base	• After cleansing and debriding the wound bed, and using sterile techniques, scrape ulcer/wound base with sterile dermal curette or scalpel to obtain tissue
	• Biopsy material from wound base	• After following the above procedure, biopsy tissue at the base of the lesion
Surgical-site infection	• Scrapings from base of surgical site	• After cleansing and debriding the wound bed, and using sterile techniques, scrape the base of the lesion with sterile dermal curette or scalpel to obtain tissue
	• Biopsy material from base of surgical site	• After following the above procedure, biopsy tissue at the base of the lesion

* Prior to collection of the ABSSSI site specimen, the ABSSSI site is to be prepared by a standard-of-care surgical site skin preparation method with the appropriate application of an antiseptic agent such as: an iodophor (e.g., 5% povidone-iodine), an alcohol-containing product (e.g., 70% ethyl alcohol, 70% isopropyl alcohol), chlorhexidine gluconate, or a combination product (e.g., 5% povidone iodine solution in 70% ethanol; or > 0.5% chlorhexidine with alcohol).

If possible, the local laboratory should retain all isolates until the end of the study, or until confirmation of a viable organism is received from the central laboratory. Back-up cultures are to be requested when the central laboratory does not receive a viable culture, or recovers an organism different from the one recorded by the local laboratory.

5.3.11.2 Gram staining

Gram stains are to be prepared and interpreted by the local laboratory according to the criteria provided in the Microbiology Manual, and results reported in the CRF. A review of each slide at the local laboratory should note the presence or absence of organisms, as well as squamous and polymorphonuclear cells. Further details are provided in the Microbiology Manual.

5.3.11.3 Cultures and susceptibility testing

Each local laboratory is to culture specimens and identify pathogens in accordance with the laboratory's standard procedures. All isolated pathogens obtained from the infection site and considered clinically relevant are to be sub-cultured and sent to the central laboratory for identification to the species level.

Each local laboratory is also to perform susceptibility testing in accordance with the laboratory's standard procedures. Gram stain, culture, and susceptibility testing must be

performed from the infection site specimens, but results are not required to be available prior to randomization. All isolates sent to the central laboratory will be susceptibility tested to study drugs and other relevant antibacterial agents to current CLSI and EUCAST standards. Further details are provided in the Microbiology Manual.

5.3.11.4 Blood cultures

Two blood samples from two venipuncture sites must be obtained for cultures from all patients within the 6 h before randomization. Blood samples are to be taken 5 minutes apart by peripheral venous blood draw using sterile techniques. Each blood sample must be at least 20 mL. The blood samples are then to be divided equally into aerobic (10 mL) and, where possible, anaerobic (10 mL) culture media, and incubated for a minimum of 5 days.

If the result of the blood culture is positive, additional blood cultures should be collected using the same method as specified above at each visit, or more frequently if clinically indicated, until two consecutive negative results are obtained on separate days.

All isolated pathogens obtained from the cultures are to be sub-cultured and sent to the central laboratory for identification to the species level, and susceptibility testing.

5.3.12 PK blood sample collection

For determination of plasma ceftobiprole, PK blood samples are to be obtained at the following time points:

Sparse PK sampling (all sites)

In total, three blood samples of approximately 2 mL each are to be collected as follows:

- Day 4: predose, 2 hours (end of infusion), and 4 to 6 hours after the start of infusion

Rich PK sampling (selected sites)

Six blood samples of approximately 2 mL each are to be collected as follows:

- Day 4: predose, 2 hours (end of infusion), 3 hours, 4 hours, 6 hours and 8 hours after the start of infusion

5.3.13 Vancomycin trough level testing (central laboratory)

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

5.3.14 Vancomycin trough level testing (local laboratory)

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

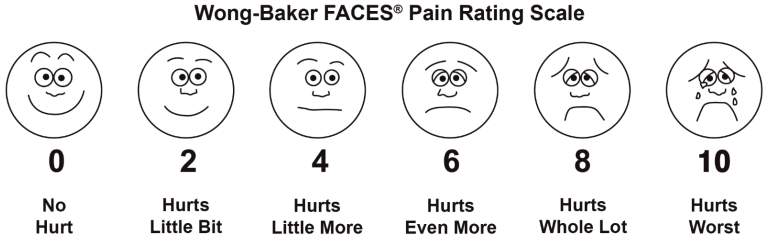
5.3.15 Patient-reported pain assessment

Patient-reported pain, assessed at baseline and throughout the study, using a VAS with a 100 mm line, on which the 0 point indicates 'no pain' and the 100 mm point indicates 'worst pain ever', and a Wong-Baker FACES® Pain Rating Scale.

Visual analog scale

0 mm	100 mm
no pain	worst pain ever

Wong-Baker FACES® Pain Rating Scale



5.3.16 Investigator infection-site assessment

Primary measurement of the target lesion size is to be performed using a flexible ruler, measuring length, and maximum width perpendicular to the length.

Length of the lesion will be measured as the longest length.

Width will be measured as the widest width perpendicular to the longest length.

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

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

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

The infection-site assessment is to include edema, erythema, induration, localized warmth, pain on palpation, tenderness on palpation, swelling, fluctuance, incision required, incision performed (on the respective day of assessment), drainage required, drainage performed (on the respective day of assessment), purulent drainage, seropurulent drainage.

5.3.17 Investigator assessment of clinical success

Clinical success will be assessed by the investigator using a 4-point scale relative to the baseline assessment: cured, improved, stable, or worsened.

If the assessment is 'worsened' (e.g., bacteremia, osteomyelitis, amputation), the signs and symptoms must be documented as AEs.

5.4 Medical history, prior and concomitant medications

5.4.1 Medical history

A full medical history, including relevant abnormalities, surgeries, diseases, or disorders, must be obtained at Screening, constituting the baseline characteristics of the patient.

Medical history also includes any relevant change in, or worsening of, a patient's condition which occurs after consent, but prior to the start of first study-drug administration (see Section 7.3.1).

5.4.2 Prior medications

All prior medications taken within 30 days of the Screening visit must be documented for each patient in the CRF, including the dosage, dose regimen, route of administration, therapeutic indication, and start/stop dates of use.

Use of any systemic antibacterial treatment within 14 days, or topical antibacterial administration on the primary lesion within 96 hours, before first infusion of study drug is not permitted, with the exception of the receipt of a single dose of a short-acting (half-life ≤ 12 h) antibacterial therapy (e.g., for surgical prophylaxis) within > 3 days before randomization (i.e., patients cannot otherwise have received any antibiotic treatment within 72 h of randomization). The number of patients who have received a single dose of a short-acting antibacterial drug within 14 days before randomization will be limited to 25% of the patient population.

A list of antibacterial therapies that meets the criterion of a half-life ≤ 12 h is provided in Appendix 1.

5.4.3 Permitted concomitant medications

All non-antibacterial standard-of-care medications are allowed as concomitant medications.

The use of acetaminophen or paracetamol is allowed when an antipyretic medication is indicated.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic steroids (≤ 40 mg per day prednisolone or equivalent) are allowed from 72 h after start of treatment, only after early clinical response has been determined.

Low-dose aspirin (≤ 200 mg per day) is allowed.

Any concomitant medications (including herbal medicines) that are taken by or administered to the patient during the course of the study must be recorded in the CRF, including the dosage, dose regimen, route of administration, therapeutic indication, and start/stop dates of use.

5.4.4 Prohibited concomitant medications

Concomitant systemic antibacterials are prohibited during the study up to the TOC visit, with the following exceptions:

1. Vancomycin PO 125 mg or 250 mg q6h, fidaxomicin PO 200 mg q12h, or metronidazole IV or PO 500 mg q8h, may be used in both treatment groups for the treatment of *C. difficile* infections.
2. Metronidazole IV may also be used as adjunctive therapy in both treatment groups for coverage of anaerobic bacteria.
3. Nitrofurantoin may be used at any time during the study in both treatment groups as it does not achieve therapeutic blood levels.

All NSAIDs are prohibited until 72 h after start of treatment, and only after early clinical response has been determined.

The administration of steroids (> 40 mg per day prednisolone, or equivalent), or immunosuppressant is prohibited between administration of first study drug and the TOC visit.

Chronic systemic therapy with calcineurin-inhibitors (e.g., tacrolimus, or ciclosporin), mycophenolate mofetil or mycophenolate sodium, azathioprine, or sirolimus, is prohibited from randomization up to the TOC visit.

The use of topical antibacterials on the primary lesion is not permitted from randomization through TOC.

The sponsor will not provide any concomitant medication.

5.4.5 Non-drug adjunctive therapy

Adjuvant surgical treatment is appropriate and necessary and is required to adequately treat wound infections and abscesses. On occasion a cellulitis will transform into an abscess which also requires proper surgical drainage of the abscess. At Screening, all patients should be evaluated, and a determination made whether or not more than one intra-operative surgical intervention should be planned.

Patients expected to require more than two surgical interventions in the operating room for the ABSSSI are excluded from the study.

When indicated, the initial procedure should be performed before randomization, and subsequent procedures performed no later than 48 h after the start of treatment.

The reasons for the need for more than one planned intra-operative intervention must be timed and dated in the study source document at the time the decision is made that more than one intra-operative intervention is needed.

The following adjunctive therapies are permitted for the treatment of ABSSSI at any time:

- debridement at the bedside
- topical solutions, including antiseptic agents such as povidone-iodine (topical solutions should not contain any microbial agents)
- local bedside wound care in accordance with hospital protocols

5.4.6 Restrictions

Patients will be encouraged to continue their usual diet and level of activity, as dictated by their clinical condition. Activities that would impact clinical outcome should be avoided during the study period.

Participation in any other clinical study, including non-interventional studies and medical device investigations, is prohibited from 30 days prior to enrollment up to and including the LFU visit.

5.5 Health economics outcome measures

Resource requirements and health economic data will be derived from study-specific data or collected ancillary to study conduct to perform a health economic analysis (ITT and CE populations). These analyses will aim to enable economic comparisons of ceftobiprole versus vancomycin and aztreonam.

Health economic outcome measures may include:

- Study treatment duration
- Total length of stay in hospital
- Location of treatment within the healthcare system (e.g., Emergency Department)
- Concomitant medications
- Post-study drug procedures and interventions
- AEs and any treatment required by these events
- Re-admission rates
- Outpatient healthcare encounters
- Emergency Department visits
- Antibacterial use
- Surgical and non-surgical procedures, e.g., debridement, grafts, amputation, prostheses

5.6 Safety assessments

The investigator will evaluate patient safety by AE monitoring, physical examination, vital signs, and safety laboratory tests.

Safety assessments must be performed at intervals indicated in the schedule of assessments (see Table 4). More frequent assessments may be performed at the investigator's discretion, if medically indicated.

5.6.1 Adverse event monitoring

The AE monitoring and collection period, and the reporting of serious AEs (SAEs), are described in Section 7.

6 STUDY DRUGS

6.1 Dose and schedule

After randomization and during active treatment, patients will receive either ceftobiprole or vancomycin plus aztreonam, according to the schedule outlined in Table 8.

The requirement for aztreonam therapy will be reassessed at the 72-h study visit (Visit 4). Termination of aztreonam is permitted when all of the following criteria are met:

- a Gram-positive pathogen has been isolated but no Gram-negative pathogen is present, and
- the presence of Gram-negative organisms is unlikely based on the investigator's assessment, and
- Gram-negative coverage is clinically not required based on the investigator's assessment

In cases where (blinded) aztreonam is discontinued after 72 h, re-administration of (blinded) aztreonam is permitted at any point during the study treatment period, at the discretion of the investigator, when there is confirmation or suspicion of a concomitant Gram-negative infection.

The dosing and schedule is to be adjusted based on five CL_{CR} categories: > 100 mL/min; 70–100 mL/min; 50–< 70 mL/min; 30–< 50 mL/min; and < 30 mL/min. The Cockcroft-Gault formula should be used to calculate the CL_{CR} for each patient.

CL_{CR} should be calculated for each patient on study Days 1, 2, 3, 5, and 8. Additional CL_{CR} calculations may be performed as clinically indicated. All CL_{CR} results obtained during the active treatment period (i.e., when the patient is receiving study medication) need to be reviewed by the unblinded pharmacist (or delegate) on the day when local laboratory serum-creatinine results are obtained and the doses of vancomycin and ceftobiprole are adjusted in accordance with Table 8.

6.2 Administration

All study drug will be administered IV. There is no switch to PO treatment in this study.

Hospitalization (in a hospital or equivalent medical confinement or clinical research unit) of study participants is required for the 72 h after start of treatment, until early clinical response has been determined. Where individual patient requirements and circumstances allow for outpatient care after this time, homecare services or site nurse visits are permitted, provided that all data relevant to the study continue to be obtained. The admission of patients to medical confinement facilities is also permitted.

For outpatients, the investigator must provide the required settings in order to ensure strict compliance with the protocol for all study-related treatments and assessments.

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

The total daily volume of study-drug infusions is 1200 mL for study participants with $CL_{CR} \geq 70$ mL/min, 950 mL for patients with CL_{CR} of 50 – < 70 mL/min, 700 mL for patients with CL_{CR} of 30 to < 50 mL/min and 450 mL for patients with CL_{CR} of < 30 mL/min (see Table 8).

Table 8 Dosing and dose adjustment for ceftobiprole and vancomycin/aztreonam based on CL_{CR}

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

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

Or 15 × CL_{CR} (as determined by Cockcroft-Gault formula) as a total daily dose distributed q12h: The decision to use vancomycin at a fixed or CL_{CR}-based dose is to be made by the investigator on the basis of the site's standard of care, and needs to be communicated prior to randomization to the unblinded pharmacist or delegate. If VTT is performed, the vancomycin dose may be adjusted according to trough levels.

† After an initial dose of 1000 mg, all subsequent maintenance doses of aztreonam should be halved (i.e. 500 mg).

6.2.1 Ceftobiprole

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

- For patients with mild renal impairment (i.e., CL_{CR} 50–80 mL/min), no dosage adjustment is necessary.
- For patients with moderate renal impairment (CL_{CR} 30–< 50 mL/min), the recommended dose of ceftobiprole is 500 mg q12h, as a 2-hour IV infusion (Table 8).
- For patients with severe renal impairment (CL_{CR} < 30 mL/min), the recommended dose of ceftobiprole is 250 mg q12h, as a 2-hour IV infusion (Table 8).

A patient who develops the need for hemodialysis must be discontinued from the study before hemodialysis commences (see Section 4.5).

6.2.2 Vancomycin

6.2.2.1 Dose in patients with a CL_{CR} > 100 mL/min

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

6.2.2.2 Dose in patients with a CL_{CR} ≤ 100 mL/min

If dose adjustments are made based on CL_{CR} values, the following recommendations apply (see Table 8):

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

A patient who develops the need for hemodialysis must be discontinued from the study before hemodialysis commences (see Section 4.5).

Dose adjustment in morbidly obese and hypermetabolic patients

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

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

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

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

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

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

Vancomycin trough level determination using local laboratories

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

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

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

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

Guidelines for the dosing of vancomycin are available in Moellering 1981.

For suggested monitoring guidelines regarding the monitoring of vancomycin serum concentrations, see Rybak 2009.

6.2.3 Aztreonam

Aztreonam 1000 mg is to be administered as a 0.5-hour IV infusion q12h. If CL_{CR} is < 30 mL/min (i.e., severe renal impairment), the aztreonam dosage regimen may be adjusted by the unblinded pharmacist or delegate (see Table 8).

The requirement for aztreonam therapy will be reassessed at the 72-h study visit (see Section 6.1).

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

A patient who develops the need for hemodialysis must be discontinued from the study before hemodialysis commences (see Section 4.5).

6.3 Randomization

Eligible patients will be randomized in a 1:1 ratio to ceftobiprole or vancomycin/aztreonam, based on a computer-generated randomization schedule.

The unblinded pharmacist or delegate will contact the IWRS to obtain the study treatment assignment, and dispense blinded therapy accordingly. The IWRS will associate that patient with the next available treatment in the appropriate stratum on randomization.

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

- study site
- type of ABSSSI (cellulitis/erysipelas, major cutaneous abscess, or wound infection)

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

Detailed randomization instructions are provided in the IWRS manual.

6.4 Blinding

The unblinded pharmacist or delegate will provide blinded and properly labeled study medication only to investigational staff.

Only the unblinded pharmacist or delegate at the site, will have access to treatment codes via IWRS.

Investigators, other site staff, sponsor employees, and others involved in the conduct of the study (with the exception of the above) will remain blinded to the treatment codes until the database has been locked for final analysis.

6.5 Methods for ensuring blinding

This study will be double-blind with regard to the administration of study drugs.

The following personnel may have access to details of the treatment allocation:

- those performing PK analyses
- those setting up the randomization scheme and IWRS

- the unblinded pharmacist or delegate responsible for blinded study-drug adjustments, preparation, and documentation
- the unblinded local lab technician responsible for VTT, reporting and documentation
- those required to break the blind for the purposes of expedited reporting to health authorities and other relevant institutions
- those responsible for unblinded monitoring of study-drug preparation and accountability, and their supervisors
- the unblinded statistician, if required for safety reasons, or producing outputs for the blinded interim analysis, or for the DSMB.

These personnel must not disclose any details of the randomization scheme or the treatment code of study drugs.

6.6 Unblinding methods

Individual treatment codes for each randomized patient will be available to investigators from the IWRS. The treatment code should only be broken in medical emergencies. It is advisable to contact the medical monitor prior to breaking the blind. The investigator will record the reason for unblinding in the patient's records/source documents. In order to maintain the blinded nature of the study, the allocation of the investigational product(s) for the patient must not be communicated further, unless required for the treatment and/or surveillance of the patient. Adverse events and SAEs must be reported as outlined in Section 7.

The sponsor/designee might break the blind via IWRS for regulatory reporting purposes. This must be fully documented, and only the minimum number of staff necessary are to have access to the unblinded information.

Detailed handling instructions are provided in the IWRS Manual.

Systematic unblinding of the clinical database will occur after database lock as described in the Data Management Plan and SAP.

6.7 Drug accountability and compliance check

The investigator, and a pharmacist designated by the investigator, must maintain records of the delivery of study drug to the site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposal of unused product.

These records must include dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the study drugs and study patients. These records must be available for monitoring by the sponsor's unblinded Monitor.

Investigators must maintain records that document adequately that the study patients were provided the doses specified by the protocol, and must reconcile all study drug received from the sponsor.

6.8 Packaging and labeling

Study drugs will be packed and labeled in accordance with local regulations and the Annex 13 Good Manufacturing Practice rules, including but not limited to the identity of

the sponsor, protocol number, drug identification, storage conditions, content of study drug, and expiry date.

Information on drug shipment, temperature logger and acknowledgement of receipt form to be completed by the receiver, will also be included.

6.9 Shipping and storage conditions

Study drug for IV administration will be presented as follows. Storage conditions are provided in the Pharmacy manual.

- Ceftobiprole medocaril: vials of sterile lyophilized ceftobiprole medocaril for intravenous use after reconstitution containing the equivalent of 500 mg ceftobiprole.
- Vancomycin: Vials of sterile vancomycin hydrochloride powder for intravenous use after reconstitution containing 500 mg, 750 mg, or 1000 mg of vancomycin; or as pre-mixed intravenous solution (e.g., GALAXY or ADD-Vantage).
- Aztreonam: Vials of sterile aztreonam powder for intravenous use after reconstitution containing 500 mg or 1000 mg of aztreonam; or as pre-mixed intravenous solution (GALAXY).

All vials/containers of study drug for IV administration must be shipped to the study centers, protected from light, and stored at the required temperature levels. All study drug must be kept under secure conditions, e.g., in the hospital pharmacy.

Further information on the handling and stability of study drug is provided in the Pharmacy manual.

6.10 Drug supply

A Drug Dispensing Log must be kept up to date, and must contain the following information:

- Site ID, subject number
- Investigator name
- Code of the drug to be dispensed
- Date(s), quantity and batch number of the drug dispensed to the patient
- Quantity of the drug remaining in stock

The inventory must be available for monitoring by the sponsor's unblinded Monitor.

6.11 Drug disposal

Any remaining drug, including empty vials, may only be returned to the study supply packaging provider, or destroyed at the site after drug accountability by the unblinded Monitor and at the request of the sponsor. If drug is destroyed at the study site, the investigator or delegate must provide the sponsor with documentation of the destruction.

Detailed study-drug handling instructions are provided in the Pharmacy manual.

7 SAFETY

7.1 Definitions

7.1.1 Adverse occurrence

An adverse occurrence is any untoward medical occurrence taking place after informed consent and before first study-drug administration.

7.1.2 Adverse event

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

7.1.2.1 Treatment-emergent adverse event

A treatment-emergent adverse event is any AE which occurs from the start of first dosing up to and including the scheduled LFU visit.

7.1.3 Serious adverse event

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

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

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

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

It should be noted that:

- Death is considered an outcome of an AE. Whenever possible the underlying cause of death must be reported as the AE.
- A life-threatening SAE is any adverse experience that places the patient at risk of death at the time of its occurrence, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization is defined as any inpatient admission, even if for less than 24 h. For chronic or long-term inpatients, inpatient admission also includes transfer within the hospital to an acute/intensive care inpatient unit (e.g., from a medical floor to the coronary care unit, or from the neurological floor to the tuberculosis unit).

  The following hospitalizations, whether planned before or during the study, should not be considered SAEs:

- Routine treatment or monitoring of the ABSSSI, not associated with any deterioration in condition (e.g., hospitalizations related to study procedures, such as study-drug administration, PK assessments, etc.).
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the ABSSSI and has not worsened.
- Admission to a hospital or other institution for general care, not associated with any deterioration in condition.
- Treatment on an emergency outpatient basis for an event which does not meet any of the above definitions of 'serious', and does not result in hospital admission.

7.1.3.1 Suspected unexpected serious adverse reaction

A suspected unexpected serious adverse reaction (SUSAR) is any SAE considered by the sponsor to be related to the study treatment and for which the nature or severity is not consistent with the applicable reference safety information.

7.2 Evaluation of adverse events

7.2.1 Severity

The intensity of an AE will be graded on the following three-point scale:

- Mild: discomfort but no disruption of normal daily activity
- Moderate: discomfort sufficient to reduce or affect daily activity
- Severe: inability to work or to perform normal daily activities

7.2.2 Relationship

The relationship of AEs to the study treatment must be assessed by the investigator as one of the following:

- not related
- unlikely
- possible
- probable

Appendix 2 provides criteria for relationship assessments.

According to the sponsor's criteria for causality assessment, a causal relationship will be suspected for all AEs reported with a relationship of 'possible' or 'probable' and those with missing or unknown relationships.

7.3 Handling of safety information and collection periods

7.3.1 Handling of safety data during the pre-treatment period

Any relevant change in, or worsening of, a patient's condition occurring after consent, but prior to the start of first study-drug administration, will be recorded in the CRF as pre-dose medical history (see Section 5.4.1).

If a change in, or worsening of, a patient's condition is considered to be serious (i.e., meets one or more of the criteria for an SAE in Section 7.1.3), this information must also be reported to the sponsor's safety representative, using the same forms and procedures as for an SAE (see Section 7.3.2.2).

7.3.2 Handling of safety data during the treatment period and up to the last scheduled follow-up

From the start of first dosing up to and including the LFU visit, any change in, or worsening of, the patient's condition must be collected and reported in the CRF as an AE (see Section 7.3.2.1). Serious adverse events must be additionally reported and recorded on SAE report forms (see Section 7.3.2.2).

7.3.2.1 Adverse event management

The investigator or the physician in attendance should administer therapy as clinically indicated for any AE/SAE that occurs.

7.3.2.1.1 Data collection

All AEs directly observed (physical examination, laboratory test, or other assessments), mentioned by the patient, or reported by the patient upon non-directive questioning, must be recorded on the AE pages of the CRF.

All AEs must be recorded in the English language in the CRF and should include the following information:

1. Term. If possible, a diagnosis should be documented rather than signs and symptoms, using self-explanatory and concise medical terminology.

   Note: Use of the AE terms 'disease progression', 'lack of efficacy', or equivalent terms, should be avoided. Instead, a diagnosis, signs, or symptoms should be used to describe the worsening of the ABSSSI.
2. Duration (start and end dates).
3. Severity grade (three-point scale, see Section 7.2.1).
4. Relationship to study treatment (see Section 7.2.2 and Appendix 2).
5. Action(s) taken with regards to the study treatment or additional treatments given for the event.
6. Whether the event is an SAE (see Section 7.1.3).
7. Outcome.

Abnormal laboratory results should not be recorded as an AE unless the abnormal result meets one or more of the following criteria:

- induces clinical signs or symptoms which require therapy or additional diagnostic evaluation
- requires changes in study-drug dosing or discontinuation of study participation
- is considered clinically significant

Signs, symptoms or diagnosis associated with these abnormal results must be recorded on the AEs page of the CRF.

Adverse events must also be reported in the source document with at least the nature of the event, the start and end date, the relationship to the study drug, and the treatment (if applicable).

7.3.2.1.2 Follow-up

Once an AE is detected, it must be proactively followed at each visit (or more frequently if necessary) for any changes in severity, relationship to the study drug, interventions required for treatment, and the event's outcome.

All AEs must be followed-up until they have returned to baseline status or have stabilized, or until the scheduled LFU visit.

In addition, an AE which remains unresolved after completion of the study (including the last scheduled follow-up contact) and meets one or more of the criteria listed below, requires detailed evaluation, follow-up and, if necessary, specific medical treatment until the AE is resolved or a reasonable explanation for its persistence is found:

- an AE evaluated as related to the study drug
- an AE that led to a patient withdrawal from the study
- an SAE

These cases will be followed-up on the CRF unless otherwise agreed with the sponsor.

7.3.2.2 Serious adverse event recording and reporting

In addition to being reported and followed-up as AEs (see Section 7.3.2.1), SAEs must be reported to the sponsor's safety representative listed below, within 24 h of awareness of the event.

The investigator must complete the 'Serious Adverse Event Report Form' in English, and send the completed, signed form by fax or email to:

PrimeVigilance Limited
The Surrey Research Park
26–28 Frederick Sanger Road
Guildford, Surrey GU2 7YD, United Kingdom
Email: Basilea@primevigilance.com
eFax (UK): +44 (0)800 0669192
eFax (US): +1 866 902 7489

Such preliminary reports must be followed by detailed anonymized descriptions, which may include copies of hospital case reports, autopsy reports, and other documents if requested and applicable.

The original SAE Report Form and the correspondence to the sponsor reporting the SAE (fax confirmation sheet/email) must be kept at the study site in the investigator Site File (ISF).

7.3.3 Handling of post-study safety data

Any AE occurring after the LFU visit which is considered to be both:

- serious (i.e., meets one or more of the criteria listed for SAEs, see Section 7.1.3), and
- related to the study drug (see Section 7.2.2 and Appendix 2)

should be reported to the sponsor's designated safety representative using the same forms and procedures as for an SAE (see Section 7.3.2.2).

Events occurring after the LFU visit should not be reported in the CRF.

7.3.4 Reporting of SAEs to regulatory authorities

7.3.4.1 Sponsor's responsibilities

The sponsor's safety representative will ensure the reporting of SUSARs and any expeditable SAEs to regulatory Authorities in accordance with applicable law.

In the event of a SUSAR, the sponsor will ensure that investigators active in Basilea-sponsored interventional studies with ceftobiprole are informed.

Expectedness of SAEs for regulatory expedited reporting will be assessed by the sponsor against the applicable reference safety information (RSI).

For ceftobiprole, the 'Undesirable effects' subsection of Section 5 ('Summary of data and guidance for investigators') in the Investigator's Brochure will serve as the RSI.

For vancomycin, expectedness for regulatory expedited reporting will be assessed against the 'Adverse reactions' section of the US Prescribing Information for submission to the US FDA, and against section 4.8 'Undesirable effects' of the UK Summary of Product Characteristics (decentralized procedure UK/H/5402/001-02/DC) for submission to non-US regulatory authorities.

For aztreonam, expectedness for regulatory expedited reporting will be assessed against the 'Adverse reactions' section of the US Prescribing Information for submission to the US FDA, and against section 4.8 'Undesirable effects' of the UK Summary of Product Characteristics of Azactam for submission to non-US regulatory authorities.

7.3.4.2 Investigator's responsibilities

The investigator is responsible for informing the local Independent Ethics Committee/Institutional Review Board (IEC/IRB), and any other applicable bodies, of SUSARs and any other expeditable SAEs, in accordance with applicable law. This activity may be delegated.

7.4 Pregnancy

7.4.1 Contraception for women of childbearing potential

There are no adequate and well-controlled studies with ceftobiprole in pregnant women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, parturition, or post-natal development. As no data in exposed human pregnancies are available, ceftobiprole should not be used during pregnancy.

The investigator must make every effort to ensure that a clinical study patient does not become pregnant during the study. This should be done, and documented, as part of the consent process, by explaining clearly to the patient the potential dangers of becoming pregnant, and providing each patient with information about appropriate medically-approved effective contraception (see below).

Women of childbearing potential must have a negative serum pregnancy test result within the 24 h prior to first dose of study drug. If results of the pregnancy test are positive (see Section 5.3.6), the patient will not be enrolled in the study.

Women of childbearing potential must agree to use one of the following methods of contraception during the study:

- Female sterilization (bilateral tubal occlusion or oophorectomy, or hysterectomy) or male partner vasectomy.
- IUD.
- Combined (estrogen- and progesterone-containing) hormonal contraception (oral, vaginal ring or transdermal patch) with an ethinylestradiol dose of at least 30 µg, plus use of male condoms (preferably with spermicides), female condoms, a female diaphragm or a cervical cap.
- Total sexual abstinence.

Women are not considered to be of childbearing potential if they are either ≥ 1 year post-menopausal (where menopause is defined as at least 12 months of amenorrhea), or have an FSH measurement consistent with post-menopausal status according to local laboratory thresholds. An FSH measurement at Screening is to be obtained for post-menopausal females aged < 50 years, or for those aged ≥ 50 years who have been post-menopausal for < 2 years.

7.4.2 Reporting and handling of pregnancies

Female patients must inform the investigator within 24 h if they have experienced a ruptured condom, or any other concerns about possible reduction of contraceptive effectivity (i.e. forgotten pill or vomiting) during the study. In these cases the patients must return to the study site as soon as possible, but not later than 24 h, after the investigator is informed.

Female patients must inform the investigator if they become pregnant during the study. The study drug must be discontinued immediately when a patient becomes pregnant. The patient must be monitored until conclusion of the pregnancy and infants must be followed-up at least for 8 weeks after delivery.

The investigator must immediately notify the sponsor's safety representative about any pregnancy by submitting a Pregnancy Report Form, in accordance with the requirements (timelines and contact details) of an SAE (see Section 7.3.2.2). In addition, pregnancy-related adverse outcomes must also be reported as AEs or SAEs (see Sections 7.3.2.1 and 7.3.2.2). Note that an induced abortion which is not required by an AE does not constitute an SAE.

The investigator must notify the local IEC/IRB about any pregnancies resulting in an adverse outcome, in accordance with applicable laws and regulations.

8 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Sample size justification

The study is designed to determine whether ceftobiprole is non-inferior to vancomycin plus aztreonam for the outcome measure of early clinical response at 48–72 h after start of treatment, defined as a ≥ 20% reduction from baseline in the area (longest length × perpendicular width of erythema, edema, or induration) of the primary lesion, survival for ≥ 72 h from the time of administration of the first dose of study drug, and no use of concomitant systemic antibacterial treatments or topical antibacterial administration on the primary lesion.

A sample size of 674 patients (337 per group) will provide at least 90% power to reject the null hypothesis (H_0) against the alternative hypothesis (H_A) at the one-sided alpha level of 0.025 as follows, using a two-group large-sample normal approximation test of proportions:

H_0: $P_{vancomycin/aztrenonam}$ minus $P_{ceftobiprole} \geq 0.10$

versus

H_A: $P_{vancomycin/aztrenonam}$ minus $P_{ceftobiprole} < 0.10$.

Early clinical response rates of an at least 20% reduction in lesion area size (primary endpoint) and clinical cure rates at the TOC visit (main secondary endpoint) from recent Phase 3 studies in ABSSSI are summarized in Table 9. These clinical study data support an estimate of early clinical response rates of > 80%. The Phase 3 ABSSSI studies with ceftaroline (CANVAS 1 and CANVAS 2) and ESTABLISH 1 (tedizolid) showed lower response rates; however the CANVAS1/CANVAS2 studies were not prospectively designed for an assessment of a primary endpoint of lesion size reduction between 48 and 72 h after start of treatment, and the result reported for ESTABLISH 1 included the absence of fever in addition to lesion size reduction.

Table 9 Early clinical response rates and clinical cure rates at the TOC visit in previous ABSSSI studies

Compound/ publication	Dosing regimen	% Success	
		Early response (ITT)	Clinical cure at TOC
Ceftobiprole Noel 2008a N=828	Ceftobiprole 500 mg q8h vs vancomycin 1000 mg q12 h plus ceftazidime 1000 mg q 8 h	Not evaluated	82 vs 81 (ITT) 91 vs 90 (CE)
Ceftaroline Corey 2010 N=1378	Ceftaroline 600 mg q12 h vs vancomycin 1000 mg q12 h plus aztreonam 1000 mg q12 h	60 vs 56	86 vs 86 (ITT) 92 vs 93 (CE)
Dalbavancin Boucher 2014 Xydalba EPAR 18 Dec 2014 N=1312	Dalbavancin 1000 mg on Day 1 and 500 mg on Day 1 vs Vancomycin 1000 mg or 15mg/kg q12 h, option to switch to PO linezolid 600 mg q12 h	89 vs 88	86 vs 86 (ITT)* 91 vs 92 (CE)*
Oritavancin Corey 2014 Corey 2015 N=1959	Oritavancin single dose of 1200 mg vs vancomycin 1000 mg or 15mg/kg q12 h	SOLO I: 87 vs 83 SOLO II: 86 vs 85	SOLO I : 80 vs 80 (ITT) 91 vs 89 (CE) SOLO II: 83 vs 80 (ITT) 93 vs 95 (CE)
Tedizolid Prokocimer 2013 Moran 2014 N=1333	Tedizolid 200 mg q24 h for 6 days vs linezolid 600 mg q12 h for 10 days (PO) Tedizolid 200 mg q24 h for 6 days vs linezolid 600 mg q12 h for 10 days (IV with optional PO switch)	ESTABLISH I: 78 vs 76** ESTABLISH II: 92 vs 90	ESTABLISH I : 86 vs 86 (ITT) 95 vs 95 (CE) ESTABLISH II: 88 vs 88 (ITT) 92 vs 96 (CE)

* Based on clinical outcome at EOT.
** Includes reduction in lesion size by at least 20% plus the absence of fever.
ITT=Intent-to-Treat; TOC=test-of-cure; CE=Clinically Evaluable; EOT=end-of-treatment.

The sample size estimate is therefore based on:

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

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

Two separate SAPs will be provided for submission to the FDA and EMA, where the SAP prepared for the FDA will use the protocol-defined primary and secondary objectives, and the SAP prepared for the EMA will use the main secondary objective as the primary objective.

For the EMA primary endpoint, the point estimates of clinical cure at the TOC visit in the co-primary ITT and CE populations are 80% and 90%, respectively, which are supported by previous ABSSSI Phase 3 studies (see table above).

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

8.2 Analysis populations

The following analysis populations are defined for this study:

Intent-to-Treat population (ITT): all randomized patients. Patients will be analyzed according to the study medication assigned at randomization.

Microbiological Intent-to-Treat population (mITT): the subset of patients in the ITT population who have had causative pathogens confirmed from skin lesion or blood cultures.

Clinically Evaluable population (CE): the subset of patients in the ITT population who have complied with important aspects of the study, e.g., no major protocol deviations, a completed response outcome assessment, and no concomitant systemic antibacterial treatment or topical antibacterial applied to the primary lesion.

Microbiologically Evaluable population (ME): the subset of patients in the mITT population who are also in the CE population.

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

Pharmacokinetic population (PK): all patients who receive at least one dose of ceftobiprole and have at least one plasma concentration measurement obtained by the appropriate methodology.

8.3 General statistical considerations

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables, will be provided. All comparisons will be for ceftobiprole versus vancomycin plus aztreonam. Exploratory analyses may also be performed.

For between-group comparisons, a two-sided 95% CI for the difference in outcome rates between the two treatment groups will be derived, unless otherwise specified.

Unless otherwise specified, the latest evaluation prior to the initiation of study drug will be considered the ‘baseline’ evaluation for statistical analyses.

8.4 Demographic and baseline characteristics

Disposition in the study, overview of analysis populations, protocol deviations, discontinuations from the study drug, and withdrawal from the study will be summarized by treatment group.

Demographics and baseline characteristics will be summarized by treatment group for all analysis populations.

8.5 Prior and concomitant medications

Prior and concomitant medications will be summarized by treatment group. Additional summaries will be provided for prior and concomitant antibacterial use.

8.6 Surgical procedures

Planned procedures and interventions used for infection management will be summarized by treatment group, and by time period of procedure (prior to randomization or during treatment) for the ITT and CE populations.

8.7 Study endpoints

The primary and the main secondary endpoints are region-specific. The primary and main secondary endpoints listed below are for submission to the US FDA. In the EU, the main secondary endpoint listed below will be the primary endpoint, and the primary endpoint listed below will be the main secondary endpoint. Two separate SAPs will be prepared for submission to the FDA and the EMA to reflect the different primary and main secondary endpoints in each region.

8.7.1 Analysis of the primary endpoint

The primary analysis will be based on the ITT population.

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

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

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

If multiple lesions measurements are taken within 48–72 hours after the first dose of study drug, the latest lesion measurement will be used.

Standardized measurement of the lesion area (i.e., erythema, edema, or induration, whichever is largest) is to be performed with a flexible plastic ruler or tape measure, by multiplying the longest length of the lesion by the widest width perpendicular to that length. In addition, a measurement of the maximum width of erythema or edema/induration from the edge of the wound (surgical or traumatic) or abscess will be

recorded. If abscess, the measurement should be taken from the end of the fluctuance before drainage or from the edge of the drainage site after drainage.

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

The numbers and percentages of responders and non-responders will be determined in each treatment group. Patients with missing data relevant for the assessment of the primary endpoint, or who are lost to follow-up, will be considered non-responders for the primary analysis. The observed difference in percentage of responders at 48–72 h (ceftobiprole group minus the vancomycin plus aztreonam group) will be determined, and a 95% CI for the observed difference will be computed, with adjustment by geographical region (North America and Europe), and type of ABSSSI. Cochran-Mantel-Haenszel weights will be used for the stratum weights in the calculation of the CI.

The non-inferiority hypothesis test is a one-sided hypothesis test performed at the 2.5% level of significance. If the lower limit of the 95% CI for the difference in response rates (ceftobiprole minus vancomycin plus aztreonam) in the ITT population is greater than −10%, the non-inferiority of ceftobiprole to vancomycin plus aztreonam will be concluded.

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

The primary efficacy analysis is based on the difference in the early clinical response rates between the two treatment groups. Analyses using risk ratio and odds ratio will also be performed.

In addition, the following sensitivity analyses will be performed for the primary outcome:

- An unadjusted analysis, i.e., the 95% CI will not be adjusted for the stratification factors of geographic region (North America and Europe) and ABSSSI type
- Patients with missing outcome values in both treatment groups will be excluded.

Subgroup analyses will be conducted for the primary efficacy outcome in the ITT and CE populations. Subgroup analyses will include, but not be limited to, the following factors: demographic characteristics (age, sex, race), geographic region, baseline pathogen (e.g., MRSA vs MSSA), baseline ABSSSI type (wound, cellulitis, major abscess), underlying medical conditions (diabetes mellitus, illicit drug use), baseline fever status, antibacterial medications prior to study drug, concomitant antibacterial medication, use of anti-inflammatory medications, and performance of surgical interventions.

8.7.2 Analysis of secondary endpoints

The main secondary endpoint is the investigator-assessed clinical success at the TOC visit according to the following definition: complete or nearly complete resolution of baseline signs and symptoms of the primary infection, such that no further antibacterial treatment is needed.

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

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

This main secondary endpoint will be specified in a separate SAP as the primary endpoint for the EMA, with non-inferiority assessed by the two-sided 95% CI of the between-group difference (ceftobiprole minus vancomycin plus aztreonam) using a 10% non-inferiority margin in the co-primary ITT and CE populations.

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

- An unadjusted analysis, i.e., the 95% CI will not be adjusted for the stratification factors of geographic region (North America and Europe) and ABSSSI type
- Patients with missing outcome values in both treatment groups will be excluded.

Subgroup analyses will be conducted for the primary efficacy outcome in the ITT and CE populations. Subgroup analyses will include, but not be limited to, the following factors: demographic characteristics (age, sex, race), geographic region, baseline pathogen (e.g., MRSA vs MSSA), baseline ABSSSI type (wound, cellulitis, major abscess), underlying medical conditions (diabetes mellitus, illicit drug use), baseline fever status, antibacterial medications prior to study drug, concomitant antibacterial medication, use of anti-inflammatory medications, and performance of surgical interventions.

In addition, the following secondary endpoints will be analysed using the same statistical methods as for the primary endpoint:

1. Early clinical response based on percentage reduction in lesion size at 48–72 h after first treatment (CE population).
2. Clinical response defined as ≥ 80% decrease in lesion area at the EOT visit, and ≥ 90% decrease in lesion area at the TOC visit (ITT population), with improvement of local signs of the infection in patients surviving up to the respective visit with no use of any concomitant systemic antibacterial treatment or topical antibacterial administration on the primary lesion, and no unplanned additional surgical procedure

(other than debridement at bedside or local bedside wound care), with the exception of cellulitis where there is a conversion into an abscess within 48 h of study treatment initiation, or, for post-surgery patients, when an extension of the original incision is indicated.

3. Sustained reduction in lesion size, defined as ≥ 20% decrease in lesion area 48–72 h after start of treatment (primary endpoint), that is sustained at the EOT and TOC visits (ITT population).
4. Investigator-assessed clinical success evaluated at 48–72 h after first treatment and the EOT visit, and sustained clinical success at the LFU visit (ITT and CE populations).
   Clinical success at the EOT visit is defined by the same criteria as for the main secondary endpoint, with an indeterminate assessment to include a missing EOT visit. Sustained clinical success requires that all criteria listed for the main secondary endpoint are met and there were no new signs or symptoms of the ABSSSI between the TOC and LFU visits.
5. ACM through Day 28 (±2 days) (ITT population).

   A time to event analysis using the Kaplan-Meier method will also be performed for ACM.
6. Microbiological response at Day 3, Day 5, and at the EOT, TOC and LFU visits in the mITT and ME populations, based on post-therapy cultures obtained from the primary infection site at the respective time points, using the following definitions:
   (a) Eradication: No growth of the baseline pathogen(s), based on post-therapy cultures obtained from the primary infection site at the respective time points.
   (b) Presumed eradication: No post-therapy culture due to lack of culturable material, accompanied by investigator-assessed clinical success.
   (c) Persistence: Evidence of continued growth of the baseline pathogen
   (d) Presumed persistence: No post-therapy culture due to lack of culturable material, accompanied by the absence of investigator-assessed clinical success.
   (e) Superinfection: Emergence of a new pathogen(s) at the primary site of infection, accompanied by the absence of investigator-assessed clinical success.
   (f) Relapse or recurrence: Pre-therapy pathogen isolated between the EOT and TOC visits, or between the TOC and LFU visits, after a pathogen response of ‘eradication’ or ‘presumed eradication’ at the EOT or TOC visits.

In addition, the absolute and percentage change in lesion area size will be analysed, and various percentage reductions from baseline (e.g., ≥ 10%, ≥ 20%, ≥ 30% at 48–72 h after start of treatment; ≥ 50%, ≥ 80%, ≥ 90%, ≥ 95% at TOC) will be summarized by treatment group in the mITT and CE populations.

Furthermore, an analysis will be performed to assess the concordance between early clinical response (primary endpoint) and clinical response at the EOT and TOC visits (Other secondary endpoint 2).

Patients’ self-assessment pain severity will be measured using a VAS (0–100 mm) and Wong-Baker FACES® Pain Rating Scale, with the change from baseline calculated and

summarized at various time points. Differences between treatment groups will be determined using an ANCOVA, with treatment group as a factor, and type of ABSSSI and baseline pain levels as covariates. Pain levels will be assessed using a 6-point numeric rating scale (NRS). The pain scores will be summarized by treatment group in the ITT and CE populations at each of the following visits: Screening, 48–72 h after start of treatments, EOT, and TOC.

Resource utilization (such as length of hospital stay, duration and dosage of IV administration, concomitant medication, diagnostic tests performed, surgery performed, and minor non-surgical procedures) will be summarized by treatment group.

Additional analyses may be conducted at the sponsor's discretion; the details of such analyses will be described in the SAPs.

8.8 Safety analyses

Safety will be assessed through summaries of AEs, safety laboratory evaluations, physical examinations, and vital signs. All safety analyses will be based on the Safety population. Analyses will be presented by treatment group.

Patients who receive the wrong dose of study drug will be analyzed in the group based on the first drug actually received.

Summary tables of AEs will be provided (see Section 7.1.1).

The incidence of AEs and SAEs will be tabulated by System Organ Class (SOC) and Preferred Term (PT) for each treatment group, and by severity, relationship to treatment, and outcome. Tables of AEs leading to study-drug discontinuation and withdrawal from the study will also be provided. AEs will be summarized separately for those events starting prior to the TOC visit, and for those occurring from the TOC visit to the LFU visit.

Non-treatment-emergent AEs will be provided in a listing.

Descriptive statistics summarizing central laboratory data will be presented by study visit. The change from baseline to each post-baseline visit and to the overall worst post-baseline value will also be summarized by treatment group.

Descriptive statistics of vital signs will be presented by treatment group and study visit, as well as the change from baseline at each study visit. The percentage of abnormalities in the physical examination will be presented by treatment group and study visit.

8.9 Pharmacokinetics

Plasma concentration data will be analyzed at each time point and will be presented as individual concentrations and with descriptive statistics (mean, standard deviation [SD], coefficient of variation [CV%], min, median, max). A retrospective population PK model will be developed as a separate study. Pharmacokinetic analyses will be based on the population PK model and the effects on the PK parameters of demographic and baseline factors such as age, weight, sex, race, and renal function will be examined. The population PK analysis will derive the $fT>MIC$ and target attainment rate, and will analyze the relationship between exposure and efficacy/safety.

8.10 Blinded interim analysis

One blinded interim analysis for sample size re-estimation will be conducted based solely on pooled information across the two treatment arms when early clinical response data are available for 60% of the patients planned to be randomized (approximately 404 patients). No statistical adjustment is required. The interim analysis will involve a sample size re-estimation to assess whether the initial sample size estimate is adequate for evaluating the primary endpoint of the study.

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

Details will be provided in the DSMB Charter.

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

9 STUDY ADMINISTRATION AND REGULATORY ASPECTS

9.1 Study records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

9.1.1 Investigator site file

The ISF must contain all essential documents as required by International Conference on Harmonisation (ICH) E6 and applicable regulations, including the protocol and any subsequent amendments, CRFs, Query Forms, documented IEC/IRB approvals, documented regulatory approvals, sample informed consent forms, drug records, staff *curriculum vitae*, and other appropriate documents/correspondence.

9.1.2 Case report forms

For each patient enrolled in the study, including patients who do not complete the study and patients for whom a CRF is initiated during Screening but are not randomized, a CRF must be completed and signed (manually or electronically) by the investigator or authorized site staff. If a patient withdraws from the study, the reason must be noted on the CRF. If a patient is withdrawn from the study because of an AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

If the CRF is to be the source document for certain data, this must be discussed and agreed with the sponsor in advance, and clearly documented.

9.1.3 Patient source documents

Patient source documents used to record key efficacy/safety parameters, independent of the CRFs, may include, but are not limited to, patient hospital/clinic records, physicians' and nurses' notes, appointment books, original laboratory reports, X-ray, pathology and special assessment reports, signed informed consent/assent forms, consultant letters, and patient screening and enrollment logs. Source documents are part of the study documents, and must be maintained and made available upon request for clinical monitoring visits, audits or inspections.

9.1.4 Document retention and archiving

The investigator must keep all study documents on file for at least 15 years after completion or discontinuation of the study. Subsequently, the sponsor will inform the investigator when the study documents can be destroyed, subject to applicable regulations.

These files must be made available for audits and inspection, upon reasonable request, to the authorized representative of the sponsor, or to regulatory authorities.

Should the investigator wish to assign the study records to another party, or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee the archiving requirement at the investigational site for any or all of the study documents, arrangements must be made between the investigator and the sponsor for appropriate storage.

9.1.5 Sample retention

All central laboratory isolates may be stored for up to 5 years after completion of the study for future medical and/or scientific research projects related to ceftobiprole. All patients will be asked to provide informed consent for this purpose, authorizing the sponsor to use their study information and samples for future research projects.

After a maximum of 5 years after completion of the study, all stored samples will be safely destroyed.

Bacterial isolates may be transferred in a fully anonymized form for use in epidemiological surveillance databases, without a time restriction.

9.2 Clinical monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, the sponsor will review the protocol, CRFs and other study documentation with the investigators and the site staff.

The Monitor (blinded and unblinded) must visit the investigator and the study facilities on a regular basis throughout the study to verify adherence to Good Clinical Practice (GCP) and the protocol, and the completeness, consistency and accuracy of the data being entered into the CRFs. The Monitor must also ensure that the study drug is being stored, dispensed, and accounted for according to specifications.

The investigator must ensure that the Monitor has direct access to all required study data (source documents) during the regular monitoring visits. This includes all patient records needed to verify the entries in the CRFs.

The investigator must cooperate with the Monitor to ensure that any protocol deviations or other issues detected in the course of monitoring visits are resolved.

Monitoring reports (blinded and unblinded) must be written after each monitoring visit, per site and per visit. These monitoring reports (blinded and unblinded) must be reviewed and approved by the respective supervisors (blinded and unblinded) of the Monitors.

Monitoring instructions are provided in the Clinical Monitoring Plan.

9.3 Audits and inspections

The study may be audited at any time, with appropriate notification, by qualified personnel from the sponsor or its designees, to assess compliance with the protocol, GCP, and regulatory requirements. These audits may also be conducted for quality assurance purposes, to ensure that complete and accurate data are submitted, and that all AEs are being identified and reported in compliance with the protocol and applicable regulations. The study may also be inspected by regulatory authority inspectors, after appropriate notification.

In the event of an audit or an inspection, the investigator must ensure that direct access to all study documentation, including source documents, is granted to the auditors or inspectors.

9.4 Protocol amendments

Protocol amendments must be prepared by a representative of the sponsor, and be reviewed and approved by the Project Physician and the Project Statistician.

All protocol amendments must be submitted to the appropriate IEC/IRB for information and approval in accordance with applicable laws and regulations, and to regulatory agencies if required.

Approval of a protocol amendment must be awaited before changes are implemented, with the exception of changes necessary to eliminate an immediate hazard to study participants, or changes involving only logistical or administrative aspects of the study (e.g., changes to Monitors, changes to telephone numbers).

9.5 Premature termination of the study

The sponsor reserves the right to terminate the study at any time. An investigator has the right to terminate his or her participation to the study at any time. Should either of these events occur, both parties will arrange the necessary procedures after review and consultation.

If the study is to be terminated early, the sponsor and the investigator must ensure that adequate consideration is given to the protection of the interests of all patients enrolled in the study.

9.6 Publication policy

The sponsor is committed to registering all therapeutic studies in a publicly accessible clinical trial registry (e.g., www.clinicaltrials.gov), and will ensure that results of these studies will be made available to the medical community consistent with applicable laws and regulations.

In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety, and not as individual center data. Authorship is to be determined by mutual agreement.

The results of this study will be made available, e.g., submitted for publication and/or presentation at scientific meetings, in a timely manner. All manuscripts or abstracts must be submitted to the sponsor prior to publication or presentation, allowing the sponsor to protect proprietary information, and to provide comments based on information from other studies that may not yet be available to an investigator.

10 ETHICS AND GOOD CLINICAL PRACTICE

10.1 Good Clinical Practice

The study must be conducted in compliance with this protocol, ICH Guideline E6 and any relevant supplementary guidance on GCP, and applicable laws and regulations.

10.2 Informed consent

Eligible patients may only be included in the study after providing written IEC/IRB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. Written informed consent must be obtained from each patient prior to initiation of any study procedures.

It is the responsibility of the investigator, or a person designated by the investigator if acceptable by local regulations, to obtain prior written informed consent from each individual participating in this study, after adequate explanation of the aims, methods, objectives and potential risks of the study. It must also be explained to patients that they are completely free to refuse to enter the study, or to withdraw from the study at any time for any reason. Appropriate forms for obtaining written informed consent will be provided to the investigator by the sponsor.

Written consent must be witnessed and countersigned by the investigator or a qualified designee, as appropriate. In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements and GCP as outlined in ICH E6 and other relevant guidelines, and the ethical principles having their origin in the Declaration of Helsinki.

Copies of signed consent forms must be given to the patient, and the originals filed at the study site.

For patients not qualified to give legal consent, or incapable of doing so, written consent must be obtained from the patient's legally acceptable representative. In the event that both the patient and his or her legally acceptable representative are unable to read the consent document, an impartial witness must be present during the entire informed consent discussion. After the patient and representative have verbally consented to participation in the study, the witness' signature must be obtained on the form to attest that the information in the consent form was accurately explained and understood.

The CRFs for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the benefit/risk assessment for ceftobiprole or for one of the comparator drugs, the consent form must be reviewed and updated. All patients currently enrolled in the study who have not yet completed the post-treatment phase must be given the new information and a copy of the revised form, and asked to give their consent to continuing in the study.

10.3 Patient confidentiality and data protection

The investigator must ensure that patient anonymity is maintained, and that patients' identities are protected from unauthorized parties. This includes any electronic data generated during the study. In the CRF, or other documents submitted to the sponsor, patients must be identified only by an identification code, and not by name. The investigator must keep a confidential patient identification code list, as described in Section 8.3.21 of ICH E6.

The sponsor is responsible for ensuring compliance with all applicable data protection laws.

10.4 Independent Ethics Committees / Institutional Review Boards

This protocol and any accompanying material provided to the patient, including patient information sheets or descriptions of the study used to obtain informed consent, as well as any advertising material and information about any compensation provided to the patient, must be submitted to an IEC/IRB operating in compliance with ICH Guideline E6 and any relevant supplementary guidance on GCP, and with applicable laws and regulations. Approval from the IEC/IRB must be obtained and documented before starting the study.

Amendments made to the protocol after receipt of IEC/IRB approval must also be submitted to the IEC/IRB in accordance with local procedures and applicable laws and regulations.

11 PROTOCOL VERSION HISTORY

In the process of designing clinical study BPR-CS-008 and submitting it for approval to regulatory authorities, the protocol went through the following stages of development before commencement of the study:

- Protocol Version 1.0 dated 31 March 2016 was submitted to the US FDA for special protocol assessment (SPA).
- Protocol Version 2.0 dated 13 October 2016 was submitted to the UK Medicines & Healthcare products Regulatory Agency (MHRA) for scientific advice.
- Protocol Version 3.0 dated 15 February 2017 was submitted to the US FDA for SPA amendment.
- Protocol Version 4.0 dated 12 April 2017 was used for regulatory and IEC/IRB approval for commencement of this clinical study.

Since commencement of the study, the following protocol amendments and updated versions have been issued:

- Protocol Amendment 1 produced Protocol Version 5.0 dated 31 May 2017.
- Protocol Amendment 2 produced Protocol Version 6.0 dated 11 July 2018 (current version).

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13 APPENDICES

Appendix 1 List of antibiotics meeting the criterion of a half-life ≤ 12 hours

Half-life ≤ 12 hours Single dose permitted within > 3 days before randomization		**Half-life > 12 hours** Not permitted within 14 days before first infusion of study drug
Amikacin	Delafloxacin	Azithromycin
Amoxicillin	Dicloxacillin	Dalbavancin
Amoxicillin/Clavulanic acid	Doripenem	Doxycycline
Ampicillin	Ertapenem	Linezolid
Ampicillin/Sulbactam	Erythromycin	Minocycline
Cefaclor	Fosfomycin	Oritavancin
Cefadroxil	Gemifloxacin	Tigecycline
Cefamandole	Gentamicin	Teicoplanin
Cefazolin	Imipenem/cilastatin	
Cefdinir	Levofloxacine	
Cefditoren pivoxil	Loracarbef	
Cefepime	Meropenem	
Cefixime	Meropenem/vaborbactam	
Cefoperazone	Metronidazole	
Cefotaxime	Mezlocillin	
Cefotetan	Moxifloxacin	
Cefoxitin	Nafcillin	
Cefpodoxime proxetil	Ofloxacin	
Cefprozil	Oxacillin	
Ceftaroline fosamil	Penicillin G	
Ceftazidime	Penicillin V	
Ceftazidime/avibactam	Piperacillin	
Ceftibuten	Piperacillin/tazobactam	
Ceftizoxime	Polymixin B	
Ceftolozane/tazobactam	Quinupristin/dalfopristin	
Cetriaxone	Rifampin	
Cefuroxime	Tedizolid	
Cephalexin	Telavancin	
Chloramphenicol	Telithromycin	
Ciprofloxacin	Tetracycline	
Ciprofloxacin extended release	Ticarcillin	
Clarithromycin	Ticarcillin/clavulanate	
Clarithromycin XL	Tobramycin	
Clindamycin	Trimethoprim	
Colistimethate sodium	Trimethoprim-sulfamethoxazole	
Daptomycin	Vancomycin	

Note: PO vancomycin, fidaxomicin and nitrofurantoin are considered as non-systemic antibiotics and may be used within the 7 days prior to first study-drug infusion.

Appendix 2 Criteria for evaluating relationship between adverse events and study treatment

NOT RELATED

This category is applicable to an AE that meets the following three criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is not plausible. If the drug was interrupted or stopped the event did not improve or disappear. (There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., [i] bone marrow depression, [ii] tardive dyskinesias.). If the drug was re-administered it did not reappear.
2. It does not follow a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It is judged to be clearly and incontrovertibly due only to extraneous causes such as the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

UNLIKELY

This category is applicable to an AE that meets the following three criteria:

1. It does not follow a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is not plausible. If the drug was interrupted or stopped the event did not improve or disappear. If the drug was re-administered it did not re-appear.
2. It does not follow a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

POSSIBLE

This category is applicable to an AE that does not meet the criteria for 'not related' or 'unlikely', nor the criteria for 'probable'. An AE would be considered possible if, or when e.g.:

1. It follows a reasonable temporal sequence from administration of the drug (see also additional explanations above) or it follows a known pattern of the response to the suspected drug or drugs of the same substance class.
2. It may or may not have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

Note: If an event neither follows a plausible temporal relationship nor a known pattern of response but there is no alternative explanation for the event, this will usually be judged a possibly related event.

PROBABLE

This category is applicable to an AE that is considered, with a high degree of certainty, to be related to the test drug. An AE event may be considered probable if it meets the following three criteria:

1. It follows a reasonable temporal sequence from administration of the drug, i.e., the time between the administration of study drug and occurrence of the event is plausible. If the drug was interrupted or stopped the event did improve or disappear. (There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., [i] bone marrow depression, [ii] tardive dyskinesias). If the drug was re-administered it did re-appear.
2. It follows a known pattern of the response to the suspected drug or drugs of the same substance class.
3. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

Regardless of the criteria mentioned above, reappearance of an event upon re-challenge must be regarded as strong evidence of probable relationship to test drug.

A causal relationship is suspected for all AEs/SAEs reported with a relationship of 'possible' or 'probable' and those with missing or unknown relationships.

Appendix 3 Investigator's protocol signature page

BASILEA

INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

Protocol	BPR-CS-008 Version 6.0	Basilea Product:	Ceftobiprole medocaril

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

Basilea Pharmaceutica International Ltd

Approval Date: 11 July 2018

Name of Principal Investigator:

Study site:

I agree to the conditions relating to this study as set out in the above named Protocol and Study Procedures. I fully understand that any changes instituted by the investigator(s) without previous discussion with the sponsor's Project Clinician, Clinical Pharmacologist and Biostatistician (only if required) would constitute a violation of the protocol, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the well-being of the subjects).

I agree to follow International Conference on Harmonisation (ICH) guidelines for good clinical practice (GCP), including the EU Clinical Trial Directive 2001/20/EC and specifically, obtain approval from the Independent Ethics Committee / Institutional Review Board prior to study start, allow direct access to source documents and agree to inspection by auditors from Basilea and regulatory authorities, as required by ICH GCP. I will ensure that the investigational product(s) supplied by the sponsor will be used only as described in the above named protocol; if *any* other use is desired, *written permission* must be obtained from the sponsor.

I acknowledge that I have read the protocol for this study, and I agree to carry out all of its terms in accordance with applicable laws and regulations.

Please print name and date next to the signature

Signature	**Name**	**Date**
Principal Investigator		