CLINICAL STUDY PROTOCOL SYNOPSIS

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
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Sponsor:	Basilea Pharmaceutica International Ltd Grenzacherstrasse 487 CH-4058 Basel/Switzerland Tel + 41 61 606 1111

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
EUDRACT NUMBER:	2017-001605-32
PROTOCOL NUMBER:	BPR-CS-008 Version 6.0

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 <u>two</u> 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 **Error! Reference source not found.**) 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 **Error! Reference source not found.**).

    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 **Error! Reference source not found.**. 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 **Error! Reference source not found.**).

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 **Error! Reference source not found.**).

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 **Error! Reference source not found.**.

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 **Error! Reference source not found.**).

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 **Error! Reference source not found.**.

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 **Error! Reference source not found.**.

Additional analyses of secondary endpoints are described in Section **Error! Reference source not found.**.

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 **Error! Reference source not found.**.

Pharmacokinetics

Plasma concentration data will be analyzed at each time point as described in Section **Error! Reference source not found.**, 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.