CLINICAL STUDY PROTOCOL
BPR-CS-009

Ceftobiprole medocaril

A randomized, double-blind, multi-center study to establish the efficacy and safety of ceftobiprole medocaril compared to daptomycin in the treatment of *Staphylococcus aureus* bacteremia, including infective endocarditis

Protocol Number/Version:	BPR-CS-009 / Version 9.0
Compound	Ceftobiprole medocaril
Phase of Development	3
IND number:	64,407
EudraCT number:	2017-001699-43
Date:	27 February 2020
[redacted]	
Sponsor:	Basilea Pharmaceutica International Ltd. Grenzacherstrasse 487 CH-4058 Basel/Switzerland Tel + 41 61 606 1111

[redacted]

SPONSOR SIGNATURES

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Protocol Synopsis

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SPONSOR:	Basilea Pharmaceutica International Ltd. (hereinafter 'Basilea')
STUDY PHASE:	3
INDICATION:	*Staphylococcus aureus* bacteremia, including infective endocarditis
U.S. IND NUMBER:	64,407
EUDRACT NUMBER:	2017-001699-43
PROTOCOL NUMBER:	BPR-CS-009 Version 9.0

OBJECTIVES

Primary objective

To demonstrate the non-inferiority of ceftobiprole to daptomycin for overall success as assessed by an independent Data Review Committee (DRC) in the treatment of *S. aureus* bacteremia (SAB), including infective endocarditis (IE), at the post-treatment evaluation (PTE) visit* in the modified intent-to-treat (mITT) population.

Secondary objectives

- To compare ceftobiprole with daptomycin with respect to:
  1. All-cause mortality through Day 70 (PTE visit) and Day 28 in the intent-to-treat (ITT) and mITT populations.
  2. Microbiological eradication rates (negative blood culture for *S. aureus*) at Day 4, Day 8, and the end-of-treatment (EOT) and PTE visits.
  3. Overall success rates in the mITT, ITT, and clinically evaluable (CE) populations:
     a) at the EOT and PTE visits (ITT and CE populations only)
     b) at the EOT and PTE visits, for IE vs non-IE SAB
     c) at the EOT and PTE visits, by renal-function status
  4. Development of new metastatic foci, or other complications of SAB, after Day 7.
  5. Time-to-first-blood-culture-negative for *S. aureus*, confirmed by a second blood-culture-negative for *S. aureus*, obtained at least 24 h after the first negative blood-culture.
  6. Safety and tolerability (Safety population).
- To assess the pharmacokinetics (PK) of ceftobiprole.

* The PTE visit will be performed 70 days (± 5 days) after randomization.

STUDY DESIGN

Randomized, double-blind, double-dummy, active-controlled, parallel-group, multi-center study in adult hospitalized (in a hospital or equivalent medical confinement or clinical research unit) patients with SAB, including IE.

In the first part of the study, the maximum duration of study antibacterial treatment was limited to 28 days. Following an interim safety analysis, this treatment duration is extended up to 42 days (i.e., 21–42 days).

PLANNED SAMPLE SIZE

Approximately 390 patients will be randomized at a 1:1 ratio to ceftobiprole or daptomycin.

PATIENT INCLUSION CRITERIA

Patients meeting all of inclusion criteria 1–5 and at least one of inclusion criteria 6–11 will be eligible for enrollment.

1. Male or female ≥ 18 years of age.
2. Informed consent signed by the patient (or by their legally acceptable representative, if appropriate) indicating that they understand the purpose of, and procedures required for, the study and are willing to participate in the study.
3. SAB, based on at least one *S. aureus*-positive blood culture obtained within the 72 h prior to randomization:
   (a) identified by culture laboratory report, or
   (b) positive diagnostic test for *S. aureus* (e.g., polymerase chain reaction [PCR], tube coagulase test and fluorescent *in situ* hybridization [FISH]) obtained from a blood culture.

   Note: The microbiological work-up of the blood culture may:
   - Occur prior to informed consent to participation in the study (see Section 5.2.1 and Table 7).
   - Be undertaken either on-site or in an external microbiology laboratory specifically appointed for the purposes of this study.
   - Use a diagnostic test:
     – routinely performed locally for the detection of *S. aureus* from blood cultures
       or
     – provided to the laboratory for the purpose of this study, if the test has regulatory approval in the country where the test is being performed

   Regardless of diagnostic method, every effort should be made to isolate and send all unique organisms from blood to the Central Microbiology Laboratory; this applies particularly to the *S. aureus* isolated from blood at the Screening visit. The Central Microbiology Laboratory will re-identify all isolates, with the results to be used to determine whether the patient meets the study inclusion criteria.

   Nevertheless, patients without a Central Microbiology Laboratory assessment may be included in the mITT population if there is unequivocal documented evidence of a baseline blood culture positive for *S. aureus* at the local laboratory.

4. At least one of the following signs or symptoms of bacteremia within the 72 h prior to randomization (may be based on measurements obtained before or after informed consent but within the 72 h prior to randomization):
   (a) fever > 38 °C / 100.4 °F measured orally, > 38.5 °C / 101.3 °F measured tympanically, > 37.5° C / 99.5 °F measured by axillary method, or > 39 °C / 102.2 °F measured rectally
   (b) white blood cell (WBC) count > 10.0×10^9/L, or < 4.0×10^9/L, or > 10% immature neutrophils (bands)
   (c) tachycardia (heart rate > 90 bpm)
   (d) hypotension (systolic blood pressure < 90 mmHg)
5. Required duration of study antibacterial treatment ≤ 42 days.
6. SAB in patients undergoing chronic intermittent hemodialysis or peritoneal dialysis.
7. Persistent SAB: documented failure of bloodstream clearance, defined as a positive blood culture for *S. aureus* within the 72 h prior to randomization, after prior appropriate anti-staphylococcal treatment (except failure under daptomycin therapy) of at least 3 complete days.
8. Other forms of complicated SAB, including the following:
   (a) Acute bacterial skin or skin-structure infections (ABSSSIs)
   (b) Metastatic infection of native tissue. Examples include but are not limited to:
      - Septic arthritis or bacterial joint infection/empyema
      - Septic or suppurative thrombophlebitis
      - Visceral soft-tissue abscesses requiring ≤ 42 days of study antibacterial treatment
      - Septic pulmonary emboli/infarction

        Note: The diagnosis of a septic pulmonary embolism will be made by the investigator based on clinical symptoms of fever, cough, sputum/hemoptysis in the presence of an extrapulmonary infection, sepsis, or risk factors for septic emboli (e.g., intravenous drug use) and will be based on the following radiological signs:

        Contrast-enhanced CT (preferred):

        Peripheral and/or subpleural multifocal nodular lesions (in different stages of cavitation) or wedge-shaped infiltrates
        – with/without a feeding vessel sign (vessel leading to the nodule)
        – with/without pleural effusion or features suggestive of pleural empyema

        Non-contrast enhanced CT (e.g., in patients with a contraindication for contrast administration):

        Peripheral and/or subpleural multifocal nodular lesions (in different stages of cavitation) or wedge-shaped infiltrates
        – with/without pleural effusion or features suggestive of pleural empyema

        Plain X-ray (e.g., in patients unable to undergo a CT):

        Multifocal nodular densities or wedge-shaped infiltrates in varying stages of cavitation with or without pleural effusion or features suggestive of pleural empyema

9. Definite native-valve right-sided IE (RIE) by Modified Duke's Criteria.

   Note: Patients with left-sided infective endocarditis (LIE) are excluded from the study. If LIE is diagnosed after onset of study therapy, patients may be maintained in the study. In the event that the investigator decides to discontinue the study therapy, the patient will be included in the mITT population and considered a failure.
   The minimum requirements for a diagnosis of RIE and LIE (Modified Duke's Criteria), and the minimum diagnostic requirements for other forms of complicated SAB, are provided in Appendix 1 and Appendix 2.

10. Osteomyelitis (including vertebral, sternal, or long-bone osteomyelitis).

11. Epidural or cerebral abscess.

Inclusion criteria 1–7 must be ascertained based on assessments within the 72-h screening window. For inclusion criteria 8–11, assessments performed up to 7 days after randomization may be used to confirm the diagnosis of complicated SAB.
Patients randomized with suspected complicated SAB who turn out not to meet at least one of inclusion criteria 6–11 (i.e., who do not have confirmed complicated SAB), will be considered to have uncomplicated bacteremia. These patients will continue in the study. The minimum treatment duration target in this study is 21 days; the maximum treatment duration is 42 days.

PATIENT EXCLUSION CRITERIA

Patients meeting any of the following exclusion criteria at Screening will be excluded from the study:

1. Treatment with potentially effective (anti-staphylococcal) systemic antibacterial treatment for more than 48 h within the 7 days prior to randomization (see Appendix 5).

   Exception: Documented failure of bloodstream clearance with prior antistaphylococcal treatment (except failure under daptomycin therapy) administered for at least 3 complete days.

2. Bloodstream or non-bloodstream concomitant infections with Gram-negative bacteria that are known (at Screening) to be non-susceptible to either ceftobiprole or aztreonam.

3. Confirmed uncomplicated SAB (e.g., catheter-related non-persistent SAB without signs of SAB complications, unless the patient has end-stage renal disease and is on intermittent hemodialysis or peritoneal dialysis).

4. Left sided infective endocarditis (known or suspected to be present at the time of randomization)
   Note: If LIE is diagnosed after onset of study therapy, patients may be maintained in the study. In the event that the investigator decides to discontinue the study therapy, the patient will be included in the mITT population and considered a failure.

5. Prosthetic cardiac valves or valve support rings, cardiac pacemakers, automatic implantable cardioverter-defibrillator, or left-ventricular assist devices.

6. Complicated SAB in patients with other foreign body material that cannot be removed within the 7 days after randomization.

   Exceptions:
   - Patients with non-infected coronary stents may be included regardless of the time of stent implantation.

- Patients with non-infected (no signs or symptoms of clinical involvement at the time of randomization) prosthetic joints, plates, spinal hardware, or other extravascular material may be included if implantation of the foreign material was performed at least 60 days before randomization.
- Patients with non-infected (no signs or symptoms of clinical involvement at the time of randomization) intravascular prosthetic material or vena cava filters may be included if implantation of the foreign material was performed at least 90 days before randomization.

7. Cardiac native-valve surgery planned within 3 days after randomization.
8. Community- or hospital-acquired pneumonia
   Note: The diagnosis of pneumonia will be made by the investigator based on respiratory complaints (e.g., cough, dyspnea, purulent secretions, and chest pain) and new or worsening infiltrates suggestive of bacterial pneumonia on a chest radiograph or a high-resolution CT. Equivocal findings on a chest radiograph should be further assessed by the conduct of a high-resolution chest CT (if feasible) and/or the conduct of lung ultrasound to support the presence or absence of a diagnosis of pneumonia.
9. High probability of death within 7 days due to the underlying SAB or SAB-associated disease, or high probability of death within 28 days from an unrelated underlying disease.
10. Clinically-relevant hypersensitivity to β-lactam antibacterials or daptomycin.
11. Known infection due to *Staphylococcus aureus* that exhibits reduced susceptibility to daptomycin (minimum inhibitory concentration [MIC] > 1 mg/L), or ceftobiprole (MIC > 2 mg/L).
12. Absolute neutrophil count $< 0.5 \times 10^9$/L.
13. Either: a) a history of opportunistic infections (e.g., invasive fungal infections or cytomegalovirus [CMV]) within 30 days prior to randomization, where the underlying cause of these infections is still active (e.g., leukemia, transplant, acquired immunodeficiency syndrome [AIDS]); or b) CD4 count < 100 cells/mm^3 in patients with AIDS; or c) patients treated with cotrimoxazole as prophylaxis for pneumocystis pneumonia.
14. Requirement or expected requirement between randomization and the PTE visit for potentially effective (anti-staphylococcal) systemic antibacterial treatment that is unrelated to the treatment of SAB, e.g., in the context of planned surgery, gynecological or other procedures requiring antibacterial prophylaxis or other anticipated uses of antibacterials such as treatment for acne vulgaris.
15. Requirement for continuous renal-replacement therapy at the time of randomization, or high likelihood of requirement for continuous renal-replacement therapy during the study period.
    Note: Patients undergoing chronic intermittent hemodialysis or peritoneal dialysis are permitted to participate in the study.
16. Alanine transaminase (ALT) or aspartate transaminase (AST) levels ≥ 8 × the upper limit of normal, or severe hepatic disease with Child-Pugh class C.
17. Women who are pregnant or nursing.

18. 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.

19. Use of an investigational drug in a Phase 1 study within the 30 days prior to the start of study treatment.
    Note: Use of investigational drugs in Phase 2 or Phase 3 studies within the 30 days prior to the start of study drug treatment is allowed.

STUDY DRUG

Patients will be randomized to double-blind, double-dummy study treatment with ceftobiprole medocaril or daptomycin in a 1:1 allocation ratio, based on a computer-generated randomization schedule. Within the 6 h prior to the scheduled first dose of study drug, the investigator/designee will contact the Interactive Web Response System (IWRS) to obtain the study treatment assignment. The IWRS will allocate the patient to the appropriate randomization stratum. Randomization will be stratified by study site, dialysis status, and prior antibacterial treatment use (i.e., use of any systemic antibacterial treatment potentially effective against *S. aureus* within 7 days of randomization).

The treatment duration will be 21–42 days, with the treatment duration within this window to be defined by the study investigator.

Ceftobiprole medocaril powder for solution for infusion will be administered as 2-h intravenous infusion according to the following schedule:

Study Day	**Normal renal function to mild renal impairment** (CL_{Cr} ≥ 50 mL/min)	**Renal impairment** (non-dialysis)	**Intermittent hemodialysis or peritoneal dialysis**
Day 1 to Day 8	500 mg q6h	CL_{Cr} 30–< 50 mL/min: 500 mg q8h CL_{Cr} <30 mL/min: 250 mg q8h	250 mg q24h
Day 9 onwards	500 mg q8h	CL_{Cr} 30–< 50 mL/min: 500 mg q12h CL_{Cr} < 30 mL/min: 250 mg q12h	250 mg q24h

CL_{Cr}=Creatinine clearance based on the Cockcroft-Gault formula.

CONCURRENT CONTROL

Daptomycin lyophilized powder for solution for infusion will be administered as 0.5-h intravenous infusion according to the following schedule:

	Normal renal function to moderate renal impairment ($CL_{Cr} \geq 30$ mL/min)	**Renal impairment** (non-dialysis) ($CL_{Cr} < 30$ mL/min)	**Intermittent hemodialysis or peritoneal dialysis**
Daptomycin (0.5-h infusion)	6 mg/kg q24h	6 mg/kg q48h	6 mg/kg q48h

CL_{Cr}=Creatinine clearance based on the Cockcroft-Gault formula.

In accordance with institutional standards, an increase in the dose of daptomycin administered (up to 10 mg/kg) may be implemented.

To maintain the blinding of study treatments, patients in the ceftobiprole group will receive dummy infusions with placebo (physiological saline, 0.9% NaCl) matching daptomycin, and patients in the daptomycin group will receive dummy infusions with placebo (physiological saline, 0.9% NaCl) matching ceftobiprole.

No switches to other systemic antibacterial treatments are permitted for any of the study drugs prior to the PTE visit. There is no intravenous-to-oral switch for any of the treatments in this study.

CONCOMITANT ANTIBACTERIAL TREATMENTS

Concomitant systemic antibacterials (other than study drugs) that provide activity against *S. aureus* are prohibited from randomization up to the PTE visit.

Aztreonam may be used in the daptomycin group for coverage of Gram-negative infections (i.e., for polymicrobial bloodstream infections or for Gram-negative non-bloodstream infections). Patients randomized to the ceftobiprole group who are considered to require coverage against Gram-negative infections will receive dummy treatment with placebo so that blinding is maintained during the active treatment phase.

Open-label metronidazole may be used in both treatment groups for coverage of anaerobic infections.

Open-label nitrofurantoin may be used in both treatment groups for urinary tract infections.

Oral vancomycin is considered a non-systemic antibiotic and may be used at any time during the study.

Antibacterial treatment against Gram-negative pathogens and/or anaerobic pathogens for polymicrobial bloodstream infections or for non-bloodstream infections:

Known or suspected infections	**Treatment arm(s)**	**Recommended treatment approach**
Infections caused by Gram-negative pathogens susceptible to ceftobiprole and aztreonam	• Daptomycin	Aztreonam using a standard-dose regimen at the respective institution.
Urinary tract infections caused by pathogens susceptible to nitrofurantoin	• Ceftobiprole • Daptomycin	Nitrofurantoin using a standard-dose regimen at the respective institution
Infections caused by anaerobic pathogens	• Ceftobiprole • Daptomycin	Metronidazole using a standard-dose regimen at the respective institution.

STUDY-DRUG ADMINISTRATION

Ceftobiprole and daptomycin will be given intravenously for 21 to 42 days.

MAIN STUDY ENDPOINTS

Primary endpoint

Overall success at the PTE visit (Day 70±5 days post-randomization) in the mITT analysis set, as assessed by the DRC (see Appendix 4). The DRC will be a group of independent clinical experts, blinded to treatment allocation and not associated with the study conduct, who will review patient profiles, including signs and symptoms of infection, and relevant microbiological and imaging findings, and will assess the patients' clinical and microbiological outcomes.

The primary endpoint will be tested for the non-inferiority of ceftobiprole versus daptomycin using a non-inferiority margin of 15%.

Overall success is defined as all of the following criteria being met:

1. Patient alive at Day 70 (±5 days) post-randomization.
2. No new metastatic foci or complications of the SAB infection.
3. Resolution or improvement of SAB-related clinical signs and symptoms.
4. Two negative blood cultures for *S. aureus* (without any subsequent positive blood culture for *S. aureus*):
   - at least one while the patient is on active study treatment; AND
   - confirmed by at least one subsequent negative blood culture for *S. aureus*
     - either in the period between 7 days after the EOT visit and the PTE visit
     - or at the PTE visit

Treatment failure is defined as any of the following:

1. Premature discontinuation of study treatment due to DRC-assessed lack of efficacy (as assessed by the DRC) or for adverse events (AEs) that represent manifestation of disease progression or relapse, at any time between first dose of study drug and the PTE visit.
2. Development of new metastatic or other complications related to SAB (see Section 5.4.5.3.2) between Day 8 and the PTE visit. Development of new metastatic or other complications of SAB prior to Day 8 will be assessed by the DRC on a case-by-case basis to assess whether these constitute a delayed manifestation of the baseline disease or new complications.
3. SAB relapse or reinfection based on evidence from a blood culture positive for *S. aureus* (after documented clearance of *S. aureus* from the bloodstream and clinical improvement) between the EOT and PTE visits.
4. Receipt of systemic non-study antibacterial treatment, other than those permitted under the protocol, for the treatment of SAB. This includes patients who are prematurely discontinued from study therapy due to an AE, but who require continuation of antibacterial treatment for SAB.
5. Treatment of infections other than SAB with systemic non-study antibacterial treatment which is potentially effective against *S. aureus* (see Appendix 5), and which is considered by the DRC to have a relevant impact on the primary endpoint in accordance with the guidelines provided in Appendix 6.

6. Death for any reason between first administration of study drug and the PTE visit.
7. Indeterminate outcome, defined as any data needed to determine whether the outcome is success or failure missing at the PTE visit, including but not limited to:
   a) missing PTE visit, or missing key data to evaluate the primary endpoint
   b) lost-to-follow-up, or patients who withdrew consent prior to the PTE visit
   c) patients not meeting the criteria for Success or Failure, or patients not meeting all criteria for overall success
8. Requirement for systemic antibacterial treatment for SAB beyond EOT.

Secondary endpoints

1. All-cause mortality (mITT population) at Day 70 (PTE visit)

All-cause mortality will also be assessed at Day 28, and in the ITT population, and will be assessed descriptively.

2. Microbiological eradication (mITT population) at Day 70 (PTE visit)

Microbiological eradication will also be assessed in the CE population, and at Day 4, Day 8, and the EOT visit, and will be assessed descriptively.

Eradication: No growth of the baseline pathogen(s), secondary to an adequate clinical response, based on a negative blood culture while the patient is on active study treatment which is confirmed by at least one subsequent negative blood culture for *S. aureus*, either in the period between 7 days after EOT and the PTE visit, or at the PTE visit.

Failure: Persistence, relapse, or reinfection of *S. aureus* infection, defined as one or more of:

- Ongoing positive blood cultures leading to discontinuation of the study drug
- Subsequent isolation of *S. aureus* from a blood culture after clearance of bacteremia and clinical improvement
  - Relapse: bloodstream infection with the same pathogen isolated at baseline based on genotyping
  - Reinfection: bloodstream infection with a different *S. aureus* strain to that isolated at baseline based on genotyping
- Absence of at least two negative blood cultures (at least one negative blood culture on active study treatment, and at least one post-treatment) to confirm eradication

Relapse or reinfection between EOT and PTE that is reported to the investigator from a healthcare provider not involved in the study (e.g., from another hospital), needs to be thoroughly documented and will be reviewed by the investigator and the DRC for determination.

3. Overall success rate at PTE (CE population)

The overall success rate will also be assessed at the EOT visit in the mITT, ITT and CE populations, and in the ITT population at the PTE visit, and will be assessed descriptively.

See definitions for the primary endpoint above.

4. Development of new metastatic foci or other complications of SAB after Day 7 (mITT population)

Development of new metastatic foci or other complications of SAB after Day 7 will also be assessed in the CE population, and will be assessed descriptively.

Timepoints: Day 8–EOT, and PTE

Newly diagnosed IE or complicated SAB with metastatic foci or other complications of *S. aureus* infection, including metastatic foci in the vertebral column (vertebral abscess, osteomyelitis, discitis or epidural abscess), cerebral abscess/infarction, splenic abscess/infarction, renal abscess/infarction, psoas abscess or other deep-tissue abscess, other metastatic infection of native tissue, septic arthritis (or bacterial joint infection/empyema), septic or suppurative thrombophlebitis and septic pulmonary emboli/infarction.

5. Time to S. aureus bloodstream clearance (mITT and CE populations)

Timepoints: Day 3–EOT

Time-to-first-blood-culture-negative for *S. aureus*, confirmed by a second blood-culture-negative for *S. aureus* obtained at least 24 h after the first negative blood-culture.

6. Safety/Tolerability (Safety population)

Timepoints: First dose of study drug–PTE

Incidence, type, severity, and relationship to study medication of AEs; and changes in laboratory tests (hematology, biochemistry including haptoglobin, urinalysis, and Coombs-test).

7. Pharmacokinetics of ceftobiprole (PK population)

Plasma levels of ceftobiprole and the β-lactam ring-open product BAL1029

Sparse PK sampling (all patients)

- Day 3: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 4 to 6 h
- Day 12: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 4 to 6 h

Rich PK sampling (selected sites, N=40 ceftobiprole-treated patients [i.e., approximately 80 patients overall])

- Day 3: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 3 h, 4 h, 6 h
- Day 12: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 4 to 6 h

Plasma-concentration data will be analyzed at each time point and will be presented as individual concentrations with descriptive statistics (mean, SD, CV%, min, median, max).

STATISTICAL ANALYSIS

Analysis populations

The following analysis populations are defined for this study:

Intent-to-treat population (ITT)

The ITT population consists of all randomized patients. Patients will be analyzed according to the study medication assigned at randomization.

Modified intent-to-treat population (mITT)
The mITT population consists of the subset of patients in the ITT population who have received any amount/dose of study medication, and who have a blood culture positive for *S. aureus* at baseline based on a central microbiology laboratory assessment.*

Clinically evaluable population (CE)
The CE population consists of the subset of patients in the mITT population who have complied with important aspects of the study, e.g., no major protocol violations, with a completed primary outcome assessment.

Safety population
The safety population consists of all randomized patients who received any amount/dose of study medication. Patients in the safety population will be analyzed according to the first medication 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.

Analysis of primary endpoint

The primary analysis will be based on the mITT population.

The study is designed to determine whether ceftobiprole is non-inferior to daptomycin for the outcome measure of overall success at the PTE visit at Day 70 (±5 days) after randomization, in the mITT population.

The observed difference in percentage of responders at PTE (ceftobiprole group minus the daptomycin group) will be determined and a two-sided 95% confidence interval (CI) for the observed difference will be computed, with adjustment for geographical region (North America, Europe, other regions), dialysis status and prior antibacterial treatment use. Cochran-Mantel-Haenszel weights will be used for the stratum weight 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 two-sided 95% CI for the difference in response rates in the mITT population is greater than −15%, the non-inferiority of ceftobiprole to daptomycin therapy will be concluded.

The primary analysis will classify as failures all patients with missing data relevant to appropriate assessment of the primary endpoint at the PTE visit.

A sensitivity analysis will be performed to exclude those patients with missing data completely, and this assumes missing at random (MAR). Additional analyses will explore the robustness of the conclusion of the non-inferiority of ceftobiprole to further missingness not at random (MNAR) assumptions. In particular, various proportions of the patients with missing data (10%, 20%, 30% and 40%) in the daptomycin group will be considered successes, while only half of the respective proportions of patients in the ceftobiprole group will be considered successes (5%, 10%, 15%, 20%), and the analysis of non-inferiority repeated for each of the assumed proportions.

* Patients who are missing a central microbiological assessment may be included in the mITT population if there is documented unequivocal evidence of a baseline blood culture positive for *S. aureus* at the local laboratory

Analysis of secondary efficacy endpoints

Two-sided 95% CIs will be constructed for the observed difference between ceftobiprole and daptomycin therapy for the endpoints of all-cause mortality, microbiological eradication, overall success, and development of new metastatic foci, using the same approach as for the primary endpoint.

In addition, a time-to-event analysis will be performed for all-cause mortality and for time-to-blood-cultures-negative for *S. aureus*.

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.

Sample size justification

The sample size estimate is based on:

- A point estimate for overall success of 40% in each treatment group in the mITT population.
- One-sided alpha level of 0.025.
- Power of > 80%.
- Non-inferiority margin of 15% for the between-group difference in the primary endpoint.

With these assumptions, enrollment of 175 patients per treatment group (total of 350 patients) is required in the mITT population. Assuming that approximately 90% of patients in the ITT population will have confirmed SAB and will therefore be included in the mITT population, 195 patients per group (total of 390 patients) will need to be randomized and receive study treatment.

Interim safety analysis

As animal studies have indicated the potential of an increased risk of convulsions with prolonged ceftobiprole therapy (> 4 weeks treatment duration), an initial cohort of patients was enrolled for a maximum treatment duration of 28 days (Cohort 1). An interim safety analysis was performed by an independent DSMB after 80 patients (approximately 40 patients per treatment group) have completed 21–28 days of treatment and safety follow-up. Based on this analysis the treatment duration was extended up to 42 days (Cohort 2)after discussion with the United States Food and Drug Administration (FDA).

The decision rules for the DSMB interim safety assessment of Cohort 1 are provided in Appendix 7.

Further interim safety assessments will be performed by the DSMB after enrollment of 200 and 300 patients; details are provided in the DSMB Charter.

PROCEDURES

Overview

The total duration of the study, including follow-up, is up to 10 weeks (70±5 days) for each patient.

Baseline assessments are defined as all relevant pre-randomization assessments that may be used for the study (see Section 5.2). Screening is defined as the period after informed consent has been obtained, i.e., a period up to 72 h prior to randomization.

Results from vital sign measurements, local safety laboratory tests, blood cultures, echocardiography or investigations to verify deep-seated infections or complications of SAB, may be used for the study if obtained prior to informed consent (i.e., outside the screening period) but within a 72-h

window prior to randomization (10 days for an echocardiography that was confirmatory for definitive right-sided endocarditis) (see Section 5.2).

Study assessments are shown in Table 6 of the protocol and summarized below.

The study comprises three phases:

- Screening of up to 72 h prior to randomization.
- Randomization and subsequent active-treatment phase with intravenous study drug (ceftobiprole or daptomycin therapy).
- Post-treatment, comprising an EOT visit (within 72 h of last study-drug administration), Day 35 (±3 days), Day 42 (±3 days), and a PTE visit on Day 70 (±5 days) post-randomization.

Patients with suspected or confirmed complicated SAB must sign informed consent within the 72 h prior to randomization. Baseline assessments must be completed according to the following timelines.

Blood cultures

Two sets of peripheral blood cultures (including aerobic and anaerobic) will be obtained from each patient at baseline. Blood cultures will be drawn at least 5 min apart, and samples for each of the two sets of blood cultures should be obtained from different anatomical locations. Blood cultures that were positive for *S. aureus* and were conducted in the context of routine clinical diagnostic work-up practice prior to obtaining informed consent, but were drawn within the 72 h prior to randomization, may be used for the study to determine patient eligibility, and do not need to be repeated.

Post-randomization blood cultures (at least one, but preferably two blood cultures) will be obtained on Days 1, 2 and 3. Thereafter, blood cultures will be obtained approximately every 48–72 h if clearance of bacteremia has not yet been confirmed, i.e., until negative test results for *S. aureus* are obtained for two cultures (or negative test result for one culture if only one culture was obtained) at two time points taken at least 24 h apart. At least one blood culture must be obtained at the PTE visit, or in the period between 7 days after the EOT visit and the PTE visit.

Specimens will be cultured by the local laboratory. The microbiological work-up of the blood culture may:

- Occur prior to informed consent to participation in the study (see Section 5.2.1 and Table 7).
- Be undertaken either on-site or in an external microbiology laboratory specifically appointed for the purposes of this study.
- Use a diagnostic test:
  - routinely performed locally for the detection of *S. aureus* from blood cultures
    or
  - provided to the laboratory for the purpose of this study, if the test has regulatory approval in the country where the test is being performed

Regardless of diagnostic method, every effort should be made to isolate and send all unique organisms from blood to the Central Microbiology Laboratory; this applies particularly to the *S. aureus* isolated from blood at the Screening visit. The Central Microbiology Laboratory will re-identify all isolates, with the results to be used to determine whether the patient meets the study inclusion criteria.

Nevertheless, patients without a Central Microbiology Laboratory assessment may be included in the mITT population if there is unequivocal documented evidence of a baseline blood culture positive for *S. aureus* at the local laboratory.

The central microbiology laboratory will also perform susceptibility testing with both study drugs. For patients with persistent SAB (see Inclusion criterion 7), the susceptibility to ceftobiprole and daptomycin may be assessed at the local microbiology laboratory, but must be confirmed by the central laboratory. If a patient is randomized based on susceptibility results from the local laboratory, and a conflicting result is obtained from the central laboratory, then the central laboratory result will be considered valid. If local susceptibility testing is performed after a patient has been randomized, and the local results show non-susceptibility to either study drug, then the continuation of the patient in the study will be at the discretion of the investigator, based on clinical assessment.

Echocardiography

Echocardiography assessments obtained within 72 h prior to randomization (or up to 10 days if definite RIE has been confirmed) may be used for patient eligibility assessment, even if the echocardiography has been performed in the context of clinical practice prior to obtaining informed consent for this study.

Transthoracic echocardiography

A transthoracic echocardiography (TTE) must be performed within the 72 h prior to randomization for all patients with the following exceptions:

- A transesophageal echocardiography (TEE) has been performed within this time window
- A diagnosis of definite RIE (according to Modified Duke's Criteria) is confirmed. For these patients, a TTE (or TEE) performed within the 10 days prior to randomization may be used to confirm patient eligibility. A TTE or TEE must be repeated within the 72 h before, or within the 7 days after, randomization, for documentation purposes.

Transesophageal echocardiography

A TEE must be performed within 72 h prior to randomization or within 7 days after randomization in all patients with the following exceptions:

- A diagnosis of definite RIE (according to Modified Duke's Criteria) is confirmed. For these patients a TEE (or TTE) performed within 10 days prior to randomization may be used to confirm patient eligibility. A TTE or TEE must be repeated within 72 h before, or within 7 days after, randomization, for documentation purposes. If the diagnosis of a definite RIE can be based on a TTE, then a TEE is not required.
- A condition associated with an increased risk of complications from TEE, including:
  - altered mental status or an uncooperative patient
  - unstable cardiorespiratory status
  - esophageal stricture or malignancy (identify esophageal location prior to TEE) or esophageal varices with recent/active bleeding
  - surgical interposition of the esophagus
  - Zenker's diverticulum (identify esophageal location prior to TEE)
  - history of odynophagia or dysphagia

- cervical spine arthritis with reduced range of motion
- severe thrombocytopenia (< 50 × 10^9/L), elevated international normalized ratio (> 4), or prolonged partial thromboplastin time (> 150 seconds)
- obstructive sleep apnea/airway compromise (consider sedation by anesthesia)

Diagnostic assessments for metastatic or other complications related to SAB

Diagnostic assessments for metastatic or other complications related to SAB (i.e., related to Inclusion criterion 8) that were conducted in the context of routine clinical diagnostic work-up practice prior to obtaining informed consent, but within the 72 h prior to randomization, may be used for the study to determine patient eligibility.

Furthermore, diagnostic assessments for metastatic or other complications related to SAB (i.e., related to Inclusion criterion 8) that are obtained within the 7 days after randomization may be used to determine the patient's baseline condition of complicated SAB.

Other screening assessments

Vital sign measurements and local safety laboratory tests that were conducted in the context of routine clinical diagnostic work-up practice prior to obtaining informed consent, but within the 72 h prior to randomization, may be used for the study to determine patient eligibility and do not need to be repeated. This includes the assessment of signs and symptoms of bacteremia for the purposes of Inclusion criterion 4.

All other screening assessments except a pregnancy test (physical examination, 12-lead electrocardiogram, central laboratory safety tests, Modified Duke's Criteria, creatinine clearance) must be performed after informed consent has been obtained, and within the 72 h prior to randomization.

A pregnancy test must be assessed within 24 h prior to randomization. Clinical signs of deep-seated infections and metastatic or other complications of SAB must be assessed within the 12 h prior to randomization.

Clinical signs of metastatic complications (assessed by the investigator) include bone or back pain, back pain elicited on percussion of spine (suggestive of vertebral osteomyelitis, discitis, or epidural abscess); joint swelling, joint pain, pain elicited on external rotation of femoral head (suggestive of septic arthritis); protracted fever and/or sweats, new regurgitant murmurs or heart failure and further clinical stigmata suggestive of IE; abdominal pain, left upper quadrant pain (suggestive of splenic infarction); costovertebral angle tenderness (suggestive of renal infarction or psoas abscess); headache, focal neurologic impairment (suggestive of central nervous septic emboli) or other findings which could reasonably be regarded as clinical signs of metastatic infection. Careful examinations regarding in-dwelling prosthetic devices and orthopedic hardware should be undertaken.

Metastatic or other complications of SAB must be supported by imaging studies (including ultrasound, computed tomography [CT], magnetic resonance imaging [MRI], and positron emission tomography/computed tomography [PET/CT]), biopsies or cultures. The minimum requirements for baseline or post-baseline diagnosis of metastatic complications of SAB are provided in Appendix 2 and Appendix 3, respectively.

For clinical signs of bacteremia see Inclusion criterion 4.

Details of the time windows for baseline screening assessments are outlined in Section 5.2.

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LIST OF ABBREVIATIONS

ABSSSI	Acute bacterial skin and skin structure infection
ACM	All-cause mortality
AE	Adverse event
ALT	Alanine transaminase
AP	Alkaline phosphatase
aPPT	Activated partial thromboplastin time
AST	Aspartate transaminase
BPR	Ceftobiprole medocaril
CAP	Community-acquired pneumonia
CE	Clinically evaluable
CI	Confidence interval
CL_{CR}	Creatinine clearance
CMV	Cytomegalovirus
CPK	Creatine phosphokinase
CRF	Case report form
CRP	C-reactive protein
cSSTI	complicated skin and soft tissue infection
CT	Computed tomography
DAP	Daptomycin
DRC	Data Review Committee
DSG	DSMB Statistics Group
DSMB	Data and Safety Monitoring Board
EOT	End-of-treatment
ESRD	End-stage renal disease
FDA	United States Food and Drug Administration
FSH	Serum follicle stimulating hormone
FISH	Fluorescent *in situ* hybridization
GGT	Gamma-glutamyl transferase
GISA	Glycopeptide-intermediate *Staphylococcus aureus*
HAP	Hospital-acquired pneumonia

HCT	Hematocrit
HGB	Hemoglobin
ICH	International Council for Harmonisation
IE	Infective endocarditis
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-treat
IUD	Intrauterine device
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LIE	Left-sided infective endocarditis
LPLV	Last Patient Last Visit
MIC	Minimum inhibitory concentration
mITT	Modified intent-to-treat
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NOEL	No-observed-effect-level
NSAID	Nonsteroidal anti-inflammatory drug
PBO	Placebo
PCR	Polymerase chain reaction
PET/CT	Positron emission tomography/computed tomography
PK	Pharmacokinetic (population)
PORT	Pneumonia Outcomes Research Team
PSI	Pneumonia Severity Index
PT	Preferred Term
PT	Prothombrin time
PTE	Post-treatment evaluation
RBC	Red blood cell
RIE	Right-sided infective endocarditis

RSI	Reference Safety Information
SAB	*Staphylococcus aureus* bacteremia
SAE	Serious adverse event
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
TEE	Transesophageal echocardiography
TOC	Test-of-cure
TTE	Transthoracic echocardiography
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia
VISA	Vancomycin-intermediate *Staphylococcus aureus*
VRSA	Vancomycin-resistant *Staphylococcus aureus*
WBC	White blood cell

1 BACKGROUND AND RATIONALE

1.1 Disease characteristics and treatment

Staphylococcus aureus bacteremia (SAB) is a leading cause of bloodstream infections, responsible for a broad variety of complications and has been associated with significant morbidity and a mortality of 20 to 40% (Jensen 2002, Wang 2008).

Standard-of-care antibacterial treatments for SAB including infective endocarditis include vancomycin or daptomycin (active against MSSA and MRSA) or oxacillin and cefazolin (active against MSSA only) (Yaw 2014). Several studies have demonstrated that MRSA bacteremia is associated with a significantly higher mortality rate compared with methicillin-susceptible *S. aureus* (MSSA) bacteremia (Blot 2002, Cosgrove 2003). However, MSSA bacteraemia is more frequent than MRSA bacteraemia. This underlines the importance of antibacterial treatments that are rapidly bactericidal against both MRSA and MSSA. Daptomycin (a lipopeptide antibacterial), and ceftobiprole (a β-lactam antibacterial), provide such rapid bactericidal activity against both MSSA and MRSA while vancomycin (a glycopetide) shows a slower bactericidal effect, is less effective for treatment of SAB than β-lactam agents and is therefore not considered as an antibacterial treatment of first choice for MSSA infections by many experts (Cosgrove 2003, Murthy 2008).

1.2 Investigational medicinal products

1.2.1 Test product

Ceftobiprole medocaril powder for solution for infusion 500 mg four times daily (q6h) for study Days 1 through 8, three times daily (q8h) from study Day 9 onwards, with dose adjustments for renal impairment.

1.2.2 Comparator regimen

Daptomycin lyophilized powder for solution for infusion 6 mg/kg once daily (q24h), with dose adjustments for renal impairment.

1.3 Nonclinical studies with ceftobiprole

1.3.1 Microbiology

1.3.1.1 In vitro studies

Ceftobiprole has a strong affinity for several penicillin-binding proteins (PBPs), including PBP2a and PBP2x, which mediate resistance to other β-lactams in staphylococci and pneumococci, respectively (Davies 2010, Davies 2007, Entenza 2002, Hebeisen 2001, Henry 2013, Lovering 2012). In contrast to earlier-generation cephalosporins, ceftobiprole effectively prevents the intracellular growth of both MSSA and MRSA strains in macrophages and keratinocytes, due in part to its strong binding affinity to 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 β-lactams, and is stable to hydrolysis by the *S. aureus* PC1 Class A β-lactamase, conserving its activity against staphylococci (Queenan 2007).

Ceftobiprole is also relatively stable against AmpC cephalosporinases and common class A β-lactamases produced by Gram-negative bacteria, but not to extended-spectrum β-lactamases (ESBLs), carbapenemases, or OXA β-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 (Bogdanovich 2005, Bogdanovich 2006, Kosowska 2005, Queenan 2005, Queenan 2007, 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 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, Deshpande 2013, Leonard 2008, Rouse 2007).

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).

1.3.1.2 Animal models of infection

The *in vivo* potency of ceftobiprole against MRSA has been demonstrated in animal models of pneumonia (Laohavaleeson 2008), *S. aureus*-mediated IE (Chambers 2005, Entenza 2011, Fernandez 2012, Tattevin 2010) and osteomyelitis (Saleh-Mghir 2012, Yin 2008) using humanized doses. In a rat model of endocarditis, ceftobiprole was superior to vancomycin in reducing the bacterial load of cardiac vegetations in animals infected with MRSA, GISA, or VISA (Entenza 2011, Fernandez 2012). In addition, depending on the strain, 47–93% of vegetations were sterilized following ceftobiprole treatment, compared to none for vancomycin. Similar results were seen using rabbit models of aortic-valve endocarditis (Chambers 2005, Tattevin 2010) and tibial osteomyelitis (Saleh-Mghir 2012, Yin 2008). One endocarditis study found ceftobiprole to be superior to vancomycin against VISA (Chambers 2005), and in another, the activity of ceftobiprole was superior to that of vancomycin, daptomycin and linezolid for the treatment of MRSA-induced endocarditis (Tattevin 2010). In this model, ceftobiprole also sterilized more vegetations than daptomycin or vancomycin.

1.3.2 Pharmacokinetics and product metabolism in animals

In animals after single intravenous dose pharmacokinetic 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 microbiologically inactive 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 with no relevant accumulation, differences related to sex, or time-dependent pharmacokinetics.

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 intravenous 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, pharmacokinetics and pharmacodynamics of ceftobiprole medocaril are provided in the ceftobiprole Investigator's Brochure.

1.3.3 Toxicology

The primary targets of toxicity after intravenous 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 intravenous 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. Animal studies in rats have indicated the potential of an increased risk of convulsions with prolonged ceftobiprole therapy (> 4 weeks treatment duration). In the 13-week studies, convulsions were only observed in male rats at high doses (no-observed-effect-level [NOEL] 250 mg/kg; mean C_{max} 84 µg/mL), and the convulsions in rats may have been confounded by nephrotoxicity. There were no convulsions in the 13-week dog study.

Further details on the nonclinical toxicology of ceftobiprole medocaril are provided in the Investigator's Brochure.

1.4 Clinical studies with ceftobiprole

1.4.1 Pharmacokinetics, product metabolism, and tissue distribution in humans

The pharmacokinetics of ceftobiprole in adult subjects 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, and no appreciable accumulation is observed in subjects 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 h.

Ceftobiprole is eliminated primarily unchanged by renal excretion, with minimal metabolism to an (inactive) 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 subjects with moderate or severe renal impairment, in end-stage renal disease (ESRD) subjects, and in subjects with CL_{CR} > 150 mL/min. Given no underlying renal impairment, the primary PK/PD driver of ceftobiprole (time that drug concentration exceeds 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.

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 CFU (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 pharmacokinetic analysis of subjects in the Phase 3 HAP study demonstrated the probability of target attainment for a dosing regimen of 500 mg q8h (administered as 2-hour [h] infusions) for a 60% T>MIC of 4 µg/mL to be 100% for Gram-positive pathogens, and 96% for Gram-negative pathogens.

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 acute bacterial skin and skin structure infection (ABSSSIs) / complicated skin and soft tissue infection (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 2008b). Study BAP00154 compared ceftobiprole 500 mg q12h (N=397) with vancomycin 1 g q12h (N=387) in patients with Gram-positive ABSSSIs/cSSTIs (Noel 2008a).

Clinical cure at the test-of-cure (TOC) visit was 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% 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 q8h to treatment with ceftriaxone 2 g q24h with or without linezolid 600 mg q12h, for subjects 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 ceftobiprole patients 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 Pneumonia Outcomes Research Team (PORT) Risk Classes ≥ III (Pneumonia Severity Index [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 500 mg q8h to ceftazidime 2 g q8h plus linezolid 600 mg q12h was demonstrated within the pre-specified 15% margin for the primary efficacy endpoint of clinical cure rate at the TOC visit for all subjects 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 prespecified subgroup of subjects with HAP (excluding ventilator-associated pneumonia [VAP]) subjects (N=571). Non-inferiority of ceftobiprole was not demonstrated in the smaller subset of VAP subjects (N=210).

1.4.7 Safety

The current safety experience from clinical studies of ceftobiprole comprises 3,037 subjects (1,404 from Phase 3 pneumonia studies, 1,633 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.

The most common adverse reactions, occurring in ≥ 3% of patients treated with ceftobiprole, were nausea, vomiting, diarrhoea, 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.

1.5 Rationale for study BPR-CS-009

Favorable pharmacological properties and a rapid bactericidal effect compared to other drug classes, make β-lactam antibacterials a mainstay treatment of SAB. However, none of the current β-lactams licensed for the treatment of SAB provide coverage against MRSA. Ceftobiprole has bactericidal activity against both MSSA and MRSA, and therefore addresses shortcomings of the alternative β-lactam antibacterials for this indication. In addition, animal studies of IE indicate that ceftobiprole may provide superior efficacy in the clearance of vegetations from heart valves (see Section 1.3.1.2).

Daptomycin, a cyclic lipopeptide, is the only antibacterial treatment licensed for SAB including infective endocarditis that provides similar bactericidal activity against both MSSA and MRSA (see Section 1.5.2.9).

The proposed study is designed to compare ceftobiprole versus daptomycin in a randomized, double-blind study. The study will include a broad spectrum of patients with complicated SAB, which is expected to enhance its applicability to clinical practice compared to existing studies. This includes subgroups such as patients on chronic hemodialysis, a population that has not been studied in other completed (daptomycin NCT00093067 [Fowler 2006]) or ongoing (telavancin NCT02208063) Phase 3 studies in SAB, based on the available published information.

As animal studies have indicated the potential of an increased risk of convulsions (see Section 1.3.3) with prolonged ceftobiprole therapy (> 4 weeks treatment duration), an initial cohort was enrolled with a maximum treatment duration of 28 days (Cohort 1). After completion of 80 patients (approximately 40 patients per treatment group) who received study medication for 21–28 days, an interim safety assessment was performed by an independent Data and Safety Monitoring Board (DSMB) (see Appendix 7). Based on this analysis, the treatment duration was extended to 42 days (Cohort 2), after discussion with the United States Food and Drug Administration (FDA).

As a consequence of the treatment duration restriction in the initial cohort to a maximum of 28 days, some forms of SAB, such as patients with osteomyelitis or brain abscesses, or right-sided infective endocarditis in patients with additional complications that necessitate more than 28 days of study treatment, were excluded from the initial phase of the study.

1.5.1 Summary of study design

This is a randomized, double-blind, multi-center study to assess the efficacy and safety of ceftobiprole medocaril (500 mg q6h, administered as an intravenous 2-h infusion from study Day 1 to Day 8, and 500 mg q8h from study Day 9 onwards, with renal function-dependent dose adjustment) compared to daptomycin (6 mg/kg, up to 10 mg/kg q24 h with renal function-dependent dose adjustment) in the treatment of complicated bacteremia, including IE caused by *S. aureus*.

In the first part of the study, the maximum duration of study antibacterial treatment was limited to 28 days. Following an interim safety analysis, this treatment duration is extended up to 42 days (i.e., 21–42 days).

1.5.2 Study design rationale

1.5.2.1 Randomization and blinding

A randomized (1:1 ratio), double-blind study with patients, investigators, and clinical staff fully blinded is considered the most robust study design. Randomization minimizes differences between treatment groups at the outset of the study (or distributes these differences at random), and blinding supports the objective assessment of efficacy and safety, and prevents potential biases due to differential treatment or differential assessment of outcomes when the treatment allocation is known by investigators.

A blinded study also minimizes potential issues with the post-randomization ascertainment of different types of complicated SAB. The determination of a final diagnosis of underlying conditions or complications of SAB frequently takes several days, during which patients are already on active antibacterial treatment. Allowance of a post-randomization ascertainment window takes this clinical reality into account, and permits enrollment of patients whose diagnostic work-up is ongoing at the time of randomization, which represent a large proportion of patients with complicated SAB. In a blinded study, this post-randomization ascertainment window is not affected by potential biases that could be introduced when investigators are unblinded and may make subjective determinations post-randomization as to which patients have confirmed SAB, and are thereby to be included in the primary analysis population.

Selected pharmacy staff will be unblinded to treatment allocation, as the conduct of the study would otherwise not be feasible. However, implementation of, and strict adherence to, site-specific blinding plans has been shown to be effective in maintaining the blind of the investigator and clinical staff in other recent Phase 3 antibacterial studies, e.g., in ABSSSI.

1.5.2.2 Randomization stratification factors

Randomization stratification factors in this study are study site, dialysis status, and prior antibacterial treatment use (i.e., use of any systemic antibacterial treatment potentially effective against *S. aureus* within 7 days of randomization). In the analysis, study sites will be pooled according to geographic region, and the primary analysis will be adjusted by geographic region, hemodialysis status, and prior antibacterial treatment use. The rationales for these factors are respectively to balance the treatment arms with respect to regional standards of medical care; to allow for the fact that hemodialysis patients may be considered a specific patient group with underlying chronic diseases, with prognoses which may differ from non-hemodialysis SAB patients, and with a presumed high prevalence of catheter- or shunt-related SAB; and to account for the potential confounding effect of prior antibacterial treatment on study outcomes. The introduction of additional stratification factors at randomization, e.g., based on different types of SAB or infective endocarditis, would be unreliable, because the final ascertainment of these conditions may not yet be available at the time of randomization.

1.5.2.3 Primary endpoint

The primary endpoint of overall success comprises several components, including survival, absence of endocarditis and SAB-related metastatic infections, resolution of SAB-related symptoms, and microbiological eradication. This is considered to be a clinically meaningful endpoint, similar to that utilized in other Phase 3 studies in SAB (daptomycin NCT00093067 [Fowler 2006], or telavancin NCT02208063).

1.5.2.4 Primary endpoint assessment

A post-therapy assessment time point 70 days after randomization provides insurance that observed favorable treatment effects are durable, and that long-lasting cure from SAB and its complications is achieved. Furthermore, the assessment by an independent blinded Data Review Committee (DRC, see Appendix 4) optimizes uniformity and homogeneity through the application of standardized assessment criteria, and supports the robustness of the primary outcome assessment in a non-inferiority study setting. The independent DRC will review detailed patient profiles, including imaging, microbiological, and laboratory results, of all patients in the ITT population, to verify the baseline condition of SAB, its complications, and the response outcome for the primary endpoint in the modified intent-to-treat (mITT) population, and for the secondary endpoints. The results of the DRC review, rather than the investigator's assessment, will form the basis for an assessment of the non-inferiority of ceftobiprole versus daptomycin.

1.5.2.5 Primary analysis population

The primary analysis population is the mITT population, defined as the subset of patients in the ITT population who receive any amount/dose of study medication, and who have a blood culture positive for *S. aureus* at baseline based on a central microbiology laboratory assessment (or unequivocal evidence of a baseline blood culture positive for *S. aureus* at the local laboratory). The double-blind nature of the study, together with a short time frame (no more than 6 h) between randomization and start of study treatment, is considered sufficient justification for the exclusion of patients from the mITT population who were randomized but did not receive any study treatment.

In this context, the blinding prevents a potential differential bias between treatment groups if investigators could withhold study treatment from randomized patients based on knowledge of the treatment group allocation.

1.5.2.6 Secondary endpoints

Secondary endpoints have been selected based on clinical relevance, and include individual components of the primary endpoint such as all-cause mortality, microbiological eradication, and development of new metastatic lesions, as well as an assessment of the primary endpoint in additional analysis populations.

1.5.2.7 Patient population

The study selection criteria allow the inclusion of a broad spectrum of patients with complicated SAB, including those on hemodialysis, a subgroup which has not been studied in other Phase 3 SAB clinical studies.

While the inclusion of a broad spectrum of patients improves the external validity of the study and its applicability to clinical practice, it also increases the heterogeneity of the study population. To limit this heterogeneity, the study has been designed to focus on patients with complicated SAB, and to exclude patients from enrollment who present with uncomplicated forms of SAB, e.g., by excluding catheter-related infections in non-hemodialysis patients or in patients without local or metastatic complications or infective endocarditis, or by excluding patients with negative follow-up blood cultures who have no signs of metastatic complications or IE. In addition, randomization is stratified by dialysis status, as patients on hemodialysis are considered a distinct group who may often present with catheter- or shunt-related complications rather than metastatic complications or IE.

An attempt to balance subgroups of various types of complicated SAB by introducing additional randomization strata would be problematic, because a final ascertainment of the type of complicated SAB may not be available at the time of randomization, especially in patients with endocarditis or osteoarticular infections.

In the pivotal Phase 3 study with daptomycin, the overall success rates were comparable for different types of complicated SAB, except for patients with left-sided endocarditis, whose success rates were very low (Table 2).

Table 2 Comparison of overall success rates with daptomycin vs standard-of-care comparators in subgroups of complicated SAB

	Overall success at PTE			
Group (mITT)	Daptomycin % (n/N)	Comparator % (n/N)	Pooled groups % (n/N)	Reference
Complicated SAB excluding endocarditis	43% (26/60)	38% (23/61)	40% (49/121)	Fowler 2006
Complicated SAB or right-sided endocarditis	43% (34/79)	39% (30/77)	41% (64/156)	Fowler 2006
Right-sided endocarditis	42% (8/19)	44% (7/16)	43% (15/35)	Fowler 2006 Kanafani 2010
Left-sided endocarditis	11% (1/9)	22% (2/9)	17% (3/18)	Fowler 2006
Osteoarticular infections	67% (14/21)	55% (6/11)	63% (20/32)	Lalani 2008
Uncomplicated SAB	56% (18/32)	55% (16/29)	56% (34/61)	Fowler 2006

SAB=*Staphylococcus aureus* bacteremia; PTE=Post-treatment evaluation; mITT=modified intent-to-treat.

Patients with left-sided endocarditis are therefore excluded from the study. Many of these patients are candidates for surgery, and those who are not represent a very unfavourable prognostic subgroup.

1.5.2.8 Prior and concomitant antibacterial treatments

As prior and concomitant antibacterial treatments that provide activity against *S. aureus* may confound the study outcomes, the permitted duration of prior antibacterial treatment has been restricted to 48 h or less within the 7 days prior to randomization.

With some exceptions (see Section 5.5.3), the use of concomitant antibacterial treatments is prohibited from the start of study medication up to the PTE visit. If it occurs, its significance is to be assessed by the blinded DRC in accordance with guidelines provided in Appendix 6, to determine whether the treatment had an impact on the primary endpoint.

1.5.2.9 Active comparator and non-inferiority margin

A non-inferiority study versus an active comparator design has been chosen due to the severe and often life-threatening nature of complicated SAB, for which a placebo-controlled study would be unethical. Daptomycin is considered the most efficacious comparator, with potent activity against both MSSA and MRSA; it is approved for the treatment of SAB, including right-sided infective endocarditis (RIE), in the US and many countries worldwide, which allows the conduct of a global study in the treatment of SAB.

The use of vancomycin as a comparator would not be clinically acceptable for a substantial proportion of study investigators, due to concerns about its weaker bactericidal activity against MSSA. This is not a concern with daptomycin, which has shown similar clinical

efficacy in a Phase 3 study to standard-of-care semi-synthetic penicillins (nafcillin, oxacillin) in patients with MSSA bacteremia (44.6% vs 46.7% overall success rate for daptomycin and semi-synthetic penicillins, respectively) (Fowler 2006). Daptomycin has also shown similar *in vitro* activity against MSSA to cloxacillin and nafcillin (Cantoni 1990, Huang 2008, LaPlante 2004).

The use of multiple comparators, or a switch between different antibacterial treatments in the control group, would preclude the conduct of a blinded study for practical reasons.

The justification for the non-inferiority margin is described in Appendix 8.

1.5.3 Dosing rationale for ceftobiprole and daptomycin

The recommended ceftobiprole dosing regimen for licensed indications is 500 mg, administered as a 2-h intravenous infusion every 8 h. The ceftobiprole dosing regimen for this study aims to achieve rapid, early killing of *S. aureus* and to optimize the ability to achieve effective bloodstream clearance in the initial treatment period. The median time to *S. aureus* bloodstream clearance, as reported in the Phase 3 study with daptomycin (Fowler 2006), is 8 to 9 days. Therefore, for the first 8 days of study treatment ceftobiprole 500 mg will be administered as 2-h infusions every 6 h instead of every 8 h. This will achieve a sustained coverage for *S. aureus* well above the ceftobiprole MIC_{90} of 2 mg/L for MRSA (Farrell 2014). Based on the need for prolonged therapy with an acceptable number of infusions per day as well as adequate coverage, from Day 9 onwards the frequency of 2-h infusions will be reduced to the standard q8h.

Daptomycin will be used in this protocol as the active control comparator antibacterial agent. Adjustments of the recommended dose of 6 mg/kg to higher doses (up to 10 mg/kg) may be implemented, according to institutional standards, to reflect the clinical-practice situation (see Section 3.1).

The duration of study treatment is up to 42 days. Within this time frame, the study investigator will determine the study treatment duration for each patient.

The minimum target treatment duration in this study is 21 days. Some guideline recommendations permit shorter durations (e.g., 14 days treatment from the first negative blood-culture) for conditions such as uncomplicated SAB or uncomplicated right-sided endocarditis caused by *S. aureus* (characterized by the absence of renal failure, extrapulmonary metastatic infections, aortic or mitral valve involvement, meningitis, or infection by MRSA); however an extended treatment duration of at least 21 days appears justified in view of the degree of uncertainty both in the literature and among practising clinicians, of whether SAB is truly uncomplicated. In this context it is important to note that recent studies have suggested that among patients identified with SAB, the majority of patients present with complicated SAB (Kaasch 2014, Incani 2013).

1.6 Benefit–risk assessment

SAB is a leading cause of bloodstream infections and is associated with significant morbidity and mortality. Currently there are only a limited number of antibiotics available for the treatment of SAB, and the resistance to these antibiotics is increasing. Therefore, there is a need to augment the existing choice of antibacterial treatment options against SAB.

Both study drugs, ceftobiprole and daptomycin, have bactericidal activity against MSSA and MRSA, and are expected to have a beneficial therapeutic impact for participating patients. Daptomycin is already approved for the treatment of SAB, including RIE, in many countries worldwide. The current study may help to develop further understanding of SAB, and may potentially result in the addition of a new treatment (ceftobiprole) for patients with SAB.

All study drugs are marketed in many countries globally. There are relatively large safety databases for both ceftobiprole and daptomycin based on previous randomized clinical studies and on post-marketing real-world experience. Both antibiotics have generally been shown to be well tolerated and to have a good safety profile. The safety risks of the investigational drug, ceftobiprole, are consistent with the cephalosporin class of antibiotics that have been used in clinical practice for decades. Current experience with ceftobiprole is described in more detail in Sections 1.2 through 1.4, including the most common adverse reactions associated with its use. Moreover, it is not anticipated that either ceftobiprole or daptomycin will interfere with other treatments the patients may receive while enrolled in this study. Patients in the study will undergo tests and procedures that represent clinical standard-of-care for the diagnosis and management of complicated SAB.

The study sites are experienced in the management of SAB and in the conduct of clinical studies. They have available procedures to provide the best possible care for the study patients, including the ability to manage possible side effects. All patients are closely monitored during the entire treatment duration and thereafter. The protocol eligibility criteria have been selected to exclude patients who may not benefit from the study drugs, are unstable, or may be at an increased risk of adverse effects from the study drugs.

Considering the potential utility of ceftobiprole as a novel broad-spectrum antibacterial treatment, the expected benefits of the current study outweigh potential risks.

2 OBJECTIVES OF THE STUDY

2.1 Primary objective

To demonstrate the non-inferiority of ceftobiprole to daptomycin for overall success as assessed by an independent DRC in the treatment of *S. aureus* bacteremia, including infective endocarditis, at the post-treatment evaluation (PTE) visit* in the modified intent-to-treat (mITT) population.

2.2 Secondary objectives

- To compare ceftobiprole with daptomycin with respect to:
  1. All-cause mortality through Day 70 (PTE visit) and Day 28 in the ITT and mITT populations.
  2. Microbiological eradication rates (negative blood culture for *S. aureus*) at Day 4, Day 8, and the end-of-treatment (EOT) and PTE visits.
  3. Overall success rates in the mITT, ITT, and clinically evaluable (CE) populations:
     a) at the EOT and PTE visits (ITT and CE populations only)
     b) at the EOT and PTE visits, for IE vs non-IE SAB
     c) at the EOT and PTE visits, by renal-function status
  4. Development of new metastatic foci, or other complications of SAB, after Day 7.
  5. Time-to-first-blood-culture-negative for *S. aureus*, confirmed by a second blood-culture-negative for *S. aureus*, obtained at least 24 h after the first negative blood-culture.
  6. Safety and tolerability (Safety population).
- To assess the pharmacokinetics (PK) of ceftobiprole.

* The PTE visit will be performed 70 days (± 5 days) after randomization.

3 STUDY DESIGN

3.1 Overview of study design and dosing regimen

This is a randomized, double-blind, double-dummy, active-controlled, parallel-group, multi-center study in adult hospitalized* patients with SAB, including IE, conducted in two parts.

In Part 1 of the study (Cohort 1), the administration of the study drug was restricted to 28 days. Exceptional cases of patients in Cohort 1 who turned out to require more than 28 days of treatment were discontinued from the study, with treatment allocation remaining blinded. These patients were switched to open-label non-study treatment according to institutional practice, and considered failures in the mITT and ITT analyses irrespective of treatment groups.

Part 2 (Cohort 2): Following a protocol pre-defined DSMB interim safety assessment after treatment of 80 patients (approximately 40 patients per treatment group) who received study medication for 21–28 days, a decision was made to extend the maximum treatment period to 42 days, and the protocol was amended accordingly.

The decision rules for the DSMB interim safety assessment of Cohort 1 are provided in Appendix 7.

The study comprises three phases (see Table 3):

1. Screening assessments of up to 72 h prior to randomization (with the possibility of utilizing existing echocardiography assessments [TTE or TEE] that demonstrated definitive RIE within 10 days of randomization) (see Section 5.2.2).
2. Randomization and subsequent active-treatment with intravenous study drug (ceftobiprole or daptomycin).
3. Post-treatment, comprising an EOT visit (within 72 h of last study-drug administration), Day 35 (±3 days), Day 42 (±3 days), and a PTE visit on Day 70 (±5 days) post-randomization.

* In a hospital or equivalent medical confinement or clinical research unit.

Table 3 Summary of treatment and follow-up schedule

Study phase			
1	2	3	
Pre-treatment	Active-treatment	Post-treatment	
Screening assessments	Randomization and study-drug treatment	End-of-treatment visit (EOT)	Post-treatment evaluation visit (PTE)
Up to 72 h prior to randomization	Day 1 up to Day 42	Within the 72 h after the last treatment administration	Day 70 (±5 days) post-randomization

3.1.1 After randomization and during active treatment, patients will receive ceftobiprole medocaril powder for solution for infusion (administered as 2-h intravenous infusion) according to the schedule outlined in Table 4Duration of treatment

The target treatment duration is 21 to 42 days of study drug, with the treatment duration within this window to be defined by the study investigator.

Exceptional cases of patients who turn out to require more than 42 days of treatment will be discontinued from the study, with treatment allocation remaining blinded. These patients are to be switched to open-label non-study treatment according to institutional practice, and considered failures in the mITT and ITT analyses irrespective of treatment groups.

Ceftobiprole medocaril powder for solution for infusion will be administered as a 2-h intravenous infusion according to the schedule in Table 4.

Table 4, or daptomycin lyophilized powder for solution for infusion (administered as 0.5-h intravenous infusion) according to the schedule outlined in Table 5.

Study assessments are shown in Table 6 and outlined in more detail in Section 5.

3.2 Endpoints

3.2.1 Primary endpoint

The primary endpoint is overall success at the PTE visit (Day 70±5 days post-randomization) in the mITT analysis set, as assessed by the DRC. The DRC will be a group of independent clinical experts, blinded to treatment allocation and not associated with the study conduct, who will review patient profiles, including signs and symptoms of infection, and relevant microbiological and imaging findings, and will assess the patients' clinical and microbiological outcomes (see Appendix 4).

The primary endpoint will be tested for the non-inferiority of ceftobiprole versus daptomycin using a non-inferiority margin of 15%.

Overall success is defined as all of the following criteria being met:

1. Patient alive at Day 70 (±5 days) post-randomization.

2. No new metastatic foci or complications of the SAB infection.
3. Resolution or improvement of SAB-related clinical signs and symptoms.
4. Two negative blood cultures for *S. aureus* (without any subsequent positive blood culture for *S. aureus*):
   - at least one while the patient is on active study treatment; AND
   - confirmed by at least one subsequent negative blood culture for *S. aureus*
     - either in the period between 7 days after the EOT visit and the PTE visit
     - or at the PTE visit

Treatment failure is defined as any of the following:

1. Premature discontinuation of study treatment due to DRC-assessed lack of efficacy (as assessed by the DRC) or for adverse events (AEs) that represent manifestation of disease progression or relapse, at any time between first dose of study drug and the PTE visit.
2. Development of new metastatic or other complications related to SAB (see Section 5.4.5.3.2) between Day 8 and the PTE visit. Development of new metastatic or other complications of SAB prior to Day 8 will be assessed by the DRC on a case-by-case basis to assess whether these constitute a delayed manifestation of the baseline disease or new complications.
3. SAB relapse or reinfection based on evidence from a blood culture positive for *S. aureus* (after documented clearance of *S. aureus* from the bloodstream and clinical improvement) between the EOT and PTE visits.
4. Receipt of systemic non-study antibacterial treatment, other than those permitted under the protocol, for the treatment of SAB. This includes patients who are prematurely discontinued from study therapy due to an AE, but who require continuation of antibacterial treatment for SAB.
5. Treatment of infections other than SAB with systemic non-study antibacterial treatment which is potentially effective against *S. aureus* (see Appendix 5), and which is considered by the DRC to have a relevant impact on the primary endpoint in accordance with the guidelines provided in Appendix 6.
6. Death for any reason between first administration of study drug and the PTE visit.
7. Indeterminate outcome, defined as any data needed to determine whether the outcome is success or failure missing at the PTE visit, including but not limited to:
   a) missing PTE visit, or missing key data to evaluate the primary endpoint
   b) lost-to-follow-up, or patients who withdrew consent prior to the PTE visit
   c) patients not meeting the criteria for Success or Failure, or patients not meeting all criteria for overall success
8. Requirement for systemic antibacterial treatment for SAB beyond EOT.

3.2.2 Secondary endpoints

1. All-cause mortality (mITT population) at Day 70 (PTE visit)

All-cause mortality will also be assessed at Day 28, and in the ITT population, and will be assessed descriptively.

2. Microbiological eradication (mITT population) at Day 70 (PTE visit)

Microbiological eradication will also be assessed in the CE population, and at Day 4, Day 8, and the EOT visit, and will be assessed descriptively.

Eradication: No growth of the baseline pathogen(s), secondary to an adequate clinical response, based on a negative blood culture while the patient is on active study treatment which is confirmed by at least one subsequent negative blood culture for *S. aureus*, either in the period between 7 days after EOT and the PTE visit, or at the PTE visit.

Failure: Persistence, relapse, or reinfection of *S. aureus* infection, defined as one or more of:

- Ongoing positive blood cultures leading to discontinuation of the study drug
- Subsequent isolation of *S. aureus* from a blood culture after clearance of bacteremia and clinical improvement
  - Relapse: bloodstream infection with the same pathogen isolated at baseline based on genotyping
  - Reinfection: bloodstream infection with a different *S. aureus* strain to that isolated at baseline based on genotyping
- Absence of at least two negative blood cultures (at least one negative blood culture on active study treatment, and at least one post-treatment) to confirm eradication

Relapse or reinfection between EOT and PTE that is reported to the investigator from a healthcare provider not involved in the study (e.g., from another hospital), needs to be thoroughly documented and will be reviewed by the investigator and the DRC for determination.

3. Overall success rate at PTE (CE population)

The overall success rate will also be assessed at the EOT visit in the mITT, ITT and CE populations, and in the ITT population at the PTE visit, and will be assessed descriptively.

See definitions for the primary endpoint above.

4. Development of new metastatic foci or other complications of SAB after Day 7 (mITT population)

Development of new metastatic foci or other complications of SAB after Day 7 will also be assessed in the CE population, and will be assessed descriptively.

Timepoints: Day 8–EOT, and PTE

Newly diagnosed IE or complicated SAB with metastatic foci or other complications of *S. aureus* infection, including metastatic foci in the vertebral column (vertebral abscess, osteomyelitis, discitis or epidural abscess), cerebral abscess/infarction, splenic abscess/infarction, renal abscess/infarction, psoas abscess or other deep-tissue abscess, other metastatic infection of native tissue, septic arthritis (or bacterial joint infection/empyema), septic or suppurative thrombophlebitis, and septic pulmonary emboli/infarction.

5. Time to S. aureus bloodstream clearance (mITT and CE populations)

Timepoints: Day 3–EOT

Time-to-first-blood-culture-negative for *S. aureus*, confirmed by a second blood-culture-negative for *S. aureus* obtained at least 24 h after the first negative blood-culture.

6. Safety/Tolerability (Safety population)

Timepoints: First dose of study drug–PTE

Incidence, type, severity, and relationship to study medication of AEs; and changes in laboratory tests (hematology, biochemistry including haptoglobin, urinalysis, and Coombs-test).

7. Pharmacokinetics of ceftobiprole (PK population)

Plasma levels of ceftobiprole and the β-lactam ring open product BAL1029

<u>Sparse PK sampling (all patients)</u>

- Day 3: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 4 to 6 h
- Day 12: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 4 to 6 h

<u>Rich PK sampling (selected sites, N=40 ceftobiprole-treated patients [i.e., approximately 80 patients overall])</u>

- Day 3: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 3 h, 4 h, 6 h
- Day 12: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 4 to 6 h

Plasma-concentration data will be analyzed at each time point and will be presented as individual concentrations with descriptive statistics (mean, SD, CV%, min, median, max).

3.3 Treatment plan

3.3.1 Duration of treatment

The target treatment duration is 21 to 42 days of study drug, with the treatment duration within this window to be defined by the study investigator.

Exceptional cases of patients who turn out to require more than 42 days of treatment will be discontinued from the study, with treatment allocation remaining blinded. These patients are to be switched to open-label non-study treatment according to institutional practice, and considered failures in the mITT and ITT analyses irrespective of treatment groups.

Ceftobiprole medocaril powder for solution for infusion will be administered as a 2-h intravenous infusion according to the schedule in Table 4.

Table 4 Ceftobiprole administration

Study day	Normal renal function to mild renal impairment $CL_{Cr} \geq 50$ mL/min	Renal impairment (non-dialysis)	Intermittent hemodialysis or peritoneal dialysis
Day 1 to Day 8	500 mg q6h	CL_{Cr} 30–< 50 mL/min: 500 mg q8h CL_{Cr} < 30 mL/min: 250 mg q8h	250 mg q24h
Day 9 onwards	500 mg q8h	CL_{Cr} 30–< 50 mL/min: 500 mg q12h CL_{Cr} < 30 mL/min: 250 mg q12h	250 mg q24h

CL_{Cr}=Creatinine clearance based on the Cockcroft-Gault formula.

Daptomycin lyophilized powder for solution for infusion will be administered as a 0.5-h intravenous infusion according to the schedule in Table 5.

Table 5 Daptomycin administration

	Normal renal function to moderate renal impairment	Renal impairment (non-dialysis)	Intermittent hemodialysis or peritoneal dialysis
Daptomycin (0.5-h infusion)	$CL_{Cr} \geq 30$ mL/min 6 mg/kg q24h	$CL_{Cr} < 30$ mL/min 6 mg/kg q48h	6 mg/kg q48h

CL_{Cr}=Creatinine clearance based on the Cockcroft-Gault formula.

In accordance with institutional standards, an increase in the dose of daptomycin administered (up to 10 mg/kg) may be implemented.

To maintain the blinding of study treatments, patients in the ceftobiprole group will receive dummy infusions with placebo (physiological saline, 0.9% NaCl) matching daptomycin, and patients in the daptomycin group will receive dummy infusions with placebo (physiological saline, 0.9% NaCl) matching ceftobiprole.

No switches to other systemic antibacterial treatments are permitted for any of the study drugs prior to the PTE visit. There is no intravenous-to-oral switch for any of the treatments in this study.

Details of treatment with active study drug and dummies, and dose adjustment of study drugs according to renal function, are provided in Section 6.4.

3.3.2 Missed-dose management

Doses are to be administered in accordance with the schedules in Table 4 and Table 5. If one or more doses are missed for administrative reasons, the investigator may consider discontinuing the patient from the study after discussion with the sponsor's medical monitor.

3.3.3 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 q8h). If an overdose occurs, it should be treated symptomatically. Ceftobiprole plasma concentrations can be reduced by hemodialysis. In a study in which six subjects with ESRD on hemodialysis received a single 250 mg dose of ceftobiprole by intravenous infusion, ceftobiprole was demonstrated to be hemodialysable, with an extraction ratio of 0.7.

Daptomycin: In the event of overdosage, supportive care is advised with maintenance of glomerular filtration. Daptomycin is cleared slowly from the body by hemodialysis (approximately 15% of the administered dose is removed over 4 h) and by peritoneal dialysis (approximately 11% of the administered dose is removed over 48 h). The use of high-flux dialysis membranes during 4 h of hemodialysis may increase the percentage of dose removed compared with that removed by low-flux membranes.

3.4 Definition of End of Study

The End of 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).

4 STUDY POPULATION

4.1 Target population

Adult male or female patients with SAB, including IE, meeting all of inclusion criteria 1–5, at least one of inclusion criteria 6–11, and none of the exclusion criteria, are eligible for enrollment in this study.

4.2 Inclusion criteria

Patients meeting all of inclusion criteria 1–5 and at least one of inclusion criteria 6–11 will be eligible for enrollment.

1. Male or female ≥ 18 years of age.

2. Informed consent signed by the patient (or by their legally acceptable representative, if appropriate) indicating that they understand the purpose of, and procedures required for, the study and are willing to participate in the study.
3. SAB, based on at least one positive blood culture obtained within the 72 h prior to randomization:
   (a) identified by culture laboratory report, or
   (b) positive diagnostic test for *S. aureus* (e.g., polymerase chain reaction [PCR], tube coagulase test and fluorescent *in situ* hybridization [FISH]) obtained from a blood culture.

   Note: The microbiological work-up of the blood culture may:
   - Occur prior to informed consent to participation in the study (see Section 5.2.1 and Table 7).
   - Be undertaken either on-site or in an external microbiology laboratory specifically appointed for the purposes of this study.
   - Use a diagnostic test:
     – routinely performed locally for the detection of *S. aureus* from blood cultures or
     – provided to the laboratory for the purpose of this study, if the test has regulatory approval in the country where the test is being performed

   Regardless of diagnostic method, every effort should be made to isolate and send all unique organisms from blood to the Central Microbiology Laboratory; this applies particularly to the *S. aureus* isolated from blood at the Screening visit. The Central Microbiology Laboratory will re-identify all isolates, with the results to be used to determine whether the patient meets the study inclusion criteria.

   Nevertheless, patients without a Central Microbiology Laboratory assessment may be included in the mITT population if there is unequivocal documented evidence of a baseline blood culture positive for *S. aureus* at the local laboratory.
4. At least one of the following signs or symptoms of bacteremia within the 72 h prior to randomization (may be based on measurements obtained before or after informed consent but within the 72 h prior to randomization):
   (a) fever > 38 °C / 100.4 °F measured orally, > 38.5 °C / 101.3 °F measured tympanically, > 37.5 °C / 99.5 °F measured by axillary method, or > 39 °C / 102.2 °F measured rectally
   (b) white blood cell (WBC) count > 10.0×10^9/L or < 4.0×10^9/L, or > 10% immature neutrophils (bands)
   (c) tachycardia (heart rate > 90 bpm)
   (d) hypotension (systolic blood pressure < 90 mmHg)
5. Required duration of study antibacterial treatment ≤ 42 days.
6. SAB in patients undergoing chronic intermittent hemodialysis or peritoneal dialysis.

7. Persistent SAB: documented failure of bloodstream clearance, defined as a positive blood culture for *S. aureus* within the 72 h prior to randomization, after prior appropriate anti-staphylococcal treatment (except failure under daptomycin therapy) of at least 3 complete days.
8. Other forms of complicated SAB, including the following:
   (a) ABSSSIs
   (b) Metastatic infection of native tissue. Examples include but are not limited to:
   - Septic arthritis or bacterial joint infection/empyema
   - Septic or suppurative thrombophlebitis
   - Visceral soft-tissue abscesses requiring ≤ 42 days of study antibacterial treatment
   - Septic pulmonary emboli/infarction

     Note: The diagnosis of a septic pulmonary embolism will be made by the investigator based on clinical symptoms of fever, cough, sputum/hemoptysis in the presence of an extrapulmonary infection, sepsis, or risk factors for septic emboli (e.g., intravenous drug use) and will be based on the following radiological signs:

     Contrast-enhanced CT (preferred):
     Peripheral and/or subpleural multifocal nodular lesions (in different stages of cavitation) or wedge-shaped infiltrates
     – with/without a feeding vessel sign (vessel leading to the nodule)
     – with/without pleural effusion or features suggestive of pleural empyema

     Non-contrast enhanced CT (e.g., in patients with a contraindication for contrast administration):
     Peripheral and/or subpleural multifocal nodular lesions (in different stages of cavitation) or wedge-shaped infiltrates
     – with/without pleural effusion or features suggestive of pleural empyema

     Plain X-ray (e.g., in patients unable to undergo a CT):
     Multifocal nodular densities or wedge-shaped infiltrates in varying stages of cavitation with or without pleural effusion or features suggestive of pleural empyema

9. Definite native-valve right-sided IE (RIE) by Modified Duke's Criteria (see Appendix 1).

   Note: Patients with left-sided infective endocarditis (LIE) are excluded from the study. If LIE is diagnosed after onset of study therapy, patients may be maintained in the study. In the event that the investigator decides to discontinue the study therapy, the patient will be included in the mITT population and considered a failure (see Section 4.7).

   The minimum requirements for a diagnosis of RIE and LIE (Modified Duke's Criteria) are provided in Appendix 1. The minimum requirements for baseline diagnosis of other forms of complicated SAB are provided in Appendix 2.

10. Osteomyelitis (including vertebral, sternal, or long-bone osteomyelitis).
11. Epidural or cerebral abscess.

Inclusion criteria 1–7 must be ascertained based on assessments within the 72-h screening window. For inclusion criteria 8–11, assessments performed up to 7 days after randomization may be used to confirm the diagnosis of complicated SAB.

Patients randomized with suspected complicated SAB who turn out not to meet at least one of inclusion criteria 6–11 (i.e., who do not have confirmed complicated SAB), will be considered to have uncomplicated bacteremia. These patients will continue in the study, with a target treatment duration of 21 days. The maximum treatment duration in this study is 42 days.

4.3 Exclusion criteria

Patients meeting any of the following exclusion criteria at Screening will be excluded from the study:

1. Treatment with potentially effective (anti-staphylococcal) systemic antibacterial treatment (see Appendix 5) for more than 48 h within the 7 days prior to randomization.
   Exception: Documented failure of bloodstream clearance with prior antistaphylococcal treatment (except failure under daptomycin therapy) administered for at least 3 complete days.
2. Bloodstream or non-bloodstream concomitant infections with Gram-negative bacteria that are known (at Screening) to be non-susceptible to either ceftobiprole or aztreonam.
3. Confirmed uncomplicated SAB (e.g., catheter-related non-persistent SAB without signs of SAB complications, unless the patient has end-stage renal disease and is on intermittent hemodialysis or peritoneal dialysis).
4. Left sided infective endocarditis.
   Note: If LIE is diagnosed after onset of study therapy, patients may be maintained in the study. In the event that the investigator decides to discontinue the study therapy, the patient will be included in the mITT population and considered a failure.
5. Prosthetic cardiac valves or valve support rings, cardiac pacemakers, automatic implantable cardioverter-defibrillator, or left-ventricular assist devices.
6. Complicated SAB in patients with other foreign body material that cannot be removed within the 7 days after randomization.
   Exceptions:
   - Patients with non-infected coronary stents may be included regardless of the time of stent implantation.
   - Patients with non-infected (no signs or symptoms of clinical involvement at the time of randomization) prosthetic joints, plates, spinal hardware, or other extravascular material may be included if implantation of the foreign material was performed at least 60 days before randomization.

- Patients with non-infected (no signs or symptoms of clinical involvement at the time of randomization) intravascular prosthetic material or vena cava filters may be included if implantation of the foreign material was performed at least 90 days before randomization.

7. Cardiac native-valve surgery planned within 3 days after randomization.
8. Community- or hospital-acquired pneumonia.
   Note: The diagnosis of pneumonia will be made by the investigator based on respiratory complaints (e.g., cough, dyspnea, purulent secretions, and chest pain) and new or worsening infiltrates suggestive of bacterial pneumonia on a chest radiograph or a high-resolution CT. Equivocal findings on a chest radiograph should be further assessed by the conduct of a high-resolution chest CT (if feasible) and/or the conduct of lung ultrasound to support the presence or absence of a diagnosis of pneumonia.
9. High probability of death within 7 days due to the underlying SAB or SAB-associated disease, or high probability of death within 28 days from an unrelated underlying disease.
10. Clinically-relevant hypersensitivity to β-lactam antibacterials or daptomycin.
11. Known infection due to *Staphylococcus aureus* that exhibits reduced susceptibility to daptomycin (minimum inhibitory concentration [MIC] > 1 mg/L), or ceftobiprole (MIC > 2 mg/L).
12. Absolute neutrophil count $< 0.5 \times 10^9$/L.
13. Either: a) a history of opportunistic infections (e.g., invasive fungal infections or cytomegalovirus [CMV]) within 30 days prior to randomization, where the underlying cause of these infections is still active (e.g., leukemia, transplant, acquired immunodeficiency syndrome [AIDS]); or b) CD4 count < 100 cells/mm^3 in patients with AIDS; or c) patients treated with cotrimoxazole as prophylaxis for pneumocystis pneumonia.
14. Requirement or expected requirement between randomization and the PTE visit for potentially effective (anti-staphylococcal) systemic antibacterial treatment that is unrelated to the treatment of SAB, e.g., in the context of planned surgery, gynecological or other procedures requiring antibacterial prophylaxis or other anticipated uses of antibacterials such as treatment for acne vulgaris.
15. Requirement for continuous renal-replacement therapy at the time of randomization, or high likelihood of requirement for continuous renal-replacement therapy during the study period.
    Note: Patients undergoing chronic intermittent hemodialysis or peritoneal dialysis are permitted to participate in the study.
16. Alanine transaminase (ALT) or aspartate transaminase (AST) levels ≥ 8 × the upper limit of normal, or severe hepatic disease with Child-Pugh class C.
17. Women who are pregnant or nursing.

18. 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.

19. Use of an investigational drug in a Phase 1 study within the 30 days prior to the start of study treatment.

    Note: Use of investigational drugs in Phase 2 or Phase 3 studies within the 30 days prior to the start of study drug treatment is allowed.

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

Reasons for discontinuation of treatment must be recorded and may include:

- AE
- abnormal laboratory value
- abnormal test procedure result
- intercurrent illness that prevents further administration of treatment
- protocol violation
- protocol non-compliance
- lost to follow-up
- administrative/logistical reasons
- need for the use of systemic non-study antibacterials to treat complicated SAB (e.g., due to lack of efficacy)
- confirmation of reduced susceptibility of *S. aureus* to either ceftobiprole or daptomycin, when a susceptibility test result is received after start of study treatment
- pregnancy
- death
- diagnosis with a condition that requires more than 42 days of antibacterial treatment for SAB (including left-sided endocarditis)

All ITT patients should be followed until complete capture of main study outcomes, including those who did not receive study treatment or had no confirmed SAB by a *S. aureus* blood culture using a standard diagnostic test, or who discontinue the study prematurely.

For all patients who discontinue the study, AE monitoring must be continued until the PTE visit at Day 70 (±5 days) after randomization (see Section 7.3.2).

If a patient who has been randomized, 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 as a result of participation up to that point, and to have the patient complete the EOT and PTE visits.

The investigator must make every effort to contact (by telephone or mail correspondence) patients who fail to return for the EOT or PTE visits. The outcome of this contact must be documented by the investigator and filed in the Investigator Site File (ISF), and the reasons for the failure to attend the visit must be recorded in the case report form (CRF).

4.6 Replacement of patients

Patients failing screening procedures are to be replaced.

Patients who for any reason discontinue participation in the study after randomization but prior to receiving the first dose of study drug, are to be replaced.

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

4.7 Patients with left-sided infective endocarditis

Patients with LIE are excluded from the study.

In Part 1 of the study (Cohort 1), if LIE was diagnosed after the commencement of study therapy, the patient must have been discontinued from the study and switched to open-label non-study standard-of-care antibacterial treatment. These patients are included in the mITT population and considered failures.

In Part 2 of the study (Cohort 2), if LIE is diagnosed after the commencement of study therapy, the patient may be maintained in the study. In the event that the investigator decides to discontinue study therapy, the patient will be included in the mITT population and considered a failure.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Summary of schedule of assessments

Table 6 presents a summary of the schedule of assessments.

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.

Table 6 Schedule of Assessments

	Baseline/ Screening	Active treatment					Post-treatment		
Time	≤ 72 h prior to randomization	Day 1	Day 2	Day 3	Days 4–12	Days 14, 21, 28, 35, 42*	EOT	Days 35 (±3), 42 (±3)*	PTE (Day 70±5 days post-randomization)
Study procedures									
Informed consent[1]	X								
Inclusion/exclusion criteria[2]	X								
Medical history/demographics/prior and ongoing therapy[3]	X								
Documentation of surgical procedures anticipated during the course of the study and planned at baseline	X								
Complete physical examination[4]	X								
Brief physical examination[4]			X	X	X	X	X	X	X
Vital signs[5]	X	X	X	X	X	X	X	X	X
Body temperature[6]	X	X	X	X	X	X	X	X	X
Transthoracic echocardiography[7]	<----------X----------> Day 7								
Transesophageal echocardiography[7]	<----------X----------> Day 7								
12-lead electrocardiogram[8]	X						X		
Pregnancy test[9]	X						X		X
Safety laboratory (local lab)[10]	X								
Safety laboratory (central lab)[10]	X			X	Day 7	X	X	X	X
Reticulocytes, haptoglobin and Coombs test (central lab)[11]	X						X		X
WBC count, CRP and procalcitonin (central lab)[12]	X		X	X	Day 7	Day 14	X		
Blood culture[13, 14]	X	X	X	X	<----------X[13]---------->				
Investigator-assessed clinical signs and symptoms of SAB[15]	X		X	X	X	X	X	X	X
Assessment of deep-seated infections and metastatic or other complications of SAB[16]	X		<----------> Day 7			X	X	X	X
Modified Duke's Criteria[17]	X		X	X	X	X	X	X	X
Randomization[18]		X							
PK blood-sample collection[19]				X	Day 12				
Study drug administration[20]		X	X	X	X	To Day 42			
Drug accountability[21]		X	X	X	X	To Day 42			
Investigator assessment of overall success[22]				X	X	X	X	X	X
Concomitant antimicrobial and other therapies[23]		X	X	X	X	X	X	X	X
Concomitant non-drug procedures[23]		X	X	X	X	X	X	X	X
Creatinine clearance[24]	X		X	X	Day 5, 7	X			
Adverse events[25]		X	X	X	X	X	X	X	X
Health economics outcome measures[26]									X

* Note: Day 35 and Day 42 may be active treatment visits for patients in Cohort 2, if treatment for longer than 28 days is required. Day 35 and Day 42 are post-treatment visits for all patients in Cohort 1, and for patients in Cohort 2 who are treated for longer than 28 days, but have not completed treatment by the Day 35 or Day 42 visits.

1. Written Informed Consent (IC) must be obtained within the 72 h prior to randomization (Section 5.4.1). No study-specific assessments will be performed prior to IC; however, blood cultures, transthoracic echocardiography (TTE), or transesophageal echocardiography (TEE) procedures performed in the context of routine clinical diagnostic practice prior to IC may be used for the study if they were conducted within the 72 h prior to randomization (or up to 10 days prior to randomization if RIE has been confirmed, see Section 5.4.4.10).
2. Inclusion and exclusion criteria (Sections 4.2 and 4.3) will be assessed at Screening.
3. At Screening the investigator must obtain the patient's medical history, demographics, and prior (within 30 days) antibacterial, other drug, and non-drug therapies (Section 5.4.2)
4. Complete physical examination (Section 5.4.4) will be performed at Screening. Thereafter, a brief physical examination (Section 5.4.4) focusing on changes from baseline will be performed at each scheduled study visit from Day 2, up to the PTE visit.
5. Vital signs (Section 5.4.4.2) will be taken once during each scheduled study visit. Baseline vital signs will be obtained at Screening. The patient's weight is to be assessed at Screening, and at a minimum on study Days 2, 3, 5, 7, 14, 21, if applicable 28/35, at the EOT visit, and at the PTE visit.
6. Body temperature (Section 5.4.4.3) will be measured every ~8 h for the first 96 h after start of treatment, and every 8 h thereafter, until a 24 h period is achieved during which no measurement is greater than 38 °C / 100.4 °F measured orally, 38.5 °C / 101.3 °F measured tympanically, 37.5° C / 99.5 °F measured by axillary method, or 39 °C / 102.2 °F measured rectally. Temperature measurements will then be taken once at each scheduled study visit.
7. TTE or TEE (Section 5.4.4.10) must be performed in accordance with the description in Table 8.
8. A standard 12-lead ECG will be performed at Screening and at the EOT visit (Section 5.4.4.4).
9. Pregnancy testing is to be performed for women of childbearing potential; at Screening a serum pregnancy test is to be obtained; at the EOT and PTE visits 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 5.4.4.5). 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).
10. Central and local safety laboratory tests (Section 5.4.4.6) will be performed at Screening, and additional local laboratory tests may be performed at any time during the study, as clinically indicated. Safety laboratory tests will be performed on Days 3, 7, 14, 21, 28, 35, and 42, at the EOT visit, and at the PTE visit, and analyzed by the central laboratory.
11. Reticulocyte counts, haptoglobin levels and Coombs tests will be measured at Screening, and at the EOT and PTE visits.
12. White blood cell (WBC) counts, C-reactive protein (CRP) levels, and procalcitonin levels will be assessed at Screening, on Days 2, 3, 7, 14, and at the EOT visit.
13. Two sets of peripheral blood cultures (including aerobic and anaerobic) (Section 5.2.1) will be obtained at baseline. Blood cultures will be drawn at least 5 minutes apart, and samples for each of the two sets of blood cultures should be obtained from different anatomical locations. Post-randomization repeat blood cultures (at least one, but preferably two blood cultures), will be obtained on Days 1, 2 and 3. Thereafter blood cultures will be obtained approximately every 48–72 h if clearance of bacteremia has not yet been confirmed, i.e., until negative-*S. aureus* test results are obtained for two blood cultures (or negative test result for one culture if only one culture was obtained) at two time points at least 24 h apart. At least one blood culture must be obtained at the PTE visit, or in the period between 7 days after EOT and the PTE visit. Performance of a Gram-stain from each positive blood culture is recommended but not mandatory.
14. Blood cultures positive for *S. aureus* that were obtained in the context of routine clinical diagnostic work-up prior to obtaining informed consent, but were drawn within the 72 h prior to randomization, may be used for the study to determine patient eligibility, and do not need to be repeated.
15. Clinical assessments of the signs and symptoms of complicated SAB (Section 5.4.5.2) will be made at Screening and at each scheduled study visit from Day 2, up until PTE.
16. Clinical signs of deep-seated infections and metastatic or other complications of SAB (Section 5.4.5.3) will be assessed at Screening and at each scheduled study visit from Day 2, up until the PTE visit. The diagnosis of deep-seated infections, metastatic or other complications of SAB must be supported by imaging studies (including ultrasound, computed tomography [CT], magnetic resonance imaging [MRI], and positron emission tomography/computed tomography [PET/CT]), biopsies or cultures within 72 h prior to randomization or within 7 days after randomization (see Table 9). The minimum requirements for baseline diagnosis of other forms of complicated SAB are provided in Appendix 2.
17. Modified Duke's Criteria (see Appendix 1) will be assessed at Screening. In patients without definite IE, Modified Duke's Criteria will be assessed at every scheduled visit from Day 2 until the PTE visit. Modified Duke's Criteria will be assessed in all patients (including those with definite IE) at Screening, EOT and PTE.
18. Patients are to be randomized (Section 5.4.3) to a study treatment within the 6 h prior to the planned time of first study-drug administration.
19. Sparse PK sampling (all patients): Days 3 and 12, pre-dose before the first BPR/PBO infusion, 2 h [end of infusion], and 4 to 6 h post-dose. Rich PK sampling (selected sites, N=40 ceftobiprole-treated patients [i.e, approximately 80 patients overall]): Day 3: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 3 h, 4 h, 6 h post-dose; Day 12: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 4 to 6 h post-dose (Section 5.4.7).

20. Intravenous study drug will be administered for up to 42 days (see Sections 3.1 and 6.4). Study drug treatment must be initiated within the 6 h after randomization. On each treatment day, study drug administration should occur within ±1 h for ≤ q6h dose regimens, and ±2 h for > q6h dose regimens, of the scheduled time point.
21. Drug accountability will be performed for each study-drug administration (Section 6.5).
22. Overall success (Section 5.4.6) will be assessed at each scheduled study visit from Day 3 to the PTE visit.
23. Concomitant antimicrobial therapies, other drug-therapies, and non-drug procedures will be assessed at each scheduled study visit from Day 1 to the PTE visit.
24. Creatinine clearance: CL_{CR} should be calculated for all patients except patients on dialysis, using the Cockcroft-Gault formula based on local laboratory results, and should be performed at Screening, and at a minimum on study Days 2, 3, 5, 7, 14, 21, and if applicable, 28/35. 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 ceftobiprole and daptomycin are adjusted in accordance with Table 13 and Table 14, respectively.
25. Adverse events and SAEs will be monitored throughout the study, from start of first dose of study treatment up to and including the PTE visit (see Sections 7.3.1 and 7.3.2).
26. Information on health economics outcome measures from baseline to the PTE visit will be collected at the PTE visit, including total length of stay in hospital, location of treatment within the healthcare system (e.g., Emergency Department), post-study drug procedures and interventions including AEs and any treatment required by these events, re-admission rates, outpatient healthcare encounters, Emergency Department visits, and surgical and non-surgical procedures, e.g., debridement, grafts, amputation, prostheses.

5.2 Time windows for baseline/screening assessments

Baseline assessments are defined as all relevant pre-randomization assessments that may be used for the study.

Screening is defined as the period after informed consent has been obtained, i.e., a period up to 72 h prior to randomization.

Results from vital sign measurements (see Table 10), local safety laboratory tests (see Table 10), blood cultures (see Table 7), echocardiography (see Table 8) or investigations to verify deep-seated infections or complications of SAB (see Table 9), may be used for the study if obtained prior to informed consent (i.e., outside the screening period) but within a 72 h window prior to randomization (10 days for an echocardiography that was confirmatory of definitive right-sided endocarditis).

The study comprises three phases:

- Screening of up to 72 h prior to randomization.
- Randomization and subsequent active-treatment phase with intravenous study drug (ceftobiprole or daptomycin).
- Post-treatment phase, comprising an EOT visit (within 72 h of last study-drug administration), Day 35 (±3 days), Day 42 (±3 days), and a PTE visit on Day 70 (±5 days) post-randomization.

  Note: Day 35 and Day 42 may be active treatment visits for patients in Cohort 2, if treatment for longer than 28 days is required. Day 35 and Day 42 are post-treatment visits for all patients in Cohort 1, and for patients in Cohort 2 who are treated for longer than 28 days, but have not completed treatment by the Day 35 or Day 42 visits.

Patients with suspected or confirmed complicated SAB must sign informed consent within 72 h prior to randomization. Baseline assessments must be completed according to the following timelines.

5.2.1 Blood cultures

Two sets of peripheral blood cultures (including aerobic and anaerobic) will be obtained from each patient at baseline. Blood cultures will be drawn at least 5 minutes apart, and samples for each of the two sets of blood cultures should be obtained from different anatomical locations. Blood cultures that were positive for *S. aureus* and were conducted in the context of routine clinical diagnostic work-up practice prior to obtaining informed consent, but were drawn within the 72 h prior to randomization, may be used for the study to determine patient eligibility, and do not need to be repeated.

Post-randomization repeat blood cultures (at least one, but preferably two blood cultures) will be obtained on Days 1, 2 and 3. Thereafter, blood cultures will be obtained approximately every 48–72 h if clearance of bacteremia has not yet been confirmed, i.e., until negative test results for *S. aureus* are obtained for two cultures (or negative test

result for one culture if only one culture was obtained) at two time points taken at least 24 h apart. At least one blood culture must be obtained at the PTE visit, or in the period between 7 days after EOT and the PTE visit.

Specimens will be cultured by the local laboratory.

Note: The microbiological work-up of the blood culture may:

- Occur prior to informed consent to participation in the study (see Section 5.2.1 and Table 7).
- Be undertaken either on-site or in an external microbiology laboratory specifically appointed for the purposes of this study.
- Use a diagnostic test:
  - routinely performed locally for the detection of *S. aureus* from blood cultures
    or
  - provided to the laboratory for the purpose of this study, if the test has regulatory approval in the country where the test is being performed

Regardless of diagnostic method, every effort should be made to isolate and send all unique organisms from blood to the Central Microbiology Laboratory; this applies particularly to the *S. aureus* isolated from blood at the Screening visit. The Central Microbiology Laboratory will re-identify all isolates, with the results to be used to determine whether the patient meets the study inclusion criteria.

Nevertheless, patients without a Central Microbiology Laboratory assessment may be included in the mITT population if there is unequivocal documented evidence of a baseline blood culture positive for *S. aureus* at the local laboratory.

The central microbiology laboratory will also perform susceptibility testing with both study drugs. For patients with persistent SAB (see Inclusion criterion 7), the susceptibility to ceftobiprole and daptomycin may be assessed at the local microbiology laboratory, but must be confirmed by the central laboratory. If a patient is randomized based on susceptibility results from the local laboratory, and a conflicting result is obtained from the central laboratory, then the central laboratory result will be considered valid. If local susceptibility testing is performed after a patient has been randomized, and the local results show non-susceptibility to either study drug, then the continuation of the patient in the study will be at the discretion of the investigator, based on clinical assessment.

5.2.2 Echocardiography

Echocardiography assessments obtained within 72 h prior to randomization (or up to 10 days if definite RIE has been confirmed) may be used for patient eligibility assessment, even if the echocardiography has been performed in the context of clinical practice prior to obtaining informed consent for this study.

5.2.2.1 Transthoracic echocardiography

A transthoracic echocardiography (TTE) must be performed within the 72 h prior to randomization in all patients, with the following exceptions:

- A transesophageal echocardiography (TEE) has been performed within this time window
- A diagnosis of definite RIE (according to Modified Duke's Criteria, see Appendix 1) is confirmed. For these patients, a TTE (or TEE) performed within the 10 days prior to randomization may be used to confirm patient eligibility. A TTE or TEE must be repeated within the 72 h before, or within the 7 days after, randomization, for documentation purposes.

5.2.2.2 Transesophageal echocardiography

A TEE must be performed within 72 h prior to randomization or within 7 days after randomization in all patients with the following exceptions:

- A diagnosis of definite RIE (according to Modified Duke's Criteria, see Appendix 1) is confirmed. For these patients a TEE (or TTE) performed within 10 days prior to randomization may be used to confirm patient eligibility. A TTE or TEE must be repeated within 72 h before, or within 7 days after, randomization, for documentation purposes. If the diagnosis of a definite endocarditis can be based on a TTE, then a TEE is not required.
- A condition associated with an increased risk of complications from TEE, including:
  - altered mental status or an uncooperative patient
  - unstable cardiorespiratory status
  - esophageal stricture or malignancy (identify esophageal location prior to TEE) or esophageal varices with recent/active bleeding
  - surgical interposition of the esophagus
  - Zenker's diverticulum (identify esophageal location prior to TEE)
  - history of odynophagia or dysphagia
  - cervical spine arthritis with reduced range of motion
  - severe thrombocytopenia ($< 50 \times 10^9$/L), elevated international normalized ratio (> 4), or prolonged partial thromboplastin time (>150 seconds)
  - obstructive sleep apnea/airway compromise (consider sedation by anesthesia)

5.2.3 Diagnostic assessments for deep-seated infections and metastatic or other complications related to SAB

Diagnostic assessments for deep-seated infections and metastatic or other complications related to SAB (i.e., related to Inclusion criterion 8) that were conducted in the context of routine clinical diagnostic work-up practice prior to obtaining informed consent, but within the 72 h prior to randomization, may be used for the study to determine patient eligibility.

Furthermore, diagnostic assessments for deep-seated infections and metastatic or other complications related to SAB (i.e., related to Inclusion criterion 8) obtained within the 7 days after randomization may be used to determine the patient's baseline condition of SAB.

5.2.4 Other screening assessments

Vital sign measurements and local safety laboratory tests that were conducted in the context of routine clinical diagnostic work-up practice prior to obtaining informed consent, but within the 72 h prior to randomization, may be used for the study to determine patient eligibility and do not need to be repeated. This includes the assessment of signs and symptoms of bacteremia for the purposes of Inclusion criterion 4.

All other screening assessments except a pregnancy test (physical examination, 12-lead electrocardiogram, central laboratory safety tests, Modified Duke's Criteria, creatinine clearance) must be performed after informed consent has been obtained, and within the 72 h prior to randomization.

A pregnancy test must be assessed within 24 h prior to randomization. Clinical signs of deep-seated infections and metastatic or other complications of SAB must be assessed within the 12 h prior to randomization. Clinical signs of metastatic complications (assessed by the investigator) include bone or back pain, back pain elicited on percussion of spine (suggestive of vertebral osteomyelitis, discitis, or epidural abscess); joint swelling, joint pain, pain elicited on external rotation of femoral head (suggestive of septic arthritis or bacterial joint infection/empyema); protracted fever and/or sweats, new regurgitant murmurs or heart failure and further clinical stigmata suggestive of endocarditis; abdominal pain, left upper quadrant pain (suggestive of splenic infarction); costovertebral angle tenderness (suggestive of renal infarction or psoas abscess); headache, focal neurologic impairment (suggestive of central nervous septic emboli) or other findings which could reasonably be regarded as clinical signs of metastatic infection. Careful examinations regarding in-dwelling prosthetic devices and orthopedic hardware should be undertaken.

Metastatic or other complications of SAB must be supported by imaging studies (including ultrasound, computed tomography [CT], magnetic resonance imaging [MRI], and positron emission tomography/computed tomography [PET/CT]), biopsies or cultures. The minimum requirements for baseline or post-baseline diagnosis of metastatic complications of SAB are provided in Appendix 2 and Appendix 3, respectively.

Details on the time windows for baseline screening assessments are outlined in Section 5.2.

The respective time windows for baseline screening assessments are shown in Table 7, Table 8, Table 9, and Table 10.

Table 7 Time windows for baseline blood cultures

Assessment	Patient description	Time window to randomization	Time relative to informed consent
Blood culture	Positive for *S. aureus*	Blood cultures positive for *S. aureus* drawn within the 72 h prior to randomization may be used for patient eligibility, regardless of whether informed consent had been obtained at the time of the blood draw.	Before or after

Table 8 Time windows for baseline echocardiography

Assessment	Patient description	Time window to randomization	Time relative to informed consent
TTE and/or TEE	Definite endocarditis	TEE or TTE within the 10 days prior to randomization may be used for patient eligibility.	Before or after
		A TTE or TEE must be repeated within the 72 h before, or the 7 days after randomization, for documentation purposes.	After
	No definite endocarditis	A TEE or TTE must be performed within the 72 h prior to randomization for patient eligibility.	Before or after
		If only a TTE is performed within the 72 h prior to randomization, a TEE must either also be performed within the 72 h prior to randomization, or be performed within 7 days after randomization (see Section 5.4.4.10 for exceptions).	After
		If only a TEE is performed within the 72 h prior to randomization, a TTE is not required.	After

TTE=transthoracic echocardiography; TEE=transesophageal echocardiography.

Table 9 Time windows for baseline assessments for confirmation of deep-seated infections and metastatic or other forms of complicated bacteremia (Inclusion criterion 8)

Assessment	Patient description/condition	Time window to randomization	Time relative to informed consent
Local findings, biopsy or drainage	ABSSSI	Within the 72 h before or 7 days after randomization	Before or after
Arthrocentesis Synovial biopsy MRI	Septic arthritis or bacterial joint infections/empyema	Within the 72 h before or 7 days after randomization	Before or after
Local findings Duplex ultrasound CT* MRI	Septic or suppurative thrombophlebitis (including peripheral, pelvic, portal veins; superior or inferior vena cava, internal jugular veins, or other veins	Within the 72 h before or 7 days after randomization	Before or after
Chest X-ray and/or chest CT	Septic pulmonary emboli/infarcts	Within the 72 h before or 7 days after randomization	Before or after
Ultrasound, CT*, MRI, biopsy or drainage as per institutional standard	Visceral soft-tissue abscesses requiring ≤ 42 days of study antibacterial treatment	Within the 72 h before or 7 days after randomization	Before or after

* Radioisotope studies (e.g., PET or PET-CT) may be conducted as adjunct to diagnosis, as primary diagnostic approach, or when radiographic changes on MRI or CT scans are absent or equivocal.
CT=computed tomography; PET/CT=positron emission tomography/computed tomography; MRI=magnetic resonance imaging.

Table 10 Time windows for other screening assessments

Assessment	Patient description	Time window to randomization	Time relative to informed consent
Demographics and medical history Concomitant medication (within the previous 30 days) Inclusion and exclusion criteria	All patients	Within 72 h prior to randomization	After
Vital signs* Body temperature* Local laboratory safety tests*	All patients	Within 72 h prior to randomization	Before or after
Complete physical examination 12-lead electrocardiogram Creatinine clearance** Central laboratory tests Safety laboratory tests WBC count, CRP and procalcitonin Reticulocytes, haptoglobin and Coombs test Modified Duke's Criteria	All patients	Within 72 h prior to randomization	After
Pregnancy test	Women of childbearing potential	Within 24 h prior to randomization	After
Clinical signs of deep-seated infections and metastatic or other complications related to SAB	All patients	Within 12 h prior to randomization	After

* Vital signs measurement and local laboratory safety tests that were conducted in the context of routine clinical diagnostic work-up practice prior to obtaining informed consent, but within the 72 h prior to randomization, may be used for the study to determine patient eligibility and do not need to be repeated. This includes the assessment of signs and symptoms of bacteremia for the purposes of Inclusion criterion 4.

** Assessment of creatinine clearance is not required for patients on dialysis.

Patients will be classified as having uncomplicated SAB if they are not diagnosed with a complication meeting one of the following criteria, up to 7 days after randomization:

- being on intermittent hemodialysis or peritoneal dialysis within the 72 h prior to randomization (during screening)
- persistent SAB
- confirmation of SAB with metastatic or other complications; or
- RIE

5.3 Study visits

The following assessments and procedures are to be performed at the respective visits.

Screening (Day −1; within the 72 h prior to randomization)

- Informed consent
- Assign patient number
- Inclusion/exclusion criteria
- Medical history/demographics/prior (within 30 days) antibacterial and other pre-study drug/non-drug therapies (including those ongoing at the time of screening, prior to randomization)
- Documentation of surgical procedures anticipated during the course of the study and planned at baseline
- Complete physical examination
- Vital signs
- Body temperature
- TTE and/or TEE – see Table 8
- 12-lead electrocardiogram
- Pregnancy test (serum; within 24 h prior to randomization)
- Safety laboratory (local and central laboratories), both blood and urine
- Reticulocytes, haptoglobin and Coombs test (central lab)
- WBC count, CRP and procalcitonin (central lab)
- Serum creatinine (local laboratory) and CL_{CR} (calculated using the Cockcroft-Gault formula)
- Blood culture including standard microbiological investigation indicating *S. aureus* infection (either by standard laboratory tests or by non-standard diagnostic tests subsequently confirmed by standard diagnostic tests for *S. aureus*)
  Note: Blood cultures positive for *S. aureus* that were obtained in the context of routine clinical diagnostic work-up prior to obtaining informed consent, but were drawn within the 72 h prior to randomization, may be used for the study to determine patient eligibility, and do not need to be repeated.
- Investigator-assessed clinical signs and symptoms of SAB
- Clinical signs of deep-seated infections and metastatic or other complications related to SAB (see Section 5.4.5.3), diagnosis of which must be supported by imaging studies (including ultrasound, CT, MRI, and PET/CT), biopsies or cultures at baseline, or within 7 days after randomization. The minimum requirements for baseline diagnosis of or forms of complicated SAB are provided in Appendix 2.
- Modified Duke's Criteria (see Appendix 1) for the diagnosis of IE.

Baseline assessments (except for a TEE) must be completed within the 72 h prior to randomization. Patients with suspected or confirmed SAB must sign informed consent prior to randomization. Blood cultures, TTE, or TEE conducted in the context of routine clinical diagnostic practice prior to obtaining informed consent, but within the 72-h window before randomization, may be used for the study and do not need to be repeated. The respective time windows for baseline screening assessments are outlined in Table 7–Table 10.

Once all screening procedures have been completed and a patient is assessed as being eligible for the study, they will randomly be assigned to treatment with ceftobiprole or daptomycin in a 1:1 ratio. Study drug treatment must be initiated within the 6 h after randomization.

Active-treatment Day 1

- Randomization: IWRS registration
- Vital signs
- Body temperature
- Blood culture, including standard microbiological investigation
- TTE and/or TEE to be performed by Day 7 – see Table 8
- Study drug administration
- Drug accountability
- Concomitant antimicrobial and other therapies
- Concomitant non-drug procedures
- Adverse events

Active-treatment Day 2

- Brief physical examination
- Vital signs
- Body temperature
- WBC count, CRP and procalcitonin (central lab)
- Serum creatinine (local laboratory) and CL_{CR} (calculated using the Cockcroft-Gault formula)
- Blood culture, including standard microbiological investigation
- TTE and/or TEE to be performed by Day 7 – see Table 8
- Study drug administration
- Drug accountability
- Investigator-assessed clinical signs and symptoms of SAB
- Clinical signs of metastatic or other complications of SAB
- Modified Duke's Criteria (see Appendix 1) in patients without definite IE
- Concomitant antimicrobial and other therapies
- Concomitant non-drug procedures
- Adverse events

Active-treatment Day 3

- Brief physical examination
- Vital signs
- Body temperature
- Safety laboratory (central lab)
- WBC count, CRP and procalcitonin (central lab)
- Serum creatinine (local laboratory) and CL_{CR} (calculated using the Cockcroft-Gault formula)
- Blood culture including standard microbiological investigation
- PK blood-sample collection
  - Sparse PK sampling: pre-dose before the first BPR/PBO infusion, 2 h post-dose, and 4 to 6 h post-dose
  - Rich PK sampling: pre-dose before the first BPR/PBO infusion, and 2, 3, 4 and 6 h post-dose
- TTE and/or TEE to be performed by Day 7 – see Table 8
- Study drug administration
- Drug accountability
- Investigator-assessed clinical signs and symptoms of SAB
- Clinical signs of metastatic or other complications of SAB
- Modified Duke's Criteria (see Appendix 1) in patients without definite IE
- Investigator assessment of overall success
- Concomitant antimicrobial and other therapies
- Concomitant non-drug procedures
- Adverse events

Active-treatment Days 4–12

- Brief physical examination
- Vital signs
- Body temperature
- Safety laboratory (central lab) (Day 7 only)
- WBC count, CRP and procalcitonin (central lab) (Day 7 only)
- Serum creatinine (local laboratory) and CL_{CR} (calculated using the Cockcroft-Gault formula) (Days 5 and 7 only)
- Blood culture including standard microbiological investigation unless negative test results have already been confirmed
- PK blood-sample collection (Day 12 only)
  - All patients: pre-dose before the first BPR/PBO infusion, 2 h post-dose, 4 to 6 h post-dose
- TTE and/or TEE to be performed by Day 7 – see Table 8
- Study drug administration
- Drug accountability
- Investigator-assessed clinical signs and symptoms of SAB

- Clinical signs of metastatic or other complications of SAB
- Modified Duke's Criteria (see Appendix 1) in patients without definite IE
- Investigator assessment of overall success
- Concomitant antimicrobial and other therapies
- Concomitant non-drug procedures
- Adverse events

Active-treatment Days 14, 21, and if applicable, Days 28, 35, and 42

- Brief physical examination
- Vital signs
- Body temperature
- Safety laboratory (central lab)
- WBC count, CRP and procalcitonin (central lab) (Day 14 only)
- Serum creatinine (local laboratory) and CL_{CR} (calculated using the Cockcroft-Gault formula)
- Blood culture including standard microbiological investigation unless negative test results have already been confirmed
- Study drug administration
- Drug accountability
- Investigator-assessed clinical signs and symptoms of SAB
- Clinical signs of metastatic or other complications of SAB
- Modified Duke's Criteria (see Appendix 1) in patients without definite IE
- Investigator assessment of overall success
- Concomitant antimicrobial and other therapies
- Concomitant non-drug procedures
- Adverse events

Post-treatment EOT visit

The EOT visit is to be performed within 72 h of last study-drug administration. For patients who prematurely discontinue study-drug treatment, the EOT visit should take place within the 72 h after discontinuation.

- Brief physical examination
- Vital signs
- Body temperature
- 12-lead electrocardiogram
- Pregnancy test (serum or urine)
- Safety laboratory (central lab)
- Reticulocytes, haptoglobin and Coombs test (central lab)
- WBC count, CRP and procalcitonin (central lab)

- Blood culture including standard microbiological investigation, unless negative test results have already been confirmed (see Section 5.2.1).
- Investigator-assessed clinical signs and symptoms of SAB
- Clinical signs of metastatic or other complications of SAB
- Modified Duke's Criteria (see Appendix 1) in all patients
- Investigator assessment of overall success
- Concomitant antimicrobial and other therapies
- Concomitant non-drug procedures
- Adverse events

Post-treatment Days 35 and 42

The following assessments and procedures are to be performed on Days 35 (±3 days) and 42 (±3 days):

- Brief physical examination
- Vital signs
- Body temperature
- Safety laboratory (central lab)
- Blood culture including standard microbiological investigation*
- Investigator-assessed clinical signs and symptoms of SAB
- Clinical signs of metastatic or other complications of SAB
- Modified Duke's Criteria (see Appendix 1) in patients without definite IE
- Investigator assessment of overall success
- Concomitant antimicrobial and other therapies
- Concomitant non-drug procedures
- Adverse events

Post-treatment PTE visit

The PTE visit should be performed 70 days (±5 days) after randomization and will constitute the last patient follow-up, with the exception of AEs that require prolonged follow-up (see Section 7.3.2.1.2).

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

- Brief physical examination
- Vital signs
- Body temperature
- Pregnancy test (serum or urine)
- Safety laboratory (central lab)
- Reticulocytes, haptoglobin and Coombs test (central lab)

* At least one blood culture must be obtained at the PTE visit, or in the period between 7 days after EOT and the PTE visit.

- Blood culture including standard microbiological investigation*
- Investigator-assessed clinical signs and symptoms of SAB
- Clinical signs of metastatic or other complications of SAB
- Modified Duke's Criteria (see Appendix 1) in all patients
- Investigator assessment of overall success
- Concomitant antimicrobial and other therapies
- Concomitant non-drug procedures
- Adverse events
- Health economic outcome measures

5.4 Study procedures

5.4.1 Informed consent

The investigator must obtain the patient's informed consent to participation in the study before carrying out any study procedures during screening. Non-study blood cultures, TTEs, and TEEs conducted prior to informed consent, but within the 72 prior to randomization, may be used for the study and do not need to be repeated.

The investigator is to assign a patient number once informed consent is obtained.

5.4.2 Medical history, demographics and prior/ongoing therapies

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 therapies (see Section 5.5), and review the inclusion/exclusion criteria (Section 4.2 and Section 4.3).

5.4.3 Patient registration and IWRS

Eligible patients will be randomized in a 1:1 ratio to ceftobiprole or daptomycin treatment, based on a computer-generated randomization schedule. An Interactive Web Response System (IWRS) will be used for this study.

Within the 6 h prior to the planned time of first study-drug administration, the investigator/designee will contact the IWRS to obtain the study treatment assignment and dispense double-blind therapy accordingly. The IWRS will associate that patient with the next available treatment in the appropriate stratum on the randomization.

Randomization will be stratified by study site, dialysis status, and prior antibacterial treatment use (i.e., use of any systemic antibacterial treatment potentially effective against *S. aureus* within 7 days of randomization).

* At least one blood culture must be obtained at the PTE visit, or in the period between 7 days after EOT and the PTE visit.

Detailed handling instructions are provided in the IWRS User's Guide.

5.4.4 Safety assessments

The investigator will evaluate patient safety by AE monitoring, physical examination, vital signs, safety laboratory tests and other assessments as indicated. Safety data will also be reviewed by the sponsor.

Safety assessments must be performed at the intervals indicated in the Schedule of Assessments (Table 6). More frequent assessments may be performed at the investigator's discretion if medically indicated.

Detailed handling instructions are provided in the Medical Monitoring Plan.

5.4.4.1 Physical examination

A complete physical examination must be performed in accordance with the Schedule of Assessments (Table 6). Physical examination includes general appearance, skin, neck inclusive thyroids, eyes, nose, throat, cardiovascular system, musculoskeletal system (spine, joints, pelvis), 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 6). Brief physical examination is to be focused on any changes from baseline.

5.4.4.2 Vital signs

Vital signs must be assessed in accordance with the Schedule of Assessments (Table 6), at the same time as the temperature assessment is performed.

Vital signs include height, weight, respiratory rate, radial pulse rate, systolic blood pressure (SBP) and diastolic blood pressure (DPB). Pulse rates and BPs 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.

The patient's height is only to be assessed during the Screening visit.

The patient's weight is to be assessed at Screening, and at a minimum on study Days 2, 3, 5, 7, 14, 21, and if applicable, 28/35, at the EOT visit, and at the PTE visit.

5.4.4.3 Body temperature measurement

Body temperature must be assessed in accordance with the Schedule of Assessments (Table 6), at the same time as the vital signs are taken. For all patients enrolled at the same site, the same method of temperature measurement should be used during the course of the study.

5.4.4.4 Electrocardiograms

Standard 12-lead ECGs will be obtained and assessed locally, in accordance with the Schedule of Assessments (Table 6).

5.4.4.5 Pregnancy testing

Women of childbearing potential must have a negative serum pregnancy test result during the 24 h prior to randomization.

At the EOT and PTE visits 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, the patient followed for safety, and the outcomes of the pregnancy assessed.

Further details regarding pregnancy are provided in Section 7.4.

5.4.4.6 Safety laboratory parameters

5.4.4.6.1 Local laboratory safety assessments

Local laboratory safety parameters include hematology, biochemistry, coagulation, blood glucose, and urinalysis.

Creatinine clearance for dose determination is to be calculated using the Cockcroft-Gault formula.

Local laboratory safety 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. 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 AE page of the CRF.

The local laboratory safety parameters are provided in Table 11.

Table 11 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	Sodium		pH
and % immature	Creatinine		Protein
neutrophils [bands] are to	Urea or BUN		Specific gravity
be obtained if required for	Glucose		Bilirubin
patient eligibility)	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.

5.4.4.6.2 Central laboratory safety assessments

The central laboratory safety parameters are provided in Table 12.

Table 12 Central laboratory safety parameters

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

Central laboratory safety testing will be conducted in accordance with the Schedule of Assessments (Table 6). Additional central testing may be performed at the discretion of the investigator when clinically indicated. All samples for a given study site 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.

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.

5.4.4.7 Reticulocytes, haptoglobin and Coombs test

Reticulocyte counts, haptoglobin measurements, and Coombs tests will be assessed by the central laboratory at baseline, and at the EOT and PTE visits.

5.4.4.8 WBC count and CRP and procalcitonin testing

WBC counts, CRP levels, and procalcitonin levels will be assessed by the central laboratory, according to the schedule shown in Table 6.

5.4.4.9 Creatinine clearance

Creatinine clearance (CL_{CR}): CL_{CR} should be calculated for all patients except patients on dialysis, using the Cockcroft-Gault formula based on local laboratory results, and should be performed at Screening, and at a minimum on study Days 2, 3, 5, 7, 14, 21, and if applicable, 28/35. 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 ceftobiprole and daptomycin are adjusted in accordance with Table 13 and Table 14, respectively.

5.4.4.10 Transthoracic and transesophageal echocardiography

Standard two-dimensional or three-dimensional TTE and/or TEE will be performed, depending on whether a definite diagnosis of IE has been made at the time of screening (see Table 8).

For patients with definite IE according to Modified Duke's Criteria (see Appendix 1), a TTE or TEE performed within 10 days prior to randomization may be used to confirm patient eligibility. In these cases, a TTE or TEE must be repeated within 72 h before, or 7 days after, randomization, for documentation purposes. If the diagnosis of a definite endocarditis can be based on a TTE, then a TEE is not required.

For patients without definite endocarditis, a TTE or TEE must be performed within 72 h prior to randomization. A TTE or TEE performed in this time window but prior to obtaining informed consent may be used for patient eligibility assessment. If a TTE is performed within 72 h prior to randomization, then a TEE must be performed within 72 h prior to randomization, or within 7 days after randomization, unless the patient has one or more of the following conditions associated with an increased risk of complications from a TEE:

- altered mental status or an uncooperative patient
- unstable cardiorespiratory status
- esophageal stricture or malignancy (identify esophageal location prior to TEE) or esophageal varices with recent/active bleeding
- surgical interposition of the esophagus
- Zenker's diverticulum (identify esophageal location prior to TEE)
- history of odynophagia or dysphagia
- cervical spine arthritis with reduced range of motion
- severe thrombocytopenia ($< 50 \times 10^9$/L), elevated international normalized ratio (> 4), or prolonged partial thromboplastin time (>150 seconds)
- obstructive sleep apnea/airway compromise (consider sedation by anesthesia)

If a TEE is performed within 72 h prior to randomization, a TTE is not required.

5.4.5 Assessments of disease status

5.4.5.1 Microbiological assessments

Two peripheral blood cultures must be obtained at least 5 minutes apart from separate peripheral-venous sites from each patient at baseline. Blood cultures that were positive for *S. aureus* and were conducted in the context of routine clinical diagnostic work-up practice prior to obtaining informed consent, but were drawn within the 72 h prior to randomization, may be used for the study to determine patient eligibility, and do not need to be repeated.

Post-randomization repeat blood cultures (at least one, but preferably two blood cultures) will be obtained on Days 1, 2 and 3. Thereafter, blood cultures will be obtained approximately every 48–72 h if clearance of bacteremia has not yet been confirmed, i.e., until negative test results for *S. aureus* are obtained for two successive cultures taken at least 24 h apart. At least one blood culture is to be taken at the PTE visit, or in the period between 7 days after the EOT visit and the PTE visit.

Specimens will be cultured by the local laboratory using standard microbiological procedures. All unique organisms from blood will be sent to the central microbiology laboratory for identification, and for susceptibility testing with both study drugs. For patients with persistent SAB (see Inclusion criterion 7), the susceptibility to ceftobiprole and daptomycin may be assessed at the local microbiology laboratory, but must be confirmed by the central laboratory. If a patient is randomized based on susceptibility results from the local laboratory, and a conflicting result is obtained from the central laboratory, then the central laboratory result will be considered valid. If local susceptibility testing is performed after a patient has been randomized, and the local results show non-susceptibility to either study drug, then the continuation of the patient in the study will be at the discretion of the investigator, based on clinical assessment.

5.4.5.2 Investigator-assessed clinical signs and symptoms of SAB

The investigator is to include body temperature, WBC count, heart rate, respiratory rate, systolic blood pressure, and signs or symptoms of localized catheter-related infection in the assessment of SAB.

5.4.5.3 Clinical signs of deep-seated infections and metastatic or other complications of SAB

Clinical signs of metastatic complications to be assessed by the study investigator include:

- Bone or back pain, back pain elicited on percussion of spine (suggestive of vertebral osteomyelitis, discitis, or epidural abscess)
- Joint swelling, joint pain, pain elicited on external rotation of femoral head (suggestive of septic arthritis or bacterial joint infection/empyema)
- Protracted fever and/or sweats, new regurgitant murmurs or heart failure and further clinical stigmata suggestive of endocarditis

- Abdominal pain, left upper quadrant pain (suggestive of splenic abscess or infarction)
- costovertebral angle tenderness (suggestive of renal abscess or infarction or psoas abscess)
- headache, focal neurologic impairment (suggestive of central nervous septic emboli or other CNS complications)

Careful examinations should also be made by the investigator regarding indwelling prosthetic devices and orthopedic hardware.

The diagnosis of deep-seated infections and metastatic or other complications related to SAB must be supported by imaging studies (including ultrasound, CT, MRI, and PET/CT), biopsies or cultures. The minimum requirements for baseline or post-baseline diagnosis of deep-seated infections and metastatic or other complications related to SAB are provided in Appendix 2 and Appendix 3, respectively.

5.4.5.3.1 Assessment of deep-seated infections and metastatic or other complications of SAB at baseline

Diagnostic assessments for deep-seated infections and metastatic or other complications related to SAB that were conducted in the context of routine clinical diagnostic work-up practice prior to obtaining informed consent, but within 7 days prior to randomization may be used for the study to determine patient eligibility.

Furthermore, diagnostic assessments for deep-seated infections and metastatic or other complications related to SAB (see Inclusion criterion 8) that are obtained within 72 h after randomization may be used to determine the patient`s baseline condition of SAB.

Baseline deep-seated infections and metastatic or other complications of SAB will be categorized as (see Appendix 2):

- ABSSSI
- Septic arthritis or bacterial joint infection/empyema
- Septic or suppurative thrombophlebitis
- Visceral soft-tissue abscesses requiring ≤ 42 days of study treatment
- Septic pulmonary emboli/infarction (as assessed by the investigator based on clinical symptoms of fever, cough, sputum/hemoptysis in the presence of an extrapulmonary infection, sepsis, or risk factors for septic emboli, and based on radiological signs as outlined in Appendix 2)

5.4.5.3.2 Assessment of new occurrences of deep-seated infections and metastatic or other complications of SAB

New occurrences of deep-seated infections and metastatic or other complications of SAB will be categorized in the same way as at baseline, and must be supported by imaging studies (including ultrasound, CT, MRI, and PET/CT), biopsies, or cultures. The minimum requirements for baseline or post-baseline diagnosis of deep-seated infections and metastatic or other complications of SAB are provided in Appendix 2 and Appendix 3, respectively.

5.4.5.4 Modified Dukes criteria

Modified Duke's Criteria (see Appendix 1) will be assessed in all patients at Screening, EOT and PTE.

For patients without definite IE, Modified Duke's Criteria will be assessed at every scheduled visit from Day 2 until the PTE visit.

5.4.6 Assessments of treatment success

5.4.6.1 Investigator-assessed overall success

Overall success requires clinical success, defined as the improvement or resolution of clinical signs and symptoms, plus confirmed negative blood culture for *S. aureus* (microbiological success) and no requirement for further systemic antibacterial treatment for SAB or its complications.

5.4.6.2 DRC-assessed overall success

Independent clinical experts, blinded to treatment allocation and not associated with the study conduct, will review all patient profiles, including signs and symptoms of infection and relevant microbiological, laboratory, and imaging findings, and will assess baseline condition of SAB, its complications, and outcomes for primary and secondary endpoints (see Appendix 4). The results of the DRC review will form the basis for assessing the non-inferiority of ceftobiprole versus daptomycin.

The definition of overall success is provided in Section 3.2.1.

5.4.7 PK blood-sample collection

Rich and sparse PK sampling will be performed to determine the secondary endpoint of plasma levels of ceftobiprole and the β-lactam ring-open product BAL1029.

Sparse PK sampling

Sparse PK sampling will be performed for all patients in the study, comprising three blood samples of approximately 2 mL, collected on Days 3 and 12 at the following timepoints:

- Day 3: pre-dose before the first BPR/PBO infusion, 2 h post-dose (end of infusion), 4 to 6 h post-dose
- Day 12: pre-dose before the first BPR/PBO infusion, 2 h post-dose (end of infusion), 4 to 6 h post-dose

Rich PK sampling

Rich PK sampling will be performed for a total of 40 ceftobiprole-treated patients (i.e., approximately 80 patients overall) at selected sites, comprising two additional samples of approximately 2 mL each on Day 3, in addition to those collected for the sparse PK sampling. In total, patients who undergo rich PK sampling will have five blood samples collected on Day 3 and three on Day 12, at the following timepoints:

- Day 3: pre-dose before the first BPR/PBO infusion, 2 h post-dose (end of infusion), and at 3, 4, and 6 h post-dose
- Day 12: pre-dose before the first BPR/PBO infusion, 2 h post-dose (end of infusion), 4 to 6 h post-dose

5.5 Prior and concomitant medication

5.5.1 Prior medication

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

5.5.2 Prohibited concomitant medication

Concomitant systemic antibacterials (other than study drugs) that provide activity against *S. aureus* are prohibited from randomization up to the PTE visit.

The use of non-study antibacterial treatment during the study (if it occurs) is not necessarily to be considered an outcome of 'failure'. The significance of concomitant potentially effective non-study antibacterial treatment (except aztreonam, metronidazole, nitrofurantoin, and oral vancomycin, see Section 5.5.3) is to be assessed by the blinded DRC in accordance with the guidelines provided in Appendix 6, to determine whether the treatment had an impact on the primary endpoint.

5.5.3 Permitted concomitant medication

5.5.3.1 Permitted non-antibacterial treatments

The following concomitant medication is permitted during the study:

- Non-antibacterial standard-of-care medication.
- Acetaminophen or paracetamol, when an antipyretic medication is indicated.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic steroids.
- Low-dose aspirin (≤ 200 mg per day) for cardiovascular prophylaxis.

Any concomitant medication (including herbal medicines) received by the patient during the study must be recorded in the CRF, including the route of administration, therapeutic indication, and start/stop dates of use.

5.5.3.2 Permitted antibacterial treatments

The following concomitant antibacterial medication is permitted during the study:

- In the daptomycin treatment group, aztreonam using a standard-dose regimen at the site for coverage of Gram-negative infections (i.e., for polymicrobial bloodstream infections, or Gram-negative non-bloodstream infections). Patients randomized to the ceftobiprole group who are considered to require coverage against Gram-negative infections will receive dummy treatment with placebo so that blinding is maintained during the active treatment phase.
- In both treatment groups,
  - nitrofurantoin for urinary tract infections
  - metronidazole using a standard-dose regimen at the site for coverage of anaerobic infections
  - oral vancomycin is considered a non-systemic antibiotic and may be used at any time during the study

5.6 Restrictions

Patients will be encouraged to continue their usual diet, as dictated by their clinical condition. Activities that would impact clinical outcome should be avoided.

Participation in any other interventional clinical study or medical device investigation is prohibited from 30 days prior to enrollment up to and including the PTE visit.

5.7 Health economic 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 daptomycin.

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 medication
- Post-study drug procedures and interventions
- Adverse events and any treatment required by these events
- Incidence of re-hospitalization
- Outpatient healthcare encounters
- Emergency Department visits
- Antibacterial treatment utilization
- Surgical and non-surgical procedures, e.g. debridement, grafts, amputation, prostheses, and others

6 STUDY DRUGS

6.1 Blinding

This is a randomized, double-blind, double-dummy, active-controlled, parallel-group, multi-center study in adult hospitalized* patients with SAB, including IE.

6.2 Randomization

Patients will be randomized to double-blind, double-dummy study treatment with ceftobiprole or daptomycin in a 1:1 allocation ratio, based on a computer-generated randomization schedule.

Within the 6 h prior to the scheduled first dose of study drug, the investigator/designee will contact the IWRS to obtain the study treatment assignment and will dispense blinded treatment accordingly. The IWRS will allocate that patient to the appropriate randomization stratum. Randomization will be stratified by study site, dialysis status, and prior antibacterial treatment use (i.e., use of any systemic antibacterial treatment potentially effective against *S. aureus* within 7 days of randomization).

Detailed randomization instructions are provided in the IWRS User's Guide.

6.3 Dose regimens and administration schedules

After randomization and during active treatment, patients will receive either ceftobiprole as 2-h intravenous infusions (Table 13), or daptomycin as 0.5-h intravenous infusions (Table 14).

Table 13 Schedule of ceftobiprole administration

Study day	Normal renal function to mild renal impairment ($CL_{Cr} \geq 50$ mL/min)	Renal impairment (non-dialysis)	Intermittent hemodialysis or peritoneal dialysis
Day 1 to Day 8	500 mg q6h	CL_{Cr} 30 – < 50 mL/min: 500 mg q8h CL_{Cr} <30 mL/min: 250 mg q8h	250 mg q24h
Day 9 onwards	500 mg q8h	CL_{Cr} 30–< 50 mL/min: 500 mg q12h CL_{Cr} < 30 mL/min: 250 mg q12h	250 mg q24h

CL_{Cr}=Creatinine clearance based on the Cockcroft-Gault formula.

* In a hospital or equivalent medical confinement or clinical research unit.

Table 14 Schedule of daptomycin administration

	Normal renal function to moderate renal impairment ($CL_{Cr} \geq 30$ mL/min)	Renal impairment (non-dialysis) ($CL_{Cr} < 30$ mL/min)	Intermittent hemodialysis or peritoneal dialysis
Day 1 onwards	6 mg/kg q24h	6 mg/kg q48h	6 mg/kg q48h

CL_{Cr}=Creatinine clearance based on the Cockcroft-Gault formula.

In accordance with institutional standards, an increase in the dose of daptomycin administered (up to 10 mg/kg) may be implemented.

To maintain the blinding of study treatments, patients in the ceftobiprole group will receive dummy infusions with placebo (physiological saline, 0.9% NaCl) matching daptomycin, and patients in the daptomycin group will receive dummy infusions with placebo (physiological saline, 0.9% NaCl) matching ceftobiprole.

No switches to other systemic antibacterial treatments are permitted for any of the study drugs prior to the PTE visit. There is no intravenous-to-oral switch for any of the treatments in this study.

The minimum treatment duration is 21 days of study medication, and the maximum treatment duration is 42 days of study medication.

Exceptional cases of patients who are considered to require further antibacterial treatment for SAB at the end of the 42-day study treatment period, and who do not meet any other failure criteria, will be switched to open-label non-study treatment according to institutional practice. These patients will be considered failures in the mITT and ITT analyses irrespective of treatment group.

6.4 Study drug administration

All study drugs will be administered intravenously. There is no option to switch to oral treatment in this study.

Hospitalization (in a hospital or equivalent medical confinement or clinical research unit) of study participants is required to initiate study treatment. 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.

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.

Study drug treatment must be initiated within the 6 h after randomization. On each treatment day, study-drug administration should occur within ±1 h for ≤ q6h dose regimens, and ±2 h for > q6h dose regimens, of the scheduled time point.

6.4.1 Ceftobiprole

- For patients with normal to mildly-impaired renal function (i.e., $CL_{Cr} \geq 50$ mL/min), ceftobiprole 500 mg is to be administered as a 2-h intravenous infusion every 6 h, from study Day 1 up to and including study Day 8. From study Day 9 until the end of treatment, ceftobiprole 500 mg is to be administered as a 2-h intravenous infusion every 8 h.
- For patients with renal impairment (i.e., $CL_{Cr} < 50$ mL/min) who do not require dialysis, the following dose adjustments will be made (see Table 13):
  - CL_{Cr} 30 – < 50 mL/min: ceftobiprole 500 mg is to be administered as a 2-h intravenous infusion every 8 h from study Day 1 up to and including study Day 8. From study Day 9 until the end of treatment, ceftobiprole 500 mg is to be administered as a 2-h intravenous infusion every 12 h.
  - $CL_{Cr} < 30$ mL/min: ceftobiprole 250 mg is to be administered as a 2-h intravenous infusion every 8 h from study Day 1 up to and including study Day 8. From study Day 9 until the end of treatment, ceftobiprole 250 mg is to be administered as a 2-h intravenous infusion every 12 h.
- For patients with renal impairment who require hemodialysis or peritoneal dialysis, ceftobiprole 250 mg is to be administered as a 2-h intravenous infusion every 24 h, from study Day 1 up to the end of treatment. On the days of hemodialysis, ceftobiprole will be administered after the hemodialysis session has been completed.

6.4.2 Daptomycin

- For patients with normal to moderately-impaired renal function (i.e., $CL_{Cr} \geq 30$ mL/min), daptomycin 6 mg/kg is to be administered as a 0.5-h intravenous infusion every 24 h, from study Day 1 until the end of treatment (see Table 14).
- For patients with renal impairment (i.e., $CL_{Cr} < 30$ mL/min) who do not require dialysis, daptomycin 6 mg/kg is to be administered as a 0.5-h intravenous infusion every 48 h, from study Day 1 until the end of treatment (see Table 14).
- For patients with renal impairment who require hemodialysis or peritoneal dialysis, daptomycin 6 mg/kg is to be administered as a 0.5-h intravenous infusion every 48 h, from study Day 1 until the end of treatment (see Table 14).

Detailed guidelines for the dosing of ceftobiprole and daptomycin are provided in the Pharmacy Manual.

6.4.3 Study drug dosing volumes and sequence

The total daily volume of study-drug infusions is shown in Table 15 (study Days 1 to 8) and Table 16 (study Days 9 to 42). The sequence of administration of study drug infusions at any time point should be maintained as per Table 15 and Table 16 whenever possible (i.e., at 0 h the DAP/PBO should be administered before BPR /PBO).

Table 15 Study drug dosing schedule: Day 1 to Day 8

	CL_{Cr} ≥ 50 mL/min		**CL_{Cr} 30 – < 50 mL/min**		**CL_{Cr} < 30 mL/min***		**Dialysis***	
Time	**BPR**	**DAP**	**BPR**	**DAP**	**BPR**	**DAP**	**BPR**	**DAP**
0 h	50 mL PBO (30 min)	50 mL DAP (30 min)	50 mL PBO (30 min)	50 mL DAP (30 min)	50 mL PBO (30 min) (q48h)	50 mL DAP (30 min) (q48h)	50 mL PBO (30 min) (q48h)	50 mL DAP (30 min) (q48h)
	250 mL BPR (120 min)	250 mL PBO (120 min)	250 mL BPR (120 min)	250 mL PBO (120 min)	125 mL BPR (120 min)	125 mL PBO (120 min)	125 mL BPR (120 min)	125 mL PBO (120 min)
6 h	250 mL BPR (120 min)	250 mL PBO (120 min)						
8 h			250 mL BPR (120 min)	250 mL PBO (120 min)	125 mL BPR (120 min)	125 mL PBO (120 min)		
12 h	250 mL BPR (120 min)	250 mL PBO (120 min)						
16 h			250 mL BPR (120 min)	250 mL PBO (120 min)	125 mL BPR (120 min)	125 mL PBO (120 min)		
18 h	250 mL BPR (120 min)	250 mL PBO (120 min)						
Vol.	1050 mL per day		800 mL per day		425/375 mL per day		175/125 mL per day	

CL_{Cr}= Creatinine clearance; BPR=ceftobiprole medocaril; DAP=daptomycin; PBO=placebo.

* To maintain blinding, it is particularly important that patients with CL_{Cr} < 30 mL/min or on dialysis receive both infusions (i.e., 50 mL DAP/PBO and 125 mL BPR/PBO) on Day 1 at time 0 h.

Table 16 Study drug dosing schedule: Day 9 to Day 42

	CL_{Cr} ≥ 50 mL/min		**CL_{Cr} 30 – < 50 mL/min**		**CL_{Cr} < 30 mL/min**		**Dialysis**	
Time	**BPR**	**DAP**	**BPR**	**DAP**	**BPR**	**DAP**	**BPR**	**DAP**
0 h	50 mL PBO (30 min)	50 mL DAP (30 min)	50 mL PBO (30 min)	50 mL DAP (30 min)	50 mL PBO (30 min) (q48h)	50 mL DAP (30 min) (q48h)	50 mL PBO (30 min) (q48h)	50 mL DAP (30 min) (q48h)
	250 mL BPR (120 min)	250 mL PBO (120 min)	250 mL BPR (120 min)	250 mL PBO (120 min)	125 mL BPR (120 min)	125 mL PBO (120 min)	125 mL BPR (120 min)	125 mL PBO (120 min)
8 h	250 mL BPR (120 min)	250 mL PBO (120 min)						
12 h			250 mL BPR (120 min)	250 mL PBO (120 min)	125 mL BPR (120 min)	125 mL PBO (120 min)		
16 h	250 mL BPR (120 min)	250 mL PBO (120 min)						
Vol.	800 mL per day		550 mL per day		300/250 mL per day		175/125 mL per day	

CL_{Cr}= Creatinine clearance; BPR=ceftobiprole medocaril; DAP=daptomycin; PBO=placebo.

6.5 Blinding

The unblinded site pharmacist/designee will provide blinded and properly-labeled study medication to investigational staff.

At the site, only the unblinded pharmacist/designee will have access to treatment codes via the IWRS.

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

6.5.1 Methods for ensuring blinding

This study will be double-blind with regard to the administration of study drugs. To ensure that the blinding is maintained, only the following personnel may have access to details of the treatment allocation:

- those setting up the randomization scheme and IWRS
- the unblinded pharmacist/designee responsible for blinded study-drug preparation, adjustments, 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
- those performing PK analyses
- the unblinded statistician, if required for safety reasons, or producing outputs for the DSMB.

These personnel must not disclose any details of the randomization scheme or treatment allocation.

6.5.2 Unblinding methods

Individual treatment codes from the IWRS for each randomized patient will be available to investigators; an investigator should only break the treatment code if this is necessary to respond to a medical emergency. It is advisable for the investigator to contact the Medical Monitor prior to breaking the blind.

If it is necessary to break the code, 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 patient's treatment allocation must not be disclosed, 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 may only break the blind, via the IWRS, if this is necessary for regulatory reporting purposes, and must ensure that this is fully documented, with only the minimum number of staff necessary having access to the unblinded information.

Detailed handling instructions in regard to blinding are provided in the IWRS User's Guide.

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

6.6 Drug accountability and compliance checks

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.

6.7 Packaging and labelling

Study drugs will be packed and labeled in accordance with local regulations and the Annex 13 Good Manufacturing Practice rules. Labels will include the identity of the sponsor and investigator, protocol number, drug identification, storage conditions, content of study drug, and expiry date.

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

6.8 Shipping and storage conditions

Study drug for intravenous administration will be presented as follows:

- vials of sterile lyophilized ceftobiprole medocaril containing the equivalent of 500 mg ceftobiprole. The dry powder must be stored in a refrigerator (2–8 °C/36–46°F).
- vials of sterile daptomycin containing 350 mg or 500 mg. The dry powder must be stored in a refrigerator (2–8 °C/36–46°F).

All vials of study drug for intravenous administration must be shipped to the study sites 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.

6.9 Drug supply

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

- Site ID, Subject ID, Random ID
- Investigator's 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 clinical monitor.

6.10 Drug disposal

Any remaining drug, including empty vials, may either be returned to the study supply packaging provider, or destroyed at the site at the request of the sponsor. If drug is destroyed at the study site, the investigator/designee 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 has been provided and before first study-drug administration (see Section 7.3.1).

7.1.2 Adverse event

An AE is any untoward medical occurrence from the start of first dosing up to and including the scheduled PTE visit 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 (see Section 7.3.2).

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
- is classified as an important medical event or a medically significant event

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:

- In this study, any convulsion event is an AE of special interest; a convulsion event is considered an ‘important medical event’, and is therefore an SAE for the purposes of the study.
- 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 SAB, not associated with any deterioration in condition (e.g., hospitalizations related to study procedures, such as study-drug administration, PK assessments, etc).
  – Elective or planned treatment, including surgical interventions, for SAB if the plan for the respective intervention has been documented prior to randomization.
  – Elective or pre-planned treatment for a pre-existing condition that is unrelated to the SAB 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 to be related to the study treatment and for which the nature or severity is not consistent with the applicable reference safety information.

7.1.4 Adverse events of special interest

In addition to convulsions, which are to be considered SAEs (see Section 7.1.3), the following are considered AEs of special interest for the purposes of this study, based on the known safety profiles of ceftobiprole and daptomycin:

- Hypersensitivity reactions
- *Clostridium difficile*-associated diarrhea
- Myopathy
- Rhabdomyolysis
- Eosinophilic pneumonia
- Peripheral neuropathy

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 9 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 informed consent has been provided but prior to the start of first study-drug administration, is to be recorded in the CRF as pre-dose medical history (see Section 5.4.2).

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 PTE 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 term '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 SAB.
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 9).
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 PTE 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 leads to a patient's 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 Recording and reporting of serious adverse events and adverse events of special interest

In addition to being reported and followed-up as AEs (see Section 7.3.2.1 and 7.3.2.2), SAEs and AEs of special interest 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:

[redacted]

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 PTE 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 9)

should be reported to the sponsor's designated safety representative using the same forms and procedures as for an SAE (see Section 7.1.3).

Events first occurring after the PTE 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 laws.

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 RSI is Section 6 of the Investigator's Brochure ('Reference safety information for assessment of expectedness of serious adverse reactions').

For daptomycin, 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 EU Summary of Product Characteristics 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 randomization. If results of the pregnancy test are positive (see Section 5.4.4.5), the patient will not be enrolled in the study.

Women of childbearing potential must agree to use one of the following methods of contraception until 7 days after the last dose of study drug:

- 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.
- 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 sample size estimate is based on:

- A point estimate for overall success of 40% in each treatment group in the mITT population
- One-sided alpha level of 0.025
- Power of > 80%
- Non-inferiority margin of 15% for the between-group difference in the primary endpoint

With these assumptions, enrollment of 175 patients per treatment group (total of 350 patients) is required in the mITT population. Assuming that approximately 90% of patients in the ITT population will have confirmed SAB and will therefore be included in the mITT population, 195 patients per group (total of 390 patients) will need to be randomized and receive study treatment.

A sample size of 350 patients in the mITT population (175 per group) will provide at least 80% 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: $P_{daptomycin}$ minus $P_{ceftobiprole} \geq 0.15$ versus H_A: $P_{daptomycin}$ minus $P_{ceftobiprole} < 0.15$

A justification of the non-inferiority margin of 15% is provided in Appendix 8. The assumption of an overall success rate of 40% in each treatment group in the mITT population is based on the respective outcomes in patients with complicated bacteremia from a previous Phase 3 study (Fowler 2006), in which overall success across treatment groups in patients with complicated SAB was 40% (49/121). Using a conservative approach in the sample size calculation, a sample size of 350 patients (175 patients per group) in the mITT population would still provide 80% power for the assessment of the primary endpoint if the overall success rate is 50% instead of 40% (see Appendix 8, Table E3).

The assumption that approximately 90% of patients in the ITT population will have confirmed SAB is based on the result from a previous Phase 3 study (Fowler 2006) in SAB, in which 96% of patients in the ITT population (235 out of 246 patients) were in the mITT population.

8.2 Analysis populations

The following analysis populations are defined for this study:

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

Modified intent-to-treat population (mITT): The mITT population consists of the subset of patients in the ITT population who have received any amount/dose of study medication, and who have a blood culture positive for *S. aureus* at baseline based on a central microbiology laboratory assessment.*

Clinically evaluable population (CE): The CE population consists of the subset of patients in the mITT population who have complied with important aspects of the study, e.g., no major protocol violations, with a completed primary outcome assessment.

Safety population: The safety population consists of all randomized patients who received any amount/dose of study medication. Patients in the safety population will be analyzed according to the first medication 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.

All ITT patients should be followed until complete capture of main study outcomes, including those who did not receive study treatment or had no confirmed SAB by a *S. aureus* blood culture using a standard diagnostic test, or who discontinue the study prematurely.

8.3 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 performed for ceftobiprole versus daptomycin. Exploratory analyses may also be performed.

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

Enrollment, 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 patient populations.

* Patients who are missing a central microbiological assessment may be included in the mITT population if there is documented unequivocal evidence of a baseline blood culture positive for *S. aureus* at the local laboratory.

8.5 Prior and concomitant medication

Prior and concomitant medication will be summarized by treatment group. Additional summaries will be provided of prior and concomitant antibacterial treatment use, including those administered concomitantly for Gram-negative coverage.

8.6 Baseline categories of complicated *Staphylococcus aureus* bacteremia

Six categories of SAB will be summarized by treatment group based on the assessment of the DRC (see Appendix 4):

1. Uncomplicated SAB.
2. Any complicated SAB.
3. SAB in patients undergoing chronic intermittent hemodialysis or peritoneal dialysis.
4. Persistent SAB
5. Forms of complicated SAB with signs or symptoms of metastatic foci of *S. aureus* infection, or other complications including the following (see Section 5.4.5.3.1):
   - ABSSSIs
   - Metastatic infection of native tissue requiring ≤ 42 days of study antibacterial treatment. Examples include but are not limited to:
     - Septic arthritis or bacterial joint infection/empyema
     - Septic or suppurative thrombophlebitis
     - Visceral soft-tissue abscesses requiring ≤ 42 days of study antibacterial treatment
     - Septic pulmonary emboli/infarction
   - Osteomyelitis (including vertebral, sternal, or long-bone osteomyelitis)
   - Epidural or cerebral abscess
6. Definite native-valve RIE and/or LIE, by Modified Duke's Criteria.

8.7 Analysis of the primary endpoint

The primary analysis will be based on the mITT population.

The primary endpoint is overall success at the PTE visit (Day 70±5 days post-randomization) in the mITT analysis set. The DRC will be a group of independent clinical experts, blinded to treatment allocation and not associated with the study conduct, who will review patient profiles, including signs and symptoms of infection, and relevant microbiological and imaging findings, and will assess the patients' clinical and microbiological outcomes (see Appendix 4).

The primary endpoint will be tested for the non-inferiority of ceftobiprole versus daptomycin using a non-inferiority margin of 15%.

Overall success is defined as all of the following criteria being met:

1. Patient alive at Day 70 (±5 days) post-randomization.
2. No new metastatic foci or complications of the SAB infection.
3. Resolution or improvement of SAB-related clinical signs and symptoms.
4. Two negative blood cultures for *S. aureus* (without any subsequent positive blood culture for *S. aureus*):
   - at least one while the patient is on active study treatment; AND
   - confirmed by at least one subsequent negative blood culture for *S. aureus*
     - either in the period between 7 days after the EOT visit and the PTE visit
     - or at the PTE visit

Treatment failure is defined as any of the following:

1. Premature discontinuation of study treatment due to DRC-assessed lack of efficacy (as assessed by the DRC) or for adverse events (AEs) that represent manifestation of disease progression or relapse, at any time between first dose of study drug and the PTE visit.
2. Development of new metastatic or other complications related to SAB (see Section 5.4.5.3.2) between Day 8 and the PTE visit. Development of new metastatic or other complications of SAB prior to Day 8 will be assessed by the DRC on a case-by-case basis to assess whether these constitute a delayed manifestation of the baseline disease or new complications.
3. SAB relapse or reinfection based on evidence from a blood culture positive for *S. aureus* (after documented clearance of *S. aureus* from the bloodstream and clinical improvement) between the EOT and PTE visits.
4. Receipt of systemic non-study antibacterial treatment, other than those permitted under the protocol, for the treatment of SAB. This includes patients who are prematurely discontinued from study therapy due to an AE, but who require continuation of antibacterial treatment for SAB.
5. Treatment of infections other than SAB with systemic non-study antibacterial treatment which is potentially effective against *S. aureus* (see Appendix 5), and which is considered by the DRC to have a relevant impact on the primary endpoint in accordance with the guidelines provided in Appendix 6.
6. Death for any reason between first administration of study drug and the PTE visit.
7. Indeterminate outcome, defined as any data needed to determine whether the outcome is success or failure missing at the PTE visit, including but not limited to:
   a) missing PTE visit, or missing key data to evaluate the primary endpoint
   b) lost-to-follow-up, or patients who withdrew consent prior to the PTE visit
   c) patients not meeting the criteria for Success or Failure, or patients not meeting all criteria for overall success
8. Requirement for systemic antibacterial treatment for SAB beyond EOT

The numbers and percentages of patients with overall success versus overall failure will be determined in each treatment group. The observed difference in percentage of responders at PTE (ceftobiprole group minus the daptomycin group) will be determined and a two-sided 95% confidence interval (CI) for the observed difference will be computed, with adjustment for geographical region (North America, Europe, other regions), dialysis status and prior antibacterial treatment use. Cochran-Mantel-Haenszel weights will be used for the stratum weight 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 two-sided 95% CI for the difference in response rates in the mITT population is greater than −15%, the non-inferiority of ceftobiprole to daptomycin therapy will be concluded.

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

The primary analysis will classify as failures all patients with missing data relevant to appropriate assessment of the primary endpoint at the PTE visit.

A sensitivity analysis will be performed to exclude those patients with missing data completely and this assumes missing at random (MAR). Additional analyses will explore the robustness of the conclusion of the non-inferiority of ceftobiprole to further missingness not at random (MNAR) assumptions. In particular, various proportions of the patients with missing data (10%, 20%, 30% and 40%) in the daptomycin group will be considered successes, while only half of the respective proportions of patients in the ceftobiprole group will be considered successes (5%, 10%, 15%, 20%), and the analysis of non-inferiority repeated for each of the assumed proportions.

Subgroup analyses will be conducted for the primary efficacy outcome in the mITT, 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 SAB category (see Section 8.6), underlying medical conditions, baseline fever status, antibacterial medication prior to study drug, and concomitant antibacterial medication including a separate analysis in patients who received concomitant antibacterial treatment for Gram-negative coverage. Further details are provided in the Statistical Analysis Plan (SAP).

8.8 Analysis of secondary endpoints

Two-sided 95% CIs will be constructed for the observed difference between ceftobiprole and daptomycin therapy for the endpoints of all-cause mortality, microbiological eradication, overall success, and development of new metastatic foci, using the same approach as for the primary endpoint.

In addition, a time-to-event analysis will be performed for all-cause mortality and for time-to-blood-cultures-negative for *S. aureus*.

The following are the secondary endpoints.

8.8.1 Secondary endpoints

1. All-cause mortality (mITT population) at Day 70 (PTE visit)

All-cause mortality will also be assessed at Day 28, and in the ITT population, and will be assessed descriptively.

2. Microbiological eradication (mITT population) at Day 70 (PTE visit)

Microbiological eradication will also be assessed in the CE population, and at Day 4, Day 8, and the EOT visit, and will be assessed descriptively.

Eradication: No growth of the baseline pathogen(s), secondary to an adequate clinical response, based on a negative blood culture while the patient is on active study treatment which is confirmed by at least one subsequent negative blood culture for *S. aureus*, either in the period between 7 days after EOT and the PTE visit, or at the PTE visit.

Failure: Persistence, relapse, or reinfection of *S. aureus* infection, defined as one or more of:

- Ongoing positive blood cultures leading to discontinuation of the study drug
- Subsequent isolation of *S. aureus* from a blood culture after clearance of bacteremia and clinical improvement
  - Relapse: bloodstream infection with the same pathogen isolated at baseline based on genotyping
  - Reinfection: bloodstream infection with a different *S. aureus* strain to that isolated at baseline based on genotyping
- Absence of at least two negative blood cultures (at least one negative blood culture on active study treatment, and at least one post-treatment) to confirm eradication

Relapse or reinfection between EOT and PTE that is reported to the investigator from a healthcare provider not involved in the study (e.g., from another hospital), needs to be thoroughly documented and will be reviewed by the investigator and the DRC for determination.

3. Overall success rate at PTE (CE population)

The overall success rate will also be assessed at the EOT visit in the mITT, ITT and CE populations, and in the ITT population at the PTE visit, and will be assessed descriptively.

See definitions for the primary endpoint above.

4. Development of new metastatic foci or other complications of SAB after Day 7 (mITT population)

Development of new metastatic foci or other complications of SAB after Day 7 will also be assessed in the CE population, and will be assessed descriptively.

Timepoints: Day 8–EOT, and PTE

Newly diagnosed IE or complicated SAB with metastatic foci or other complications of *S. aureus* infection, including metastatic foci in the vertebral column (vertebral abscess,

osteomyelitis, discitis or epidural abscess), cerebral abscess/infarction, splenic abscess/ infarction, renal abscess/infarction, psoas abscess or other deep-tissue abscess, other metastatic infection of native tissue, septic arthritis (or bacterial joint infection/empyema), septic or suppurative thrombophlebitis, and septic pulmonary emboli/infarction.

5. Time to *S. aureus* bloodstream clearance (mITT and CE populations)

Timepoints: Day 3–EOT

Time-to-first-blood-culture-negative for *S. aureus*, confirmed by a second blood-culture-negative for *S. aureus* obtained at least 24 h after the first negative blood-culture.

6. Safety/Tolerability (Safety population)

Timepoints: First dose of study drug–PTE

Incidence, type, severity, and relationship to study medication of AEs; and changes in laboratory tests (hematology, biochemistry including haptoglobin, urinalysis, and Coombs-test).

7. Pharmacokinetics of ceftobiprole (PK population)

Plasma levels of ceftobiprole and the β-lactam ring open product BAL1029

Sparse PK sampling (all patients)

- Day 3: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 4 to 6 h
- Day 12: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 4 to 6 h

Rich PK sampling (selected sites, N=40 ceftobiprole-treated patients [i.e., approximately 80 patients overall])

- Day 3: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 3 h, 4 h, 6 h
- Day 12: pre-dose before the first BPR/PBO infusion, 2 h (end of infusion), 4 to 6 h

Plasma-concentration data will be analyzed at each time point and will be presented as individual concentrations with descriptive statistics (mean, SD, CV%, min, median, max).

8.9 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.

An AE is defined in Section 7.1.2 as an event which occurs from the start of first study-drug administration up to and including the scheduled PTE visit (see also Section 7.3.2). Summary tables of AEs will be provided. (An adverse occurrence after informed consent has been provided but prior to the start of first study-drug administration is to be recorded in the CRF as pre-dose medical history; see Sections 7.1.1 and 7.3.1).

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. Adverse occurrences (as defined in Section 7.1.1) 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.

8.10 Pharmacokinetics

Pharmacokinetic analyses will be based on the PK population. Blood-concentration data will be analyzed at each time point and will be presented as individual concentrations and with descriptive statistics (mean, SD, 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 of demographic and baseline factors such as age, weight, sex, race, and renal function on the PK parameters 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.

8.11 Interim safety analysis

As animal studies have indicated the potential of an increased risk of convulsions with prolonged ceftobiprole therapy (> 4 weeks treatment duration), an initial cohort of patients was enrolled for a maximum treatment duration of 28 days (Cohort 1). An interim safety analysis was performed by an independent DSMB after 80 patients (approximately 40 patients per treatment group) had completed 21–28 days of treatment and safety follow-up. Based on this analysis the treatment duration is extended up to 42 days (Cohort 2), after discussion with the United States FDA.

The decision rules for the DSMB interim safety assessment of Cohort 1 are provided in Appendix 7.

At a minimum, further interim safety assessments will be performed by the DSMB after enrollment of 200 and 300 patients; details are provided in the DSMB Charter.

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 Council for 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 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 must be written after each monitoring visit, per site and per visit. These monitoring reports must be reviewed and approved by the respective supervisors 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 multi-center 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 Guideline 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 treatment or post-treatment phases must be given the new information and a copy of the revised form, and asked to give their consent to continuing in the study.

Blood cultures that were positive for *S. aureus* and were conducted in the context of routine clinical diagnostic work-up practice prior to obtaining informed consent, but were drawn within the 72 h prior to randomization, may be used for the study to determine patient eligibility (see Section 5.2.1). Details of the microbiological work-up are provided in Section 5.2.1 and Table 7.

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 Guideline 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-009 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 27 April 2016 was submitted to the US FDA for special protocol assessment (SPA).
- Protocol Version 2.0 dated 26 August 2016 (synopsis only) was submitted to the US FDA.
- Protocol Version 3.0 dated 30 November 2016 was submitted to the US FDA.
- Protocol Version 4.0 dated 9 February 2017 was submitted to the US FDA for SPA.
- Protocol Version 5.0 dated 20 April 2017 was used for regulatory and IEC/IRB approval for commencement of this clinical study.
- Protocol Version 6.0 dated 25 May 2018 implemented Protocol Amendment 1 dated 25 May 2018.
- Protocol Version 7.0 dated 31 July 2018 implemented Protocol Amendment 2 dated 31 July 2018.
- Protocol Version 8.0 dated 5 April 2019 implemented Protocol Amendment 3 dated 5 April 2019.
- Protocol Version 9.0 dated 27 February 2020 implemented Protocol Amendment 4 dated 27 February 2020.

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13 APPENDICES

Appendix 1 Modified Duke's Criteria for the diagnosis of infective endocarditis

Established in 1994 by the Duke Endocarditis Service and revised in 2000, Duke's Criteria are a collection of major and minor criteria used to establish a diagnosis of infective endocarditis (IE).

These criteria have been adjusted for the definition of SAB, i.e. microbiological criteria related to organisms other than *S. aureus* have been removed. In addition, references to prosthetic valve infections have been removed, as these patients will be excluded from the study.

According to Duke's Criteria, diagnosis of IE can be definite, possible, or rejected.

A diagnosis of IE is definite if either the following pathological or clinical criteria are met:

1. Pathologic criteria:
   - pathologic lesions: vegetation or intracardiac abscess demonstrating active endocarditis on histology, or
   - microorganism: demonstrated by culture or histology of a vegetation or intracardiac abscess
2. One of these combinations of clinical criteria (see definitions below):
   - two major clinical criteria
   - one major and three minor criteria
   - five minor criteria

Diagnosis of IE is possible if one of the following combinations of clinical criteria (see definitions below) are met:

- one major and one minor criteria
- three minor criteria are fulfilled

Diagnosis of IE is rejected if one of the following criteria are met:

- a firm alternate diagnosis is made
- resolution of clinical manifestations after ≤ 4 days of antibacterial treatment
- no pathological evidence of IE is found at surgery or autopsy after antibacterial treatment therapy for ≤ 4 days
- clinical criteria for possible or definite IE are not met

Major criteria for the diagnosis of infective endocarditis

1. Positive blood culture with *S. aureus* from two separate blood cultures
2. Evidence of endocardial involvement with positive echocardiogram defined as
   - oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets in the absence of an alternative anatomic explanation
   - abscess
   - new valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor criteria for the diagnosis of infective endocarditis

1. Predisposing factor: intravenous drug use or presence of a predisposing heart condition (a valve lesion associated with significant regurgitation or turbulence of blood flow)
2. Fever ≥ 38 °C (100.4 °F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages or Janeway lesions
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, Rheumatoid factor
5. A single positive blood culture with *S. aureus*

Table A1 Description of minor criteria

Criterion	Description
Glomerulonephritis	Glomerular disease that usually presents with one of two patterns, nephrotic or nephritic, based upon the urine sediment and the degree of proteinuria.
Janeway lesions	Nontender erythematous macules on the palms and soles (reflecting microabscesses with neutrophil infiltration of capillaries).
Mycotic aneurysm	Abnormal focal arterial dilation due to *S. aureus* infection.
Osler nodes	Tender subcutaneous violaceous nodules mostly on the pads of the fingers and toes, which may also occur on the thenar and hypothenar eminences (assumed to reflect sequelae of vascular occlusion by microthrombi leading to localized immune-mediated vasculitis).
Rheumatoid factor	Antibodies directed against the Fc portion of immunoglobulin G (IgG); commonly measured in clinical practice, is an IgM RF.
Roth spots	Exudative, edematous hemorrhagic lesions of the retina with pale centers (assumed to reflect sequelae of vascular occlusion by microthrombi leading to localized immune-mediated vasculitis).

Appendix 2 Minimum diagnostic requirements for the assessment of deep-seated infections and metastatic or other complications related to *S. aureus* bacteremia (related to Inclusion criterion 8) at baseline

Condition	Minimum diagnostic requirement
ABSSSI	Clinical findings consistent with major wound, abscess, or erysipilas.
Septic arthritis or bacterial joint infection/empyema	Positive culture or Gram stain suggestive of *S. aureus* from arthrocentesis and/or synovial biopsy showing polymorphonuclear leukocytes or causative organism and/or MRI with typical findings for acute intraarticular infection (e.g., combination of bony erosions with marrow edema).
Septic or suppurative thrombophlebitis	Local findings of induration, redness, and tenderness along the course of the vein plus thrombus imaging using duplex ultrasound for peripheral septic or suppurative thrombophlebitis; CT*, MRI, ultrasound for pelvic vein, portal vein, superior or inferior vena cava, internal jugular vein or other veins.
Visceral soft-tissue abscesses requiring ≤ 42 days of study antibacterial treatment	Positive imaging finding based on CT (including PET/CT)* and/or MRI and/or ultrasound and/or positive culture (e.g., through drainage).
Septic pulmonary emboli/infarction	The diagnosis of a septic pulmonary embolism will be made by the investigator based on clinical symptoms of fever, cough, sputum/hemoptysis in the presence of an extrapulmonary infection, sepsis, or risk factors for septic emboli (e.g., intravenous drug use) and will be based on the following radiological signs: Contrast-enhanced CT (preferred): Peripheral and/or subpleural multifocal nodular lesions (in different stages of cavitation) or wedge-shaped infiltrates – with/without a feeding vessel sign (vessel leading to the nodule) – with/without pleural effusion or features suggestive of pleural empyema Non-contrast enhanced CT (e.g., in patients with a contraindication for contrast administration): Peripheral and/or subpleural multifocal nodular lesions (in different stages of cavitation) or wedge-shaped infiltrates – with/without pleural effusion or features suggestive of pleural empyema Plain X-ray (e.g., in patients unable to undergo a CT): Multifocal nodular densities or wedge-shaped infiltrates in varying stages of cavitation with or without pleural effusion or features suggestive of pleural empyema

* Radioisotope studies (e.g., PET or PET-CT) may be conducted as an adjunct to diagnosis, as primary diagnostic approach, or when radiographic changes on MRI or CT scans are absent or equivocal.

Abbreviations: ABSSSI=acute bacterial skin and skin structure infection; CT=computed tomography; PET/CT=positron emission tomography/computed tomography; MRI=magnetic resonance imaging.

Appendix 3 Minimum diagnostic requirements for the assessment of deep-seated infections and metastatic or other complications related to *S. aureus* bacteremia post-baseline

Condition	Minimum diagnostic requirement
Metastatic foci in the vertebral columns (vertebral abscess, osteomyelitis, discitis or epidural abscess)	Positive imaging finding based on CT (including PET/CT)* and/or MRI and/or positive biopsy/culture
Cerebral abscess or infarction	Positive imaging finding on MRI and/or contrast CT (including PET/CT)* and/or positive biopsy/culture
Splenic abscess or infarction	Positive imaging finding based on ultrasound and/or contrast CT (including PET/CT)* and/or MRI and/or positive culture (e.g., from samples obtained during surgery)
Renal abscess or infarction	Positive imaging finding based on ultrasound and/or contrast CT (including PET/CT)* and/or MRI and/or positive culture (e.g., through drainage or urine)
Psoas abscess	Positive imaging finding based on ultrasound and/or contrast CT (including PET/CT)* and/or positive culture (e.g., through drainage)
Other metastatic infection of native tissue	Positive imaging finding based on CT (including PET/CT)* and/or MRI and/or ultrasound and/or positive biopsy/culture
Septic arthritis or bacterial joint infection/empyema	Positive culture or Gram stain suggestive of *S. aureus* from arthrocentesis and/or synovial biopsy showing polymorphonuclear leukocytes or causative organism and/or MRI with typical findings for acute intraarticular infection (e.g., combination of bony erosions with marrow edema)
Septic or suppurative thrombophlebitis	Local findings of induration, redness, and tenderness along the course of the vein plus thrombus imaging using duplex ultrasound for peripheral septic or suppurative thrombophlebitis; CT*, MRI, ultrasound for pelvic vein, portal vein, superior or inferior vena cava, internal jugular vein, or other veins.
Septic pulmonary emboli/infarction	The diagnosis of a septic pulmonary embolism will be made by the investigator based on clinical symptoms of fever, cough, sputum/hemoptysis in the presence of an extrapulmonary infection, sepsis, or risk factors for septic emboli (e.g., intravenous drug use) and will be based on the following radiological signs: Contrast-enhanced CT (preferred): Peripheral and/or subpleural multifocal nodular lesions (in different stages of cavitation) or wedge-shaped infiltrates – with/without a feeding vessel sign (vessel leading to the nodule) – with/without pleural effusion or features suggestive of pleural empyema Non-contrast enhanced CT (e.g., in patients with a contraindication for contrast administration): Peripheral and/or subpleural multifocal nodular lesions (in different stages of cavitation) or wedge-shaped infiltrates – with/without pleural effusion or features suggestive of pleural empyema Plain X-ray (e.g., in patients unable to undergo a CT): Multifocal nodular densities or wedge-shaped infiltrates in varying stages of cavitation with or without pleural effusion or features suggestive of pleural empyema

* Radioisotope studies (e.g. PET or PET-CT) may be conducted as adjunct to diagnosis, as primary diagnostic approach or when radiographic changes on MRI or CT scans are absent or equivocal.

Appendix 4 DRC process

The DRC process is briefly outlined below. More details are provided in the DRC Charter.

Role of the DRC

For each patient randomized in study BPR-CS-009 who has confirmed SAB based on a blood culture obtained within 72 h prior to randomization and who has received study medication (the mITT population), the Data Review Committee will adjudicate, independently from the sponsor and the study investigators:

- the diagnosis (SAB, complicated forms of SAB, uncomplicated SAB)
- the response to study treatment (overall success or failure)
- for deaths occurring during the study, a blinded assessment of the attribution of death to the SAB or to another cause

Organization and communication

The DRC will comprise independent experts with experience in the diagnosis and management of patients with SAB. The DRC Chair will be responsible for final sign-off of the Charter on behalf of all DRC members, and for working with the sponsor to manage any procedural or other issues that may be raised by DRC members throughout the DRC process. Each DRC member will remain blinded to patient treatment assignment until the study is completed.

Review of patient data

Each patient randomized in study BPR-CS-009 who has confirmed SAB based on a blood culture obtained within 72 h prior to randomization and who has received study medication, will be reviewed independently by a minimum of two DRC members. Signs and symptoms will be assessed by the investigator on a predefined scale to assess whether signs and symptoms have resolved or improved from baseline or are unchanged or worsened, and this scaled assessment will be reviewed by the DRC. For each case, one DRC member will be designated as the primary reviewer, and one DRC member as the secondary reviewer.

Case assessment is to be initiated when the data for a given patient are considered clean. The Data Management Group will generate patient profiles, which will be assigned to DRC reviewers. Patient profiles will include all data relevant to assessment of the SAB baseline condition and the response to study treatment (overall success or failure), including medical history, demographics, prior and ongoing therapy and concomitant non-drug procedures, vital signs, physical examination, microbiological and laboratory results, investigator-assessed clinical signs and symptoms of complicated SAB, evidence of metastatic or other complications of SAB, modified Duke's criteria, and AEs.

The DRC may request supporting information or source documentation via the Basilea DRC Manager or designee, as needed. These requests will be forwarded to the investigator for a response. The blinded sponsor's Clinical Program Manager or designee will be responsible for tracking queries, ensuring their resolution in a timely manner, and providing the site response to the DRC.

Radiological imaging results (e.g., CT, MRI, ultrasound) will be captured in a consistent way across all study sites using a standardized form which includes method details, summary of results and assessments. These forms will be provided to the DRC members as part of the patient profiles.

The DRC members will review, independently from each other, the data for the assigned patients, and will give their opinion on the diagnosis and classification of the SAB (Table B1), and the response assessment (overall success or failure) at the PTE visit (Table B2).

A successful outcome will be defined as the normalization of all (resolution) or some (improvement) baseline symptoms, without deterioration in any baseline symptoms or the occurrence of any new symptoms. Patients in whom no improvement or resolution of symptoms is observed (i.e., whose baseline symptoms remain unchanged or worsen) will be considered failures.

In addition, for deaths occurring during the study, a blinded assessment of the attribution of death to the SAB or to another cause will be performed by the DRC members.

Reconciliation and finalization of DRC assessments

The DRC reviewers will enter their individual assessments into an electronic CRF system. Once the database contains the individual assessments of the assigned DRC reviewers, the sponsor or a designated third party will compare the DRC members' assessments for consensus, and provide the reviewers and the DRC Chair with a concordance report. Each case will be discussed at a consensus meeting which includes at least three DRC members, including the DRC Chair and the assigned primary and secondary reviewers of the cases to be adjudicated. If necessary, the DRC Chair may decide that a case should be deferred for discussion with additional DRC members or with the full DRC.

The primary reviewer will be responsible for presenting each case to the DRC for discussion. When possible, the DRC reviewers should reach a consensus on an overall DRC opinion. However, if consensus is not reached, the majority opinion will prevail, and if there is no majority opinion, the opinion of the DRC Chair will prevail.

The final opinion of the DRC is to be entered into the CRF by the assigned primary reviewer.

Table B1 Confirmation and baseline classification of the diagnosis of SAB

	Criterion	Source for assessment by the DRC
1	Uncomplicated SAB	Clinical database/patient profiles: • Medical history and demographics, prior and ongoing therapy • Vital signs • Physical examination • Laboratory assessments • Investigator-assessed clinical signs and symptoms of complicated SAB • Investigator-assessed evidence of metastatic or other complications of SAB, including examinations regarding intravascular or extravascular devices and foreign materials Central and local microbiology laboratory reports Structured imaging reports Modified Duke's criteria
2	Any complicated SAB	
3	SAB in patients undergoing chronic intermittent hemodialysis or peritoneal dialysis	Patients meeting the criteria for complicated SAB who have a medical history of undergoing chronic intermittent hemodialysis or peritoneal dialysis
4	Persistent SAB	Central and local microbiology laboratory reports
5	Forms of complicated SAB with signs or symptoms of metastatic foci of *S. aureus* infection, or other complications	Clinical database/patient profiles: • Vital signs • Physical examination • Laboratory assessments • Investigator-assessed clinical signs and symptoms of complicated SAB • Investigator-assessed evidence of metastatic or other complications of SAB Central and local microbiology laboratory reports Structured imaging reports
6	Definite native-valve RIE, by Modified Duke's Criteria.	Modified Duke's criteria

Table B2 Efficacy response assessments at the PTE visit (overall success or failure)

	Success criterion	**Source for assessment by the DRC**
1	Patient alive at Day 70 (± 5 days) post-randomization.	Clinical database/patient profiles: • Vital status
2	No new metastatic foci or complications of the SAB infection.	Clinical database/patient profiles: • Investigator-assessed clinical signs and symptoms of complicated SAB • Investigator-assessed evidence of metastatic or other complications of SAB • Laboratory assessments Central and local microbiology laboratory reports Structured imaging reports
3	Resolution or improvement of SAB-related clinical signs and symptoms.Signs and symptoms will be assessed by the investigator on a predefined scale to assess whether signs and symptoms have resolved or improved from baseline or are unchanged or worsened.	Clinical database/patient profiles: • Investigator-assessed clinical signs and symptoms of complicated SAB • Vital signs • Physical examination • Laboratory assessments
4	Two negative blood cultures for *S. aureus* (without any subsequent positive blood culture for *S. aureus*): • at least one while the patient is on active study treatment; AND • confirmed by at least one subsequent negative blood culture for *S. aureus* – either in the period between 7 days after the EOT visit and the PTE visit – or at the PTE visit	Clinical database/patient profiles: • Study treatment duration information Central and local microbiology laboratory reports
	Failure criterion	**Source for assessment by the DRC**
1	Premature discontinuation of study treatment due to DRC-assessed lack of efficacy (e.g., worsening of signs and symptoms) or for an AE that represents manifestation of disease progression or relapse, at any time between first dose of study drug and the PTE visit.	Clinical database/patient profiles: • Study treatment duration information • Study completion information and/or investigator-assessed reason for premature study discontinuation • Laboratory assessments • AEs • Investigator-assessed clinical signs and symptoms of complicated SAB • Investigator-assessed evidence of metastatic or other complications of SAB • Laboratory assessments Central and local microbiology laboratory reports Structured imaging reports
2	Development of new metastatic or other complications related to SAB (see Section 5.4.5.3.2) between Day 8 and the PTE visit. (Development of new metastatic or other complications of SAB prior to Day 8 is to be assessed by the DRC on a case-by-case basis to assess whether these constitute a delayed manifestation of the baseline disease or new complications).	
3	SAB relapse or reinfection based on evidence from a positive blood culture (after documented clearance of *S. aureus* from the bloodstream and clinical improvement) between the EOT and PTE visits.	

	Failure criterion	**Source for assessment by the DRC**
4	Receipt of systemic non-study antibacterial treatment, other than those permitted under the protocol, for the treatment of SAB. This includes patients who are prematurely discontinued from study therapy due to an AE, but who require continuation of antibacterial treatment for SAB.	Clinical database/patient profiles: • Study treatment duration information • Concomitant medication with information on the indication for which the medication was used • Study completion information and/or investigator-assessed reason for premature study discontinuation • AEs
5	Treatment of infections other than SAB with systemic non-study antibacterial treatment which is potentially effective against *S. aureus* (see Appendix 6), and which is considered by the DRC to have a relevant impact on the primary endpoint in accordance with the guidelines provided in Appendix 7.	Clinical database/patient profiles: • Study treatment duration information • Concomitant medicationswith information on the indication for which the medication was used DRC assessment to be based on the process described in Appendix 7.
6	Death for any reason between first administration of study drug and the PTE visit.	Clinical database/patient profiles: • Study treatment duration information • Vital status information
7	Indeterminate outcome, defined as any data needed to determine whether the outcome is success or failure missing at the PTE visit, including but not limited to: a) missing PTE visit, or missing key data to evaluate the primary endpoint b) lost-to-follow-up, or withdrawal of consent prior to the PTE visit c) not meeting the criteria for success or failure, or not meeting all criteria for overall success	Clinical database/patient profiles: • Study treatment duration information • Study completion information • Missing PTE visit, or missing relevant microbiology laboratory or imaging data
8	Requirement for systemic antibacterial treatment for SAB beyond EOT.	CRF: Clinical database/patient profiles: • Study treatment duration information • Concomitant medication with information on the indication for which the medication was used • Study completion information and/or investigator-assessed reason for premature study discontinuation

Appendix 5 Systemic antibacterial treatments considered to be potentially effective against *S. aureus*

Half-life ≤ 12 h		Half-life > 12 h
Amoxicillin	Dicloxacillin	Azithromycin
Amoxicillin/Clavulanic acid	Doripenem	Dalbavancin
Ampicillin	Ertapenem	Doxycycline
Ampicillin/Sulbactam	Erythromycin	Linezolid
Cefaclor	Flucloxacillin	Minocycline
Cefadroxil	Fosfomycin	Oritavancin
Cefamandole	Gemifloxacin	Tigecycline
Cefazolin	Imipenem/cilastatin	Teicoplanin
Cefdinir	Levofloxacine	Omadacycline
Cefditoren pivoxil	Loracarbef	
Cefepime	Meropenem	
Cefixime	Meropenem/vaborbactam	
Cefoperazone	Mezlocillin	
Cefotaxime	Moxifloxacin	
Cefotetan	Nafcillin	
Cefoxitin	Ofloxacin	
Cefpodoxime proxetil	Oxacillin	
Cefprozil	Penicillin G	
Ceftaroline fosamil	Penicillin V	
Ceftazidime	Piperacillin	
Ceftazidime/avibactam	Piperacillin/tazobactam	
Ceftibuten	Quinupristin/dalfopristin	
Ceftizoxime	Rifampin	
Ceftolozane/tazobactam	Tedizolid	
Cetriaxone	Telavancin	
Cefuroxime	Telithromycin	
Cephalexin	Tetracycline	
Chloramphenicol	Ticarcillin	
Ciprofloxacin	Ticarcillin/clavulanate	
Clarithromycin	Trimethoprim	
Clindamycin	Trimethoprim-sulfamethoxazole	
Daptomycin	Vancomycin	
Delafloxacin		

Note: The table should be considered as a general guide for potentially effective antibacterials against *S.aureus*, without differentiation between MSSA and MRSA.
Oral vancomycin is considered a non-systemic antibiotic and may be used at any time during the study.

Appendix 6 DRC assessment of potentially-effective antibacterial treatment

Each patient enrolled in study BPR-CS-009 who has received at least one dose of study drug is to be reviewed by at least two members of the DRC. The DRC comprises experts in the field of SAB who will review, independently of each other, the data for the assigned patients related to categorization of the SAB (uncomplicated or complicated), and to the primary and selected secondary endpoints. Details of these DRC assessments are provided in the DRC charter.

In addition to these functions, the DRC is also required to review and assess the impact on the primary endpoint of potentially effective concomitant systemic antibacterial treatment received by patients enrolled in the study. This assessment must take into account:

1. The susceptibility of the SAB-causing *S. aureus* strain to the concomitantly-administered antibacterial agent, and
2. The clinical status of the patient (improved or cured, versus ongoing, unchanged, or worsened SAB) at the time of concomitant use of the antibacterial treatment, and
3. The duration of the concomitantly-administered antibacterial treatment.

The use of systemic non-study antibacterial treatment is not considered to impact the primary outcome if any of the following conditions apply (see Table C1):

- The *S. aureus* strain causing the SAB is not susceptible to the concomitantly-administered antibacterial agent.
- The patient is clinically improving or cured, and received the concomitant antibacterial agent for no more than the maximum allowable duration shown in Table C1.
- The patient is clinically not improving, and has received no more than a single dose of a non-study antibacterial agent.

All other instances of the use of concomitant systemic non-study antibacterial treatment should be assessed by the DRC as an outcome of failure for the primary endpoint, unless it is the opinion of all DRC members that the overall clinical context strongly indicates that the concomitant non-study systemic antibacterial did not impact the primary outcome.

Any deviation by the DRC from the algorithm described above must be clearly documented, including the rationale for the DRC's assessment.

The following is the rationale for these stipulations:

- Concomitant treatment with a non-study antibacterial agent to which the *S. aureus* strain causing the SAB is not susceptible is not expected to influence outcomes related to the SAB.

- If study treatment has already led to clinical improvement prior to receiving systemic non-study antibacterial treatment (to which the *S. aureus* strain causing the SAB is susceptible), then the effect of the study treatment may still be considered a successful outcome, depending on the timing and extent of the non-study antibacterial treatment
- If study treatment has not led to clinical improvement prior to receiving systemic non-study antibacterial treatment (to which the *S. aureus* strain causing the SAB is susceptible) then only a minimal amount of non-study antibacterial treatment should be allowable: i.e., any administration of more than a single dose of another antibiotic (which may have been administered e.g., for surgical prophylaxis, or given inadvertently) would mean the patient is considered a failure.

The proposed decision rules related to concomitant systemic non-study antibacterial treatments are summarized in Table C1.

Table C1 Maximum duration of concomitant systemic non-study antibacterial treatment that would permit a non-failure classification by the DRC

1. *S. aureus* strain causing SAB is <u>not</u> susceptible to antibacterial agent			
Concomitant antibiotic will not impact assessment of failure.			
2. *S. aureus* strain causing SAB is susceptible to antibacterial agent			
Study treatment period	<u>Patient clinically improved or cured</u>		<u>Patient clinically unchanged or worsened</u>
	sABT $t_{1/2}$ ≤ 12 h*	sABT $t_{1/2}$ > 12 h*	sABT $t_{1/2}$ ≤ 12 or > 12 h
Day 1 – 7	≤ 1 day#	≤ a single dose	≤ a single dose
Day 8 – 14	≤ 2 days#	≤ 1 day#	≤ a single dose
Day 15 – 28	≤ 4 days#	≤ 2 days#	≤ a single dose
Day 29 – 42	≤ 6 days#	≤ 4 days#	≤ a single dose

*See Appendix 5# ≤ specified days of the maximum approved daily dose according to the US prescribing information
sABT=systemic antibacterial treatment.

Appendix 7 DSMB Process and decision criteria for DSMB interim safety assessment of Cohort 1 and at subsequent DSMB meetings

1. Overview of the Data and Safety Monitoring Board process

Independent DSMB

An independent Data and Safety Data Monitoring Board (DSMB) will be commissioned by the sponsor to evaluate accumulating safety data in patients enrolled in study BPR-CS-009, to ensure the safety of the patients in the study, and to provide recommendations to the clinical teams in charge of conducting the study.

The DSMB will comprise one or several experts in the field of infectious diseases, at least one member with expertise in the assessment of convulsion events, and at least one expert in statistics. All DSMB members will disclose their financial interests to the sponsor. None of the DSMB members may be involved in the conduct or reporting of any ongoing Basilea clinical study.

DSMB statistics Group

The DSMB Statistics Group (DSG) will be a separate statistics/data management group, which is independent of the blinded study statistician and the data management group. The DSG will receive study data from the blinded statistician and the data management group, and will separately receive patient treatment assignment data from the IWRS vendor. The data from the blinded study statistician and data management group, including all summary tables and listings specified in the DSMB statistical analysis plan, will use dummy randomization codes to maintain full blinding of the study. The DSG will then re-generate the summary tables and listings using true treatment assignments received from the IWRS vendor, and will mark treatment groups as A or B in the data presentation and distribute them to the DSMB members. DSMB members will also be separately provided with the actual treatment group assignment, i.e., will receive a separate notification whether group A is the ceftobiprole group or the daptomycin group, to enable a fully unblinded assessment by the DSMB.

Outputs provided to the DSMB members will include (but are not limited to):

- Cumulative patient enrollment and patient exposure, and enrollment by center
- Demographic description of the study cohort
- Reasons for premature study discontinuation
- Serious adverse events (including deaths) and non-serious AEs by Preferred Term and System Organ Class, subclassified by severity and relatedness to study drug
- Convulsion events (including narratives)

- Other events of special interest for ceftobiprole and/or daptomycin based on the known safety profile of both compounds:
  - Hypersensitivity reactions
  - *Clostridium difficile*-associated diarrhea
  - Myopathy
  - Rhabdomyolysis
  - Eosinophilic pneumonia
  - Peripheral neuropathy

The DSMB chair will receive:

- SUSARs as 7-day or 15-day reports
- Adverse events of special interest that do not qualify as SUSARs within 15 days of the investigator becoming aware of the event
- Other SAEs on a quarterly basis
- Non-serious AEs for scheduled or ad hoc DSMB meetings

Details of analyses provided to the DSMB will be specified in the DSMB statistical analysis plan.

Convulsion event assessment by the investigator and the DSMB

Convulsion events will be assessed as reported by the investigator using the Standard MedDRA Query 'Convulsions (narrow)'.

In addition, convulsion events will be independently adjudicated by a member of the DSMB with expertise in the assessment of convulsion events, to permit an assessment of these events according to uniform criteria. Results of both the investigator-assessed convulsions and the DSMB-adjudicated events of convulsions will be separately analyzed and presented.

DSMB-adjudicated events of convulsions will be the primary analysis.

Expedited reporting of adverse events of special interest to the DSMB

All convulsion events will be considered SAEs, and reporting of these events from the investigator to the sponsor will be expedited (reporting within 24 h of awareness of the investigator); these events will then be forwarded to the DSMB within 15 days of receipt by the sponsor.

The timelines outlined in Table D1 will apply to informing the DSMB about other AEs of special interest.

Table D1 Timelines for reporting adverse events to the DSMB

Type of adverse event	Reporting timeline to DSMB
SUSAR	7-day or 15-day reports, as required by applicable regulations
Adverse event of special interest	Within 15 days (unless to be reported as a 7-day SUSAR)
Non-SUSAR/non-special interest SAE	Every 3 months
Other non-serious AE	At each DSMB meeting

DSMB meetings

Following a first organizational meeting, the need for DSMB data review meetings will be assessed on a 3-monthly basis between the DSMB Chair and the sponsor, with meetings scheduled based on patient enrollment. At a minimum, DSMB meetings will take place after enrollment of:

- 60 patients who received at least 21 days of study treatment, if no convulsion events were observed in the ceftobiprole group or
- 80 patients who received at least 21 days of study treatment, if at least one-convulsion event was observed in the ceftobiprole group
- 200 patients
- 300 patients

The DSMB will review the data received, and at any time the DSMB Chair may convene an ad hoc DSMB meeting, or request unblinded patient information.

For AEs of special interest, the DSMB chair should consider convening a DSMB meeting, using the criteria in Table D2 as guidance.

Table D2 Thresholds for convening a DSMB meeting for adverse events of special interest

Adverse event of special interest	Frequency (%) threshold for convening a DSMB meeting*	Threshold number of events for convening a DSMB meeting*
Rhabdomyolysis	NA	≥ 2
Convulsions	NA	≥ 3
Hypersensitivity reactions	≥ 1% of SAEs	≥ 2 SAEs
Clostridium difficile-associated diarrhea	≥ 2 %	≥ 2
Myopathy	≥ 2 %	≥ 3 SAEs
Peripheral neuropathy	≥ 2 %	≥ 3 of moderate or severe intensity
Eosinophilic pneumonia	≥ 1 %	≥ 2

*A DSMB meeting should be convened if both the frequency (%) threshold (if applicable) AND the threshold number of events are met.

It should be noted that the DSMB will receive cases of convulsions on an expedited basis (see above), and will be consulted as needed to assess any relevant emerging safety signal.

DSMB members are expected to participate in each meeting, preferably in person; however, if the DSMB members cannot meet in person, meetings may be held by videoconference or teleconference.

The DSMB meeting may begin with an open session followed by a closed session. Investigators or experts serving as *ad hoc* advisors may be requested to attend the open session of the meeting, during which only blinded data are discussed. The closed session will be limited to the DSMB members and designated staff from the DSG for the presentation of unblinded data. At the request of the DSMB, the sponsor's Head of Global Drug Safety may also be invited to closed DSMB sessions.

DSMB meeting minutes

DSMB meeting minutes and the DSMB Meeting Report summarizing the conclusions and recommendations of the DSMB are to be drafted after each meeting, without any reference to unblinded data. The DSMB Chair will oversee finalization of the DSMB meeting minutes and the DSMB Meeting Report and will sign both documents The DSMB meeting minutes should include important considerations that led to the DSMB recommendations; the meeting minutes will not be sent to the sponsor until after the completion of this study, and database lock of the relevant clinical database. The DSMB Meeting Report, which is sent to the sponsor's Head of Global Drug Safety, will include DSMB conclusions and recommendations without reference to unblinded data.

2. Overview of the decision criteria for the DSMB regarding the interim safety assessment of Cohort 1

After finalization of the study treatment and post-treatment observation period of 80 patients who received at least 21 days of study treatment, the DSMB will review the unblinded safety data of this initial Cohort 1, and provide a decision whether:

- The study can continue, with or without additional safety measures
- The maximum study drug treatment duration can be extended from 28 to 42 days

3. Decision Rules 1 and 2

Decision Rules 1 and 2 are not binding. They may be used as a guide which can be considered by the DSMB in making the safety-related decision to assess whether an extension of the maximum study drug treatment duration from 28 days (Cohort 1) to 42 days (Cohort 2) is justified.

Decision rule 1 is based on the number of ceftobiprole-treated patients with convulsion events during treatment Weeks 3–4 (Period 2) versus treatment Weeks 1–2 (Period 1). A threshold of $p \leq 0.1$ (one-sided) for the difference in the number of patients with events (Period 2 − Period 1) will be used to guide the decision on whether the study continues from Cohort 1 to Cohort 2.

Decision rule 2 is based on the number of ceftobiprole-treated patients with convulsion events during the entire 28-day treatment period for Cohort 1. The difference in the number of patients with events observed in this study (BPR-CS-009) versus the expected number of convulsions based on the pooled Phase 3 pneumonia studies (CAP-3001 and BAP248/307) will be used to guide the decision on whether the study continues from Cohort 1 to Cohort 2, with a threshold of ≥ 2 patients (difference observed versus expected) with convulsion events.

Decision rule 2 (convulsion events over the entire 28-day period) will take into account the convulsion rate observed in daptomycin-treated patients. As daptomycin has not been associated with drug-related convulsions, convulsion events observed with daptomycin in this study will be considered to be reflective of the background rate of convulsions in the study population of SAB patients. An adjustment for daptomycin events will not be performed for Decision rule 1 because the temporal distribution of background convulsion events may be different from the temporal distribution of ceftobiprole-related convulsion events, e.g., background events could occur predominantly early during treatment when patients are more sick, and ceftobiprole-related events could occur predominantly later during treatment.

Decision rule 1: Convulsion events in Period 2 versus Period 1 in the ceftobiprole group

Under Decision Rule 1, a comparison of Period 2 (Weeks 3–4) versus Period 1 (Weeks 1–2) would be based on:

- the observed convulsion events within the first 14 days of treatment (Period 1), using the expected total N=60 patients in the ceftobiprole group in Cohort 1 as denominator
- the observed convulsion events within Days 15–28 of treatment (Period 2), using an expected n=45 patients in the ceftobiprole group with >14 days of treatment in Cohort 1 as denominator

A '$p \leq 0.1$' (1-sided Fisher's exact test) threshold would result in the following example decisions:

Ceftobiprole events Period 2 (n/N)	**Ceftobiprole events Period 1** (n/N)	**p-Value**	**Decision**
1/45	0/60	0.43	Continue to Cohort 2
2/45	0/60	0.18	Continue to Cohort 2
3/45	0/60	**0.08**	Additional safety review (based on Decision rule 1)
2/45	1/60	0.39	Continue to Cohort 2
3/45	1/60	0.21	Additional safety review (based on Decision rule 2)
4/45	1/60	0.11	Additional safety review (based on Decision rule 2)
5/45	1/60	0.05	Additional safety review (based on Decision rules 1+2)

Decision rule 2: Convulsion events in the entire 28-day study period

Under Decision Rule 2, the second assessment would be based on the total number of ceftobiprole-treated patients with convulsion events observed in the entire 28-day period.

In the pooled pneumonia studies (CAP-3001 and BAP248/307), the rate of convulsion events in the ceftobiprole group was 0.00196 events per study drug treatment day. With this rate, a total of 2 convulsion events would be expected under the following assumptions regarding days of treatment for the 60 patients treated with ceftobiprole in Cohort 1:

Days of treatment (average)	No. of patients
28	10
21–27 (24)	30
15–20 (17)	5
1–14 (7)	15

This scenario would result in a total of 1190 treatment days, and an expected number of 2 convulsion events at the rate of 0.00196 convulsion events per treatment day observed in the pooled pneumonia studies.

A difference of ≥ 2 'observed minus expected' convulsion events with ceftobiprole (adjusted for daptomycin events) would suggest grounds for an additional safety review, regardless of the outcome under Decision rule 1 ('P2 versus P1'), resulting in the following example decisions:

Cefto-biprole events P2 (n/N)	**Cefto-biprole events P1** (n/N)	**Cefto-biprole events** (total)	**Dapto-mycin events*** (total)	**Ceftobiprole events Diff vs expected** (corrected for daptomycin)	**Decision**
2/45	0/60	2/60	0	0	Continue to Cohort 2
2/45	1/60	3/60	0	1	Continue to Cohort 2
2/45	2/60	4/60	0	**2**	Additional safety review (Decision rule 2)
3/45	0/60	3/60	0	1	Additional safety review (Decision rule 1)
2/45	2/60	4/60	1	1	Continue to Cohort 2
2/45	3/60	5/60	1	**2**	Additional safety review (Decision rule 2)

*Ceftobiprole convulsion events observed in the entire 28-day treatment period will be corrected by the number of observed events in the daptomycin group, i.e. '(ceftobiprole minus daptomycin events)'

4. Early decision to continue to Cohort 2

If no events of convulsion have been observed after treatment of a total of 80 patients with approximately 60 patients treated for 21–28 days, the likelihood of observing three events of convulsion in the remaining 40 patients (assuming 120 patients would need to be enrolled for 80 patients to be treated for 21–28 days) is low (one-sided p-value = 0.04). A situation of no convulsion events in 80 patients may therefore allow for a DSMB recommendation of an early decision to continue to Cohort 2.

If one convulsion event has been observed after treatment of 80 patients in total and 60 patients treated for 21–28 days, then the DSMB will be unblinded to the treatment allocation of this patient; if the patient was in the daptomycin group, this may allow for a DSMB recommendation to proceed to Cohort 2. In this scenario, the likelihood of observing three events of convulsion in the remaining 20 patients in the ceftobiprole group, having seen no events among the first 40 patients in that group, is also low (one-sided p-value = 0.03).

The same process will apply if two convulsion events have been observed after treatment of 80 patients in total and 60 patients treated for 21–28 days; if the convulsion events were both in patients in the daptomycin group, this may allow for a DSMB recommendation to proceed to Cohort 2.

5. DSMB reviews after completion of Cohort 1

After completion of Cohort 1, for subsequent safety reviews, interim unblinded DSMB safety analyses are planned after enrollment of 200 and 300 patients.

In addition, an *ad hoc* DSMB meeting will be organized if the convulsion rate in the entire study population, or the rate of another event of special interest (hypersensitivity reactions, *Clostridium difficile*-associated diarrhea, myopathy, rhabdomyolysis, eosinophilic pneumonia, or peripheral neuropathy) first exceeds the threshold provided in Table D2.

The assessment of convulsions after completion of Cohort 1 would follow similar principles to those described for the assessment of Cohort 1, i.e., an analysis of convulsion events would be based on a comparison of early versus late-onset convulsion events, and an assessment of convulsion events across the entire treatment period up to 42 days.

Further details are provided in the DSMB Charter.

Appendix 8 Justification of the non-inferiority margin

Determination of M1

M1 is defined as the entire effect of the active control assumed to be present, i.e., the effect of the active control compared with placebo.

Outcome (mortality) in untreated SAB patients

In the absence of placebo-controlled studies in SAB, literature from the pre-penicillin era (i.e., prior to 1942) was reviewed to determine the clinical outcome of patients with SAB who did not receive antibacterial treatment. As a standard search in Pubmed did not result in a consistent list of potentially relevant publications, these were derived from the reference lists of three review articles describing SAB outcomes in the pre-penicillin era: Mendell, 1939 (Mendell 1939), Spink and Hall, 1944 (Spink 1945), and Di Fiore, 1956 (Di Fiore 1956).

From these review articles, seven original articles were identified that described outcomes in case series of SAB in patients who did not receive antibacterial treatments: Lowenstein, 1936 (Lowenstein 1936), MacNeal and Frisbee, 1936 (MacNeal 1936), Mendell, 1939 (Mendell 1939); Neuhof, 1934 (Neuhof 1934); Rosenow et al., 1938 (Rosenow 1938); Scott, 1935 (Scott 1935); and Skinner and Keefer, 1941 (Skinner 1941). The characteristics of these studies are summarized in Table E1.

It should be noted that clinical/overall success was not separately reported in these studies and that survival in itself was considered success.

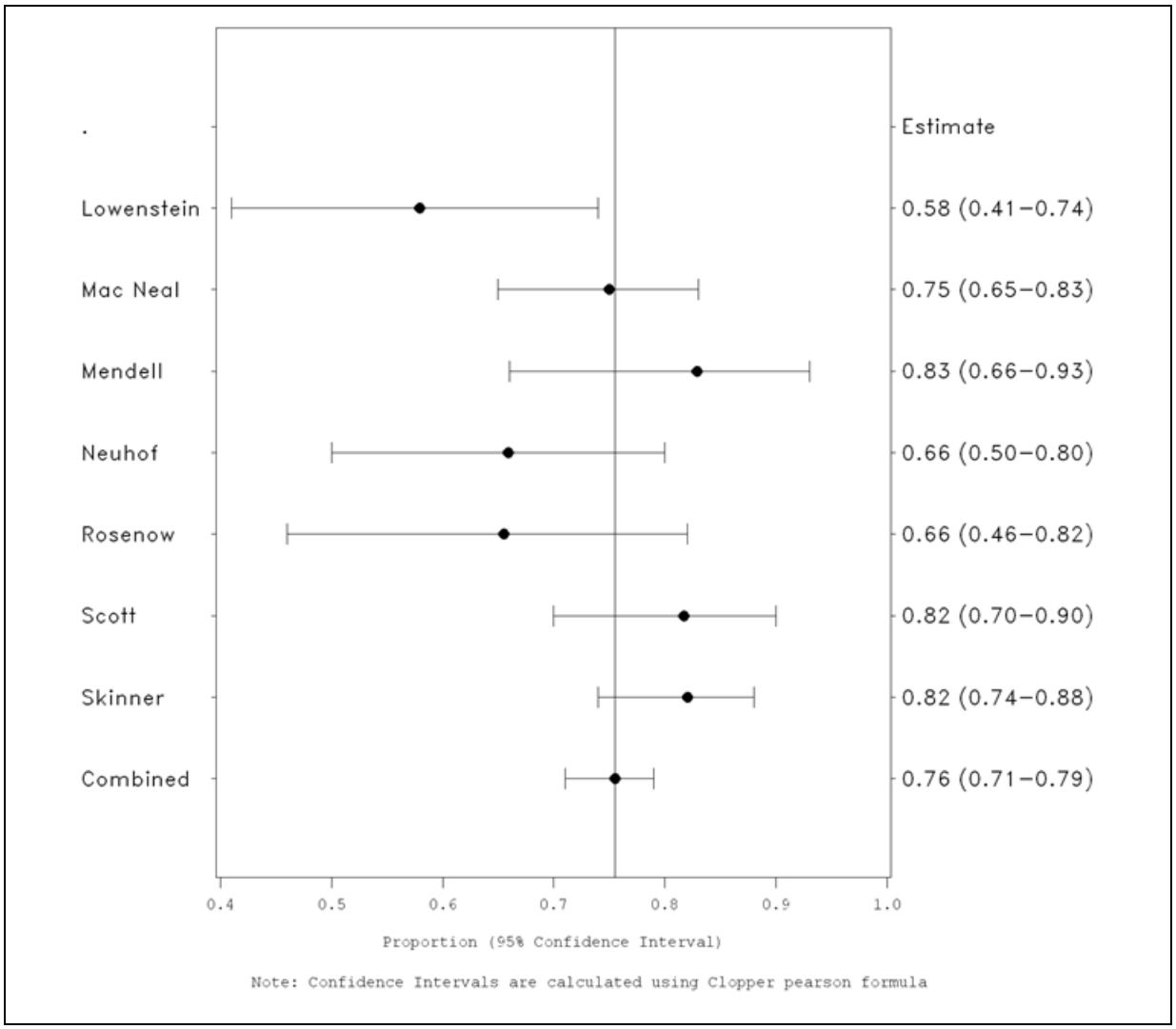
Table E1 Overview of studies from the pre-penicillin era reporting clinical outcome (survival) in untreated patients with SAB

Study	N with SAB	Setting	Predominant clinical manifestation	ACM (n/N)	ACM %
Lowenstein, 1936 (Lowenstein 1936)	38	US case series and literature review of staphylococcal septicaemia (St. Louis)	Skin	22/38	58%
MacNeal and Frisbee, 1936 (MacNeal 1936)	100	US case series of SAB, bacteriophage treatment (NY)	Skin, Osteoarticular	75/100	75%
Mendell, 1939 (Mendell 1939)	35	US case series of SAB (Philadelphia/NY, 8-year period)	Skin, Osteoarticular	29/35	83%
Neuhof, 1934 (Neuhof 1934)	44	US case series of pyogenic sepsis (NY, 5-year period)	Skin, Osteoarticular	29/44	66%
Rosenow et al., 1938 (Rosenow 1938)	29	US case series of SAB and streptococcal septicaemia, (Mayo Clinic, 3-year period)	Not specified for SAB	19/29	66%
Scott, 1935 (Scott 1935)	60	US case series septicaemia (Rochester, 9-year period)	Not specified for SAB	49/60	82%
Skinner and Keefer, 1941 (Skinner 1941)	122	US case series septicaemia (Boston, 7-year period)	Skin, Respiratory, Osteoarticular	100/122	82%

ACM= all-cause mortality.

The results of the random effects meta-analysis are shown in Figure E1, and suggest an all-cause mortality (ACM) of 76% (95% CI 0.71–0.79). The lower bound of the 95% CI of this mortality estimate is 0.71, suggesting a conservative estimate of 71% mortality for patients with SAB who did not receive antibacterial treatment.

Figure E1 Random effects meta-analysis of clinical outcome (mortality) in untreated patients with SAB



Outcome (mortality) in SAB patients receiving antibacterial treatment

The outcome of SAB patients treated with antibacterial treatment is based on three randomized studies published since 1985. The characteristics of these studies are summarized in Table E2.

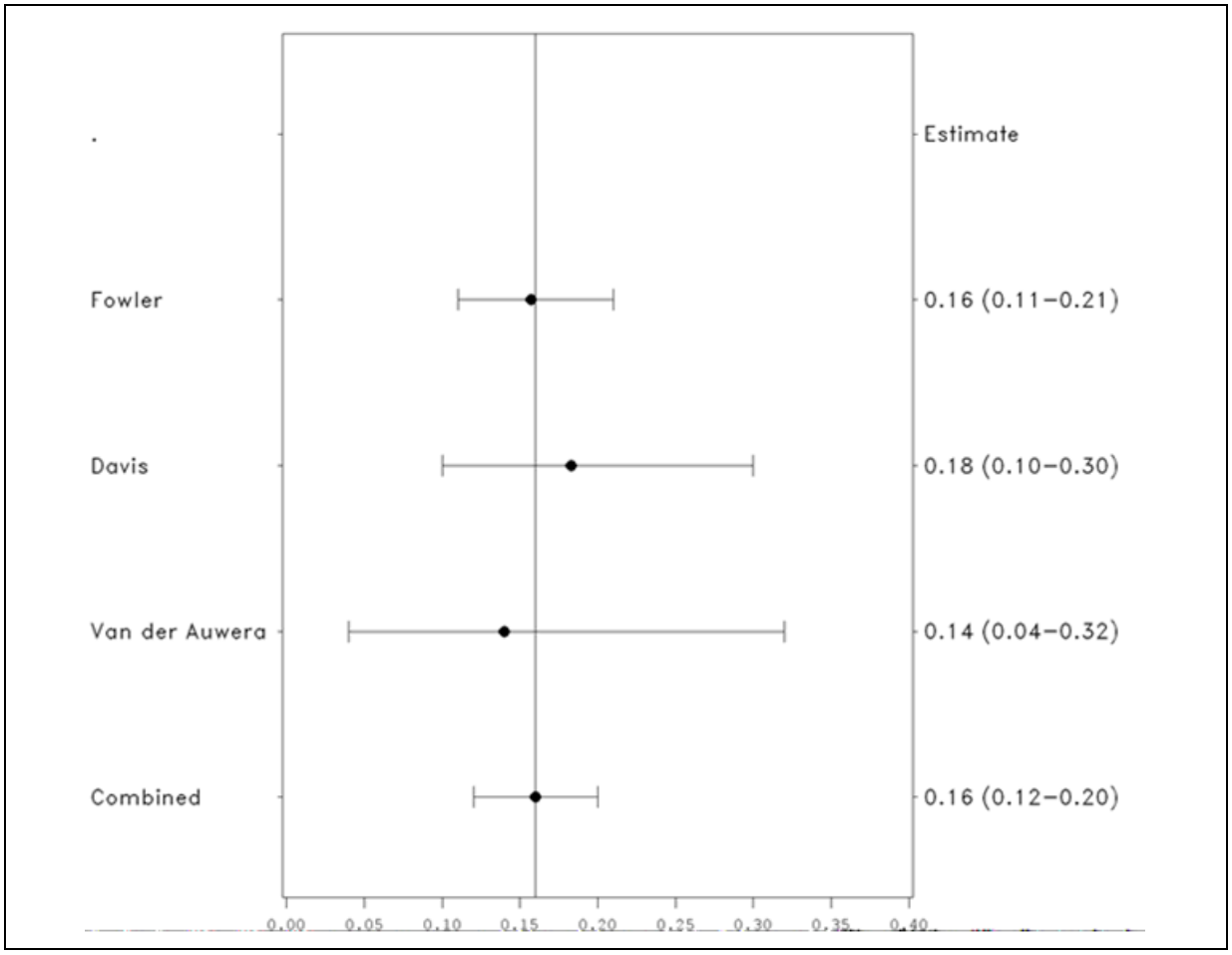
Table E2 Overview of studies reporting clinical outcome (survival) in patients receiving antibacterial treatment

Study	N with SAB	Setting	Predominant clinical manifestation	ACM (n/N)	ACM %
Fowler et al., 2006 (Fowler 2006)	235 (mITT)	Randomized clinical trial of daptomycin vs an antistaphylococcal penicillin or vancomycin	74% complicated SAB; endocarditis, osteoarticular	37/236	16%
Davis et al., 2016 (Davis 2016)	60	Randomized clinical trial of vancomycin vs vancomycin plus flucloxacillin	Primary bloodstream (28%), skin (22%)	11/60 (90 day)	18%
Van der Auwera et al., 1985 (Van der Auwera 1985)	29	Randomized clinical trial of oxacillin or vancomycin alone vs combined with rifampicin	Primary bloodstream (24%); skin/bone (48%)	4/29	14%

ACM=all-cause mortality.

The results of the random effects meta-analysis are shown in Figure E2, and suggest an ACM of 16% (95% CI 0.12–0.20). The upper bound of the CI of the mortality estimate is 0.20, suggesting an estimate of (up to) 20% mortality for patients with SAB who receive antibacterial treatment.

Figure E2 Random effects meta-analysis of clinical outcome (mortality) in patients with SAB who receive antibacterial treatment



M1 conclusion

Based on the review of historical studies from the pre-penicillin era suggesting a mortality rate of at least 71%, and the review of mortality in contemporary studies in patients undergoing effective antibacterial treatment with a mortality rate of up to 20%, the M1 is estimated to be 51% for ACM.

An estimation of M1 for an overall success endpoint is not possible, as this was not reported in the historical studies, which considered survival to be success. However, the mortality data suggest that M1 for a clinical/overall success outcome for SAB would similarly be very large, i.e., in the range of 50%, when outcomes are compared for untreated patients and patients who received effective antibacterial treatment.

Selection of a non-inferiority margin for SAB (M2)

M2 is defined as the largest clinically acceptable difference (degree of non-inferiority) of the test drug compared to the active control.

The comparison of mortality data in untreated patients with SAB and patients receiving antibacterial treatment suggests that M1 is large (approximately 50%, see above), and that an M2 preserving half of the active-control-treatment effect (over untreated patients) could be defined at ≥ 20%.

As M2 is a matter of clinical judgement, and considering that the pivotal SAB study supporting the regulatory approval of daptomycin (Fowler 2006) used a non-inferiority margin (NIM) of 20%, NIMs of ≤ 20% could be considered clinically reasonable. To further explore the performance of NIMs ≤ 20%, the maximum allowable difference of the point estimate (investigational drug [ceftobiprole] minus the active comparator [daptomycin]) that would allow a conclusion of non-inferiority has been assessed for various margins and for various sample sizes, assuming a success rate of 40% in the active-control arm (see Table E3).

Table E3 Maximum allowable difference in the point estimate of overall response (investigational drug minus active comparator) that allows for determination of non-inferiority at margins of 15, 17.5 and 20%, assuming an overall response rate of 40 or 50% in the active-control group

	Comparator Group = Active Group				
N (mITT)	Assumed response rate	N with response	**NIM**	Maximum difference in point estimate that still meets NI*	Statistical Power
350	40	70	**15**	**−5****	**81**
350	40	70	**17.5**	**−7**	**91**
350	40	70	**20**	**−10**	**96**
350	50	88	**15**	**−4**	**80**
350	50	88	**17.5**	**−7**	**90**
350	50	88	**20**	**−9**	**96**
300	40	60	**15**	**−4**	**75**
300	40	60	**17.5**	**−6**	**87**
300	40	60	**20**	**−9**	**94**
250	40	50	**15**	**−2**	**67**
250	40	50	**17.5**	**−5**	**80**
250	40	50	**20**	**−8**	**89**

N=number of subjects; NI=non-inferiority; NIM= non-inferiority margin.
* values rounded to nearest whole number.
** actual value is 4.6.

This analysis shows that for a sample size of 250–350 patients (in the mITT population), an NIM of 15% would allow for the determination of non-inferiority only if the point estimate between ceftobiprole and daptomycin is < 5%. For an NIM of 17.5%, the allowable difference in the point estimates would be in a range of 5–7%, and for an NIM of 20%, the allowable differences in point estimates would be 8–10%.

Non-inferiority margin conclusion

Based on mortality, the overall data support a large treatment difference attributable to the active-control arm over untreated patients of approximately 50% in the treatment of SAB. While the treatment difference for an endpoint of overall success cannot be reliably estimated due to lack of reported data in the historical studies, the M1 for this endpoint is also estimated to be large.

The selection of an NIM therefore needs to be primarily based on clinical judgement. Assuming an overall success rate of 40% in the active-control group, a NIM that allows for a maximum difference in the point estimates of < 5% appears to be clinically justifiable. The scientific data thus provide support for the selection of an NIM of 15%, based on an endpoint of overall success.

Using an NIM of 15% in the context of a point estimate for overall success of 40% in each treatment group in the mITT population, tested at a one-sided alpha level of 0.025 and power of > 80%, a sample size of 350 patients in the mITT population is required.

With this sample size, the allowable differences in point estimates would be approximately 5%, which is considered reasonable based on clinical judgement. If the overall success rate is 50% (see Section 8.1), a sample size of 350 patients in the mITT population would still provide a power of 80% (see Table E3); in this case the allowable differences in point estimates using a NIM of 15% would be approximately 4%.

Appendix 9 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 10 Investigator's protocol signature page

BASILEA

INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

Protocol	BPR-CS-009 Version 9.0	Basilea Product:	Ceftobiprole medocaril
Protocol Title:	**A randomized, double-blind, multi-center study to establish the efficacy and safety of ceftobiprole medocaril compared to daptomycin in the treatment of *Staphylococcus aureus* bacteremia, including infective endocarditis**		

Basilea Pharmaceutica International Ltd.

Approval Date: 27 February 2020

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 Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), including the EU Clinical Trial Directive 2001/20/EC and specifically, to 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