Official Title: Randomized Open-label Active-controlled Study to Assess the Safety, Tolerability and Efficacy of Afabicin IV/oral in the Treatment of Patients with Bone or Joint Infection due to Staphylococcus

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STUDY PROTOCOL

Randomized Open-label Active-controlled Study to Assess the Safety, Tolerability, and Efficacy of Afabicin IV/oral in the Treatment of Patients with Bone or Joint Infection due to *Staphylococcus*

Investigational Medicinal Product	Afabicin (Debio 1450)
Study Number:	Debio 1450-BJI-205
IND Numbers:	IND 117'899; IND 122'530
Current Protocol Version:	13.0, dated 11 APR 2024, integrating Amendment 10
Previous Protocol Versions:	12.0, dated 28 NOV 2023, integrating Amendment 9 11.0, dated 27 APR 2023, integrating Amendment 8 10.0, dated 02 FEB 2023, integrating Amendment 7 (applicable only in Argentina) 9.0, dated 02 DEC 2022, integrating Amendment 6 (applicable only in South Africa) 8.0, dated 24 AUG 2022, integrating Amendment 5 7.0, dated 14 APR 2022, integrating Amendment 4 6.0, dated 01 NOV 2021, integrating Amendment 3 5.0, dated 14 OCT 2020, integrating Amendment 2 4.0, dated 17 DEC 2018, integrating Amendment 1 3.0, dated 09 AUG 2018 (final protocol) 2.0, dated 07 JUN 2018 (final protocol) 1.0, dated 07 DEC 2017 (final initial protocol)
Sponsor:	Debiopharm International S.A. Forum "*après-demain*" Chemin Messidor 5-7 1006 Lausanne, Switzerland

The information in this study protocol is confidential and is provided to every potential Investigator and their team and to the Independent Ethics Committee(s)/Institutional Review Board(s) reviewing the protocol. No information can be provided to a third party without the written agreement of Debiopharm International S.A., except medical personnel directly concerned by the trial and the patient and their family.

Study Sponsor	Debiopharm International S.A., Forum "*après-demain*", Chemin Messidor 5-7, CH-1006 Lausanne, Switzerland
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Principal Investigator	Name: Title: Site address: Phone: Fax: Email: _____ _____ Signature Date
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STUDY SYNOPSIS

STUDY TITLE	Randomized Open-label Active-controlled Study to Assess the Safety, Tolerability, and Efficacy of Afabicin IV/oral in the Treatment of Patients with Bone or Joint Infection due to *Staphylococcus*
STUDY NUMBER	Debio 1450-BJI-205
STUDY PHASE	2a
STUDY PERIOD	Nov 2018 – Dec 2026
STUDY OBJECTIVES	1. Primary: To assess the safety and tolerability of afabicin in the treatment of patients with bone or joint infection (BJI) (septic arthritis, osteomyelitis, prosthetic joint infection [PJI]) due to *Staphylococcus aureus* (both methicillin-susceptible *S. aureus* [MSSA] and methicillin-resistant *S. aureus* [MRSA]) and/or coagulase-negative staphylococci (CoNS) and to compare it to standard of care (SoC). 2. Secondary: To assess the efficacy of afabicin in the treatment of patients with BJI due to *S. aureus* (both MSSA and MRSA) and/or CoNS. 3. Exploratory: To determine the microbiological outcome. In afabicin-treated patients, to describe the pharmacokinetics (PK) profile, to explore biomarkers linked with response, toxicity, and PK, and to assess the potential for drug-drug interaction (DDI) towards cytochromes P450 (CYPs) using endogenous biomarker(s).
STUDY DESIGN	Interventional, randomized, multicenter, open-label, active-controlled study. The study consists of Part A and Part B. PART A: Patients will be recruited into 3 cohorts: patients in Cohort 1 will be treated for 2-3 weeks, patients in Cohort 2 will be treated for 3-6 weeks and patients in Cohort 3 for 6-12 weeks. At the end of treatment of the initial evaluable 8 patients (6 in afabicin and 2 in SoC arm) in each cohort, and including a minimum of 2-week post-treatment follow-up, [redacted] and the Independent Data Monitoring Committee (IDMC) will assess the safety outcomes and recommend whether the next cohort of patients may be initiated and/or the current cohort may continue recruitment. In each cohort, up to 20 patients (16 afabicin + 4 SoC) will be recruited. The overall allocation ratio of afabicin: SoC in Part A will be 4:1 for evaluable patients in each cohort. After confirmation of a *S. aureus* (MSSA or MRSA) and/or CoNS, afabicin treatment will be initiated intravenously at a dose of 160 mg twice daily (BID). An early switch to oral regimen at a dose of 240 mg BID will be at the Investigator's discretion; however, intravenous (IV) treatment should not be administered for more than 2 weeks. Total treatment duration with afabicin cannot exceed 12 weeks. A pre-defined choice of SoC monotherapy will be based on the antibiotic safety profile and the current treatment guidelines for bone and joint infections. The SoC control arm will be matched for treatment duration. All patients will be followed up for 12 weeks post end of treatment (EOT). The overall study duration for the patient will be ≤ 25 weeks (including an up to 7-day screening period). [redacted] PART B: Patients will be recruited into the following cohorts: • Cohort 1B (2-3 weeks of treatment) • Cohort 2B (3-6 weeks of treatment) • Cohort 3B (6-12 weeks of treatment) Up to 24 patients will be recruited per cohort and randomized at a 5:1 ratio (20 to afabicin: 4 to SoC per cohort). Upon completion of Cohort 1B, the study will be paused and the IDMC [redacted] will review the data of the cohort and assess any potential [redacted]. Additionally, data of Cohort 1B will be submitted to the concerned Health Authorities, when deemed necessary, before initiation of the next cohort. Cohorts 2B and 3B will only be initiated after completion of the preceding cohort, following endorsement from the IDMC [redacted] and, if necessary, by the concerned Health Authorities. In all B cohorts, patients will receive an afabicin dose of 55 mg IV BID, followed by 80 mg BID per os (PO). Two weeks after the EOT of Cohort 2B and Cohort 3B, [redacted] the IDMC will assess the available safety and efficacy data and will evaluate whether the next cohort may be initiated. If safety of any given cohort is adequate, but the efficacy criteria are not met (see futility criteria below), a new cohort with the same treatment duration but at a higher dose of 80 mg IV BID/ 120 mg PO BID could be opened (Cohorts 1C, 2C or 3C).

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If the efficacy criteria are met at the higher dose, the higher dose will be used for all subsequent cohorts. If the higher dose fails to meet the efficacy criteria, the study will be terminated for futility, but the patients will be followed up according to the protocol.

The summary of treatment information for all cohorts is outlined below:

Part	Cohort	Dosing	Treatment duration (weeks)
A	1	160 mg IV BID / 240 mg oral BID	2-3
	2		3-6
	3		6-12
B	1B	55 mg IV BID / 80 mg oral BID	2-3
	2B		3-6
	3B		6-12
	1C	80 mg IV BID / 120 mg oral BID*	2-3
	2C		3-6
	3C		6-12

* Higher dose of afabicin will only be tested if the lower dose will not show sufficient activity as per futility criteria and will show adequate safety.

Antibiotics with short half-lives may be administered during the screening period for up to 7 days, while awaiting the microbiological culture results to confirm the patient eligibility to be randomized to study treatment. These antibiotics should be stopped prior to initiating study treatment.

STUDY POPULATION

Adult patients with a confirmed infection due to *S. aureus* and/or CoNS of the bone or joint, namely septic arthritis, osteomyelitis, or PJI.

In Part A, enrolment of up to 60 patients was initially planned. [redacted]

In Part B up to 96 patients will be enrolled (max 4 cohorts with 24 patients each).

The number of patients may be increased if deemed necessary to assess any emerging safety signal(s).

INCLUSION CRITERIA

1. Able to provide written informed consent and to comply with study procedures.
2. Adult male and female patients (≥ 18 years of age).
3. Diagnosis of septic arthritis, osteomyelitis, or PJI which fulfils the following conditions:
   a. Infection is due to *S. aureus* (MSSA or MRSA) and/or CoNS only; and
   b. Patient had received no more than 7 days of empiric antibiotics prior to initiating treatment with study drug unless the pathogen isolated was resistant to the administered empiric antibiotics; and
   c. Biofilm is not considered to be yet established and/or has been mechanically eradicated. Therefore, orthopedic hardware associated with the primary site of bone infection should be removed before randomization (e.g., in cases of implant-associated osteomyelitis or PJI with explantation in a 2-stage strategy); and
   d. Infection is not associated with an ischiatic or a sacral osteomyelitis; and
   e. Infection can involve periosteal or soft tissue.
4. All female patients who are of childbearing potential (defined as not postmenopausal for at least 12 months or not surgically sterile for at least 7 months), must have a negative pregnancy test at screening and agree to use a highly effective contraception method until at least 60 days after dosing. An acceptable method of contraception includes a double-barrier method (diaphragm, condoms, spermicides) or mechanical products such as an intrauterine device along with at least a single-barrier method (diaphragm, condoms, spermicides).
5. Able to tolerate at least one of the proposed SoC treatments, as appropriate for the indication.
6. Anticipated duration of treatment does not exceed the maximum treatment duration for the enrolling cohort (i.e., 3 weeks for Cohorts 1, 1B or 1C, 6 weeks for Cohorts 2, 2B or 2C, and 12 weeks for Cohorts 3, 3B or 3C).
7. Patient with controlled human immunodeficiency virus (HIV) infection on stable anti-retroviral treatment (ART) can be included (undetectable viral load for at least 10 months [HIV RNA < 50 copies/ mL], stable ART for more than 11 months, CD4 ≥ 200 cells/ mm^3,

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	stable weight and no opportunistic infections) - Criterion only applicable in South Africa and Argentina according to local regulatory requirement.
EXCLUSION CRITERIA	1. Presence of co-infection with non-staphylococcal bacteria at the affected joint or bone site or in the blood. 2. Patients at an increased risk of developing liver injury, such as: [redacted] d. Obesity (elevated BMI ≥ 30) or poorly controlled diabetes mellitus (i.e., blood levels of Glycosylated Haemoglobin HbA1C ≥ 8.0%), or hypertriglyceridemia CTCAE ≥ grade 2 (serum triglycerides > 300 mg/dL), or concomitant CTCAE grade 1 hypertriglyceridemia (150-300 mg/dL) and abnormally low High Density Lipoprotein (HDL) levels, or e. Metabolic syndrome - according to the NCEP ATP III definition, metabolic syndrome is present if 3 or more of the following 5 criteria are met: waist circumference over 40 inches [101 cm] (men) or 35 inches [89 cm] (women), blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dL, fasting HDL cholesterol level less than 40 mg/dL (men) or 50 mg/dL (women) and fasting blood sugar over 100 mg/dL. 3. [redacted]. 4. Patients who have any of the following medical conditions that increase the risk of QT prolongation: a. Prolonged QTcF interval (> 450 ms in men and > 470 ms in women using Fridericia formula at screening). b. Heart rate (on ECG) ≤ 40 beats/min (bpm) and > 100 bpm. c. Congenital long QT syndrome or family history of sudden death. d. Hypokalemia, hypocalcemia and/or hypomagnesemia CTCAE grade ≥ 2. Correction of electrolytes levels with supplements to meet eligibility criterion is allowed. 5. Medical history within the previous 3 months of: myocardial infarction, unstable angina pectoris, coronary artery or cerebral revascularization procedure or stroke, ventricular tachycardia, multifocal ventricular ectopics requiring treatment, or any other clinically relevant symptomatic ventricular arrhythmias. 6. Any of the following comorbidities: a. Clinical or laboratory signs of sepsis: score of ≥ 2 on the Sequential Organ Failure Assessment (SOFA) scale at screening. Note that patients with uncomplicated bacteremia (defined as bacteremia that does not meet criteria for complicated bacteremia) may enter the study. b. Heart failure with reduced left ventricular function and those patients meeting the New York Heart Association (NYHA) class III or IV. c. Severe and frequent migraine headaches (recurring weekly). d. Immunosuppression or immune deficiency or immunotherapy (steroid therapy is allowed if judged not to be associated with immunosuppression by the Investigator). e. Measured or estimated creatinine clearance (CL) < 30 mL/min. 7. Prothrombin time prolongation or partial thromboplastin time prolongation > 1.5 x ULN or platelets <100 000/µL. 8. Patients who are treated or have been treated with prohibited medications within a period less than 5 half-lives of the drugs (this applies to the following drugs which have the potential for PK or pharmacodynamics (PD) interactions): a. Phosphodiesterase 3 (PDE3) inhibitors. b. More than one antiplatelet/anticoagulant agent. c. Drugs or herbal products that are known to be moderate or strong inhibitors of cytochrome P450 (CYP) 3A4. d. [redacted] 9. Patient who are treated or have been treated with drugs or herbal products that are known inducers of CYP 3A4 within a period less than 5 half-lives of the drugs or 2 weeks (whichever is longer). 10. Documented history of alcohol or drug abuse within the previous 12 months.

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	11. Known or suspected allergies or hypersensitivities to any of the components of the study drugs (refer to the afabicin Investigator's Brochure and to the local labelling for SoC treatments). 12. Received any investigational medication during the last month (30 days or 5 half-lives, whichever is longer) prior to enrolment in the current study or previously received afabicin. 13. Any condition that, in the view of the Investigator, renders the patient unlikely to benefit from treatment or place him/her at a high risk of unwarranted side effects or prevent him/her from completing the study. 14. Pregnant or breast-feeding women. 15. Any contraindications to <u>each</u> of the proposed SoC treatments, based on the local labelling for each SoC, such that none of the proposed SoC therapies could be administered. **For Part B only:** 16. Neutrophil counts < 1000 cells/mm^3. 17. Signs of clinically relevant abnormalities of the liver, pancreas, gall bladder and bile ducts, as assessed by ultrasound examination. 18. Circulatory shock or any medical condition associated with acute risk of death. 19. Life expectancy of less than 1 year. 20. For patients with diabetic foot osteomyelitis (DFO): a. Severe peripheral arterial disease (PAD) requiring revascularization; however patients with peripheral artery disease are eligible for inclusion, provided they have undergone successful revascularization or it has been deemed unnecessary by a vascular surgeon. b. Necrotizing fasciitis or gangrene requiring complete lower extremity amputation (of all infected bone and soft tissue). c. Patients with Charcot foot (suspected neuro-osteoarthropathy according to Investigator's judgment). d. Need for digital amputation.
INVESTIGATIONAL MEDICINAL PRODUCTS	**Debiopharm product** Afabicin IV: vial of 160 mg powder for solution for infusion Afabicin oral: 80 mg, 120 mg and 240 mg film-coated tablets
COMPARATOR AND/OR ASSOCIATED PRODUCTS	Investigator's choice following pre-specified recommended SoC options for comparator arm, as appropriate for the indication: Overall, for oxacillin-/methicillin-susceptible staphylococci, the recommended SoC for the comparator arm are: • IV - Cefazolin or vancomycin or linezolid or clindamycin • Oral - Linezolid or clindamycin For oxacillin-/methicillin-resistant staphylococci, the recommended SoC for the comparator arm are: • IV - Vancomycin or clindamycin or linezolid • Oral - Linezolid or clindamycin
MODE OF ADMINISTRATION	IV infusion (over 2 hours), oral.
TREATMENT DURATION	Minimum of 2 weeks; maximum up to 12 weeks.
DOSING SCHEME	PART A: Dosing for Cohorts 1, 2, and 3: afabicin IV 160 mg BID for a maximum of 2 weeks, followed by a switch to afabicin oral 240 mg BID. PART B: Dosing for Cohorts 1B, 2B and 3B: Afabicin IV 55 mg BID for a maximum of 2 weeks, followed by a switch to afabicin oral 80 mg BID. In case of lack of efficacy of this dosing regimen and in the absence of safety issues (as assessed by [redacted] IDMC), the following dosing regimen will be evaluated in Cohorts 1C, 2C and/or 3C: afabicin IV 80 mg BID for up to 2 weeks, followed by a switch to afabicin oral 120 mg BID. SoC should be administered per approved local labelling and accepted clinical guidelines.
ENDPOINTS	**Primary endpoint:**

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The nature, incidence, severity, seriousness, and outcome of treatment-emergent adverse events (TEAEs), and the incidence of clinically significant laboratory abnormalities (grades 1, 2, 3, and 4) compared to baseline and the SoC arm, assessed up to 12 weeks post-EOT.

Secondary endpoints:

The secondary efficacy endpoints are the proportion of patients with clinical response at (1) 8 days, (2) 28 days (for Cohorts 2, 2B, 2C & 3, 3B, 3C only), (3) 42 days from randomization (for Cohorts 2, 2B, 2C & 3, 3B, 3C only), (4) at EOT, (5) at 4 weeks post-EOT, and (6) at 12 weeks post-EOT.

Patient status will be classified as responders, non-responders, or indeterminate.

Responders are defined as patients meeting all the following criteria:

- Improvement of disease-specific signs and symptoms and no new signs, symptoms or complications attributable to the initial infection.
- No evidence of drainage, sinus tract formation or infection-related bone instability.
- No requirement for subsequent antibiotics with activity against *Staphylococcus* to treat the initial infection after the start of study treatment.
- Microbiological eradication of the baseline pathogen (if post-baseline sample[s] available).
- Imaging test at 12 weeks post-EOT showing no worsening of baseline pathology or presence of signs indicating resolution or healing of the infection. This will only be assessed if baseline and 12 weeks post-EOT imaging are available using the same modality, otherwise imaging will not be considered for the criteria of response. Imaging indicating a worsening of the condition will be considered as clinical failure. For each patient, the same method of imaging should be used throughout the study. The type of imaging (magnetic resonance imaging [MRI], computed tomography [CT]-Scan, etc.) and additional imaging assessments between screening and 12 weeks post-EOT are at the investigator's discretion.

Non-responders will be defined as patients with available follow-up assessment(s) who do not meet at least one of the criteria for clinical response.

Indeterminate status will be applied in cases where the patient is lost to follow-up or had an amputation at the site of the initial infection due to vascular pathology without signs of infection.

Improvement of disease-specific signs and symptoms is defined as:

- No new sign, symptoms, or complications post baseline and attributable to the initial infection,
- Reduction of the number of disease-specific signs and symptoms compared to baseline and
- Resolution of infection-related fever (< 38°C).

Exploratory endpoints:

1. The PK and PK/PD analyses will include the following parameters:
   - PK after first IV dose (Day 1): area under the concentration vs time curve $(AUC)_{0\text{-}12h}$ and, if applicable, maximum (peak) serum concentration (C_{max}), time to reach maximum plasma concentration following drug administration (t_{max}), $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $t_{½}$, mean residence time (MRT), CL or CL/F, V_z or V_z/F for afabicin and/or its active moiety Debio 1452, as applicable.
   - PK at steady-state (ss) (after oral morning dose in fasted conditions on Day 28 or EOT): AUCt and, if applicable, tmax,ss, Cmax,ss, CLss/F, Ctrough, Cav, peak trough fluctuation (PTF) for Debio 1452.
   - PK-PD index on Day 1 and at steady-state: Debio 1452 free-drug plasma $AUC_{0\text{-}24h}$:minimal inhibitory concentration (MIC) (*f*AUC:MIC).
2. Decrease of C-reactive protein (CRP) levels at EOT and 12 weeks post-EOT visit for patients whose baseline level is above the normal range.
3. Microbiological outcomes at each on-site follow-up visit, based on culture results (if available).
4. [redacted] and [redacted] gene variants linked with response, toxicity, and PK, and plasma biomarkers suspected to be linked with toxicities.
5. Change from baseline in 4β-OH-cholesterol plasma concentrations and/or 4β-OH-cholesterol/cholesterol ratio (and other endogenous DDI biomarkers if applicable) after repeated administration of afabicin.
6. Changes compared to baseline in relative abundance of microbial taxa and antimicrobial resistance (AMR) genes in the stool of patients at EOT and 4 weeks post-EOT.

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	7. Key metabolites in the stool including, but not limited to, bile acids and short chain fatty acids (SCFA) at baseline, and temporal within-patient metabolic changes during the study (baseline, EOT, and 4 weeks post-EOT).
STUDY VISITS	The following on-site visits are planned during the study for all patients: • **Screening** visit: to take place between Day -10 and Day -1. During this visit, samples (following standard procedures) will be taken for microbiological assessment of the pathogen. The pathogens must be identified prior to the start of study medication. • **Day 1** visit: start of IV study medication. The first infusion will be administered in the morning in order to facilitate Day 1 assessments. • **Day 8** visit: a visit to assess the safety and efficacy of treatment. • **Day 28** visit: a visit to assess the safety (if the patient is still on study medication) and efficacy of treatment. • **Day 42** visit: a visit to assess the safety (if the patient is still on study medication) and efficacy of treatment. • **EOT** visit treatment duration will depend on the patient's diagnosis (i.e., septic arthritis, osteomyelitis, or PJI) and will be at the Investigator's discretion but no longer than 12 weeks (84 days). • Follow-up visit: **4 weeks post-EOT.** • Follow-up visit: **12 weeks post-EOT.** In addition to the on-site visits, safety visits will be performed on Day 3 or Day 4, weekly thereafter (starting at Day 8) during study treatment (for both hospitalized and non-hospitalized patients) and weekly for the first 6 weeks post-EOT. The study physician will assess the safety of the patient, including monitoring adverse events (AEs), obtaining a blood sample for hepatic enzyme assessment, performing an ECG, and reviewing the diary card. Each study site will have a dedicated study physician to oversee the safety of the patients when out of hospital and to ensure a timely follow-up on any events.
STATISTICAL METHODS	**Sample size:** This is an exploratory study and the sample size is not based on formal statistical calculations. PART A: For this part of the study, it was initially planned to recruit 60 evaluable patients (48 in afabicin and 12 in the control arm [overall ratio 4:1]; approximately 20 patients per cohort). This number of patients is expected to be sufficient to detect any safety signals with afabicin treatment in patients with BJI. [redacted] PART B: For this part of the study, it is planned to recruit up to 96 evaluable patients who will be randomized 5:1 to afabicin or SoC (20 afabicin + 4 SoC patients per cohort). [redacted] **Futility analysis (for PART B only):** Efficacy will be monitored on an ongoing basis, and a continuous futility analysis will be carried out to ensure that patients are not under-exposed to afabicin. Since the control response rate is assumed at 70%, the futility criterion is defined as < 70% of patients with clinical response at EOT. The cohort will be stopped if 5 out of the first 9 evaluable patients are non-responders. The data of the first Cohort 1B will be reviewed by [redacted] IDMC and health authority before proceeding to the next cohort. Data of the subsequent cohorts will continue to be reviewed by [redacted] IDMC and, if warranted, by Health Authority. In case futility is met in Cohorts 1B, 2B or 3B, Cohorts 1C, 2C or 3C could be initiated, unless there is a safety concern. If the futility is met for any of the Cohorts C, the study will be terminated. If the futility is not met the study will continue with a subsequent cohort. **Statistical analysis (PART A and PART B):**

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	Safety: Incidence of TEAEs and serious adverse events (SAEs) will be summarized by system organ class (SOC), preferred term (PT) and grade. Shift tables based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grading will be presented for laboratory and ECG parameters between baseline and worst case on-treatment including follow-up period. Efficacy: Patients with clinical response at Day 8, Day 28, Day 42, EOT, at 4 weeks post-EOT, and 12 weeks post-EOT will be described by count and percentage along with 95% confidence interval (CI) based on the Clopper-Pearson method. PK and PK-PD: Plasma concentrations of afabicin and of its active moiety (Debio 1452) will be listed and summarized by time point of collection. Summary statistics in the tabulation will include number of non-missing value, mean, standard deviation, coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric CV%. As applicable, PK parameters will be calculated by non-compartmental analysis and/or derived by population PK data analysis using a nonlinear mixed-effects modelling approach and summarized by descriptive statistics as above. The PK-PD index *f*AUC:MIC will be derived for Debio 1452 as applicable, and relationships between MIC, PK-PD index, and observed clinical and microbiologic outcomes will be evaluated. Microbiological outcome: Microbiological outcome categories (Documented Eradication, Presumed Eradication, Documented Persistence, Presumed Persistence, Recurrence, Super-infection, New Infection, and Unknown) will be summarized by visit, including unscheduled visits (if any), on a patient level. DDI potential with CYP endogenous biomarkers: The absolute and percentage change from baseline of 4β-OH-cholesterol and of 4β-OH-cholesterol/Cholesterol ratio will be calculated for each patient, and summary statistics will be presented by dosing regimen. If applicable, data from other CYP endogenous biomarkers will be presented similarly.

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ABSSSI	Acute bacterial skin and skin structure infection
ACP	Acyl carrier protein
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANOVA	Analysis of variance
anti-HCV	Hepatitis C virus antibody
ART	Anti-retroviral treatment
AMR	Antimicrobial resistance
AST	Aspartate aminotransferase
aPTT	Activated partial thromboplastin time
ATC	Anatomical therapeutic chemical (class)
AUC	Area under the concentration vs time curve
BES	Bis ethanolamine salt
BID	Bis in die (twice a day)
BJI	Bone or Joint Infection
BMI	Body mass index
CFU	Colony-forming units
CI	Confidence interval
CKMB	Creatine kinase-MB isozyme expressed primarily in myocardium
CL	Clearance
C_{max}	Maximum (peak) serum concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CoA	Certificate of Analysis
CoNS	Coagulase-negative staphylococci
CPK	Creatine phosphokinase
C-QT	Concentration-QT
C-QTc_	Concentration-QT interval corrected
CRO	Contract Research Organization
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
CV%	Coefficient of variation
CYP	Cytochrome P450
D5W	Dextrose 5% in water
[redacted]	[redacted]
DDI	Drug-drug interaction
DFO	Diabetic Foot Osteomyelitis
[redacted]	[redacted]
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECR	Early clinical response
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOT	End of treatment
EOS	End of study
*f*AUC:MIC	Free-drug plasma $AUC_{0\text{-}24h}$:minimal inhibitory concentration
GCP	Good clinical practice
GGT	Gamma-glutamyltransferase
[redacted]	[redacted]
GMP	Good manufacturing practice
[redacted]	[redacted]
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
hERG	human Ether-a-go-go-Related Gene
HIV	Human immunodeficiency virus
[redacted]	[redacted]
HSV	Herpes simplex virus
IDB	Investigator's Drug Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

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Abbreviation	Explanation
IDSA	Infectious Disease Society of America
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ISR	Infusion Site Reaction
ITT	Intent to Treat
IV	Intravenous
IWRS	Interactive Web Response System
LFT	Liver Function Test
MALDI-TOF	Matrix-Assisted Laser Desorption/Ionization Time-of-Flight
MedDRA	Medical Dictionary for Regulatory Activities
MCSF-R1	Macrophage colony-stimulating factor receptor 1
MIC	Minimal inhibitory concentration
mITT	Microbiological intent to treat
MRI	Magnetic resonance imaging
MRT	Mean residence time
MRSA	Methicillin resistant *Staphylococcus aureus*
ms	Millisecond
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect level
NSAIDs	Nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
OtC	Over the Counter
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PDE3	Phosphodiesterase 3
PES	Polyethersulfone
PFGE	Pulsed-Field Gel Electrophoresis
PI-NRS	Pain Intensity Numerical Rating Scale
PJI	Prosthetic Joint Infection
PK	Pharmacokinetics
PO	Per os (oral)
PPI	Proton pump inhibitor
PP	Per Protocol (population)
PT	Preferred Term
PTA	Probability of PK/PD target attainment
PTF	Peak Trough Fluctuation
PVL	Panton-Valentine Leukocidin
Q12h	Every 12 hours
QD	Once a day
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SCFA	Short Chain Fatty Acids
SOC	System Organ Class
SoC	Standard of care
SOFA	Sequential Organ Failure Assessment
Spp	Species
ss	Steady-state
TdP	Torsade de Pointes
TEAE	Treatment-emergent adverse event
TG	Triglyceride
T_{max}	Time to reach maximum plasma concentration following drug administration
TQT	Thorough QT
ULN	Upper limit of normal
WBC	White blood cell (count)
WHO-DD	World Health Organisation Drug Dictionary

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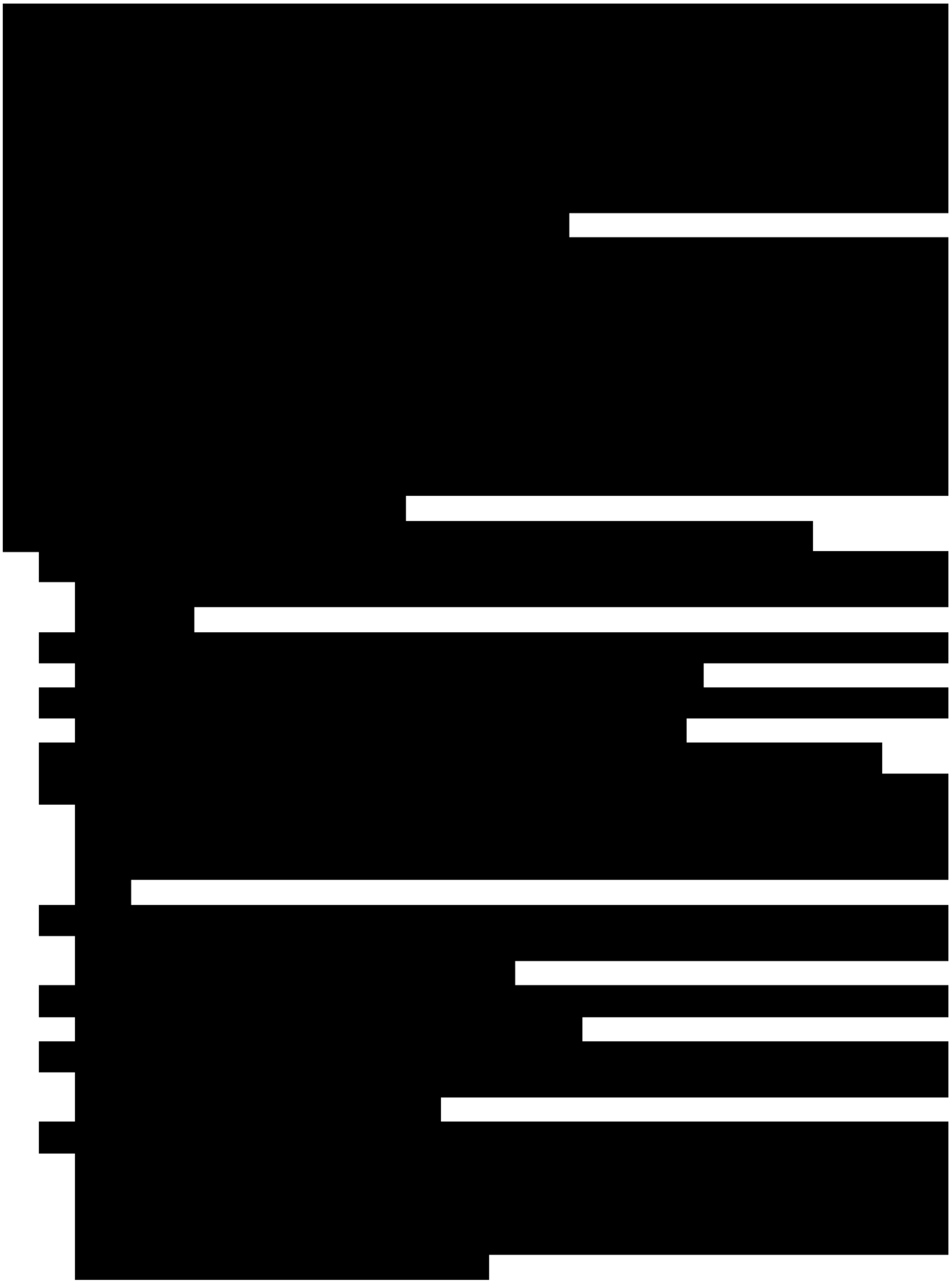
DEFINITIONS

Baseline	Last non-missing assessment prior to randomization, unless otherwise specified. Unscheduled assessments are also considered for identification of the baseline value, unless stated otherwise. All baseline measurements must have been collected prior to randomization. After this moment, all measurements will be considered as post-baseline values, unless otherwise specified.
Childbearing potential	A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as women over the age of 50 who have been amenorrheic for at least 12 consecutive months). Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier method (diaphragm, condoms, spermicides) to prevent pregnancy, even whose partner is sterile (e.g., vasectomy), should be considered to be of childbearing potential.
End of Treatment (EOT)	Defined as a scheduled assessment within 72 hours after the administration of the final dose of study drug.
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form. According to the above definition, the Debiopharm International SA active substance being tested during the study is considered as IMP.
Study drug	Active substance being tested (i.e., afabicin) and standard of care (SoC)
Treatment period	Defined as the period between first dose date of any study drug up to the EOT visit, inclusive.

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1 RATIONALE FOR THE PROTOCOL AMENDMENTS

1.1 Protocol Version 5.0, amendment 2



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10. [redacted]

1.2 Protocol V6.0, amendment 3

Exclusion criterion 2c of the protocol has been modified by adding clinically relevant details to better define dyslipidaemia and hypertriglyceridemia. Revised exclusion criterion 2c is:

"Obesity (elevated body mass index [BMI] ≥ 30), OR diabetes mellitus, OR hypertriglyceridemia Common Terminology Criteria for Adverse Events (CTCAE) ≥ grade 2 (serum Triglycerides > 300 mg/dL), OR concomitant CTCAE grade 1 hypertriglyceridemia (150-300 mg/dl) and abnormally low serum high-density lipoprotein (HDL) levels; or"

1.3 Protocol V7.0, amendment 4

[redacted]

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[redacted]

1.4 Protocol V8.0, amendment 5

[redacted]

1.5 Protocol V9.0, amendment 6

This amendment is only applicable in South Africa and was triggered by a request from the local health authority. As the result, the following inclusion criterion has been added:

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Patient with controlled human immunodeficiency virus (HIV) infection on stable anti-retroviral treatment (ART) can be included (undetectable viral load for at least 10 months [HIV RNA < 50 copies/mL], stable ART for more than 11 months, CD4 ≥ 200 cells/mm^3, stable weight and no opportunistic infections).

1.6 Protocol V10.0, amendment 7

This amendment is only applicable in Argentina and was triggered by a request from the local health authority. As the result, the following inclusion criterion has been added:

Patient with controlled HIV infection on stable ART can be included (undetectable viral load for at least 10 months [HIV RNA < 50 copies/ mL], stable ART for more than 11 months, CD4 ≥ 200 cells/ mm^3, stable weight and no opportunistic infections).

In addition, Table 9-1 has also been updated.

1.7 Protocol V11.0, amendment 8

Recent safety and C-QT modeling data suggest that afabicin is not associated with a risk of QTc prolongation when used at the current dosing regimen (55mg IV BID/80 mg PO BID). Accordingly, patients taking concomitant medicines that prolong QT interval and those with risk factors for TdP will be allowed to participate in the study. Therefore, the following changes have been made:

1. Exclusion criterion 4.e. (“Drugs that prolong the QT interval and are associated with a known or possible risk of TdP - e.g., amiodarone, methadone.”) has been removed.
2. Exclusion criterion 5 has been amended to allow participation of patients with atrial tachy-arrhythmias, which can be managed with anticoagulation and anti-arrhythmic drugs. Therefore, only ventricular arrythmias remain as exclusion criterion.
3. Drugs associated with a risk of TdP were reclassified from “prohibited” to “to be used with caution”. Accordingly, Section 8.7.3 has been expanded to include an algorithm explaining how drugs associated with TdP should be used in the study (new subsection in Section 8.7.3.).
4. Section 3.6. Benefit-risk assessment has been updated to reflect the new information.

Previously and as requested by the local health authorities in South Africa and Argentina (see Sections 1.5. and 1.6.), the list of inclusion criteria was updated in relation to patients with HIV infection. This change was introduced initially as country specific protocol amendments. To harmonize the study protocol across different countries, further clarification has been provided for inclusion criterion 7:

1. Patient with controlled HIV infection on stable ART can be included (undetectable viral load for at least 10 months [HIV RNA < 50 copies/mL], stable ART for more than 11 months, CD4 ≥ 200 cells/mm^3, stable weight and no opportunistic infections) - Criterion only applicable in South Africa and Argentina according to local regulatory requirement.
2. Table 9-1 (“Laboratory assessments: full panel") has been updated to include HIV serology testing at screening according to local regulatory requirement.

In addition to the main points described above, minor typographical changes have been made in Table 14-1 Part B and throughout the protocol.

1.8 Protocol V12.0, amendment 9

The rationale for the changes introduced by the current amendment is summarized below:

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1) Inclusion of patients with Diabetic Foot Osteomyelitis

The most common pathogens in Diabetic Foot Osteomyelitis (DFO) are aerobic gram-positive cocci, especially *S. aureus*. There is a high unmet need in the treatment of DFO, especially those caused by staphylococci.

The 2019 (current) international guidelines for the treatment of Diabetic Foot Infections [1] recommend that antibiotics to treat DFO should have activity in osteomyelitis. Afabicin achieves adequate bone concentration, has high oral bioavailability, and has shown preliminary promising clinical activity in staphylococcal acute bacterial skin and skin structure infection (ABSSSI) [2]. Promising preliminary activity in osteomyelitis has also been shown in Cohort 1B of this study (Debio 1450-BJI-205). All Cohort 1B patients treated with afabicin 55 mg IV BID/80 mg PO BID up to 21 days were responders and the treatment was well tolerated. Osteomyelitis was the most common disease observed in randomized patients (17 of 20). Therefore, it is plausible to assume that afabicin may achieve similar success rates in DFO patients.

In addition, the guidelines also recommend that preference should be given to antibiotics that avoid collateral damage to gut microbiota [1, 3]. Recently, it was shown that the gut microbiota of healthy volunteers who had received 20 days of treatment with afabicin (240 mg PO BID) was not altered [4]. These data suggest that oral treatment with afabicin might be associated with preservation of the gut microbiota in healthy subjects.

Based on the above, and considering that as of protocol version 7.0 (dated 14 April 2022) patients with well-controlled diabetes mellitus are eligible for participation in the study, the following changes are introduced:

- Inclusion criterion 3d has been amended to allow participation of patients with DFO (Section 7.1).
- A new exclusion criterion 20 has been included to further clarify the DFO patient population eligible for the study (Section 7.2).

2) Modification of the wash-out period for prohibited medications

The exclusion criterion related to the washout of prohibited medications (exclusion criterion 8) has been refined to distinguish between CYP 3A4 inducers for which a washout of at least 2 weeks is necessary to return to baseline enzyme levels; and other drugs for which a washout period of 5 half-lives is considered sufficient to avoid a clinically significant interaction. This leads to the following changes:

- Exclusion criterion 8 has been amended to exclude patients who are treated or have been treated with prohibited medications within a period less than 5 half-lives of the drugs. This applies to prohibited medications listed in Section 7.2:
    - Exclusion criterion 8a: PDE3 inhibitors,
    - Exclusion criterion 8b: Antiplatelet/anticoagulant agent,
    - Exclusion criterion 8d: Moderate or strong inhibitors of cytochrome P450 (CYP) 3A4, and
    - [redacted]
- A new exclusion criterion 9 has been added to specify a washout period of at least 5 half-lives or 2 weeks (whichever is longer) for drugs that are CYP 3A4 inducers.

3) Increase of the duration of screening period

The screening period has been increased from 7 days to 10 days (see Section 6.3). A screening period of 7 days poses an unnecessary logistical burden for study sites. An extension of this period to 10 days does not impact the scientific nor the clinical aspects of the study.

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4) Reduction of the number of required afabicin IV administrations before switch to the oral dosage form

Based on feedback from Investigators, requiring 2 afabicin IV administrations will unnecessarily prolong the hospital stay of some patients, who otherwise could be discharged. Additionally, the OVIVA trial [5] results provide good evidence that BJI patients can be adequately treated with oral regimens. Thus, the minimum required number of afabicin IV administrations before the switch to the oral dosage form was reduced from 2 to 1 (see Section 6.2.1).

5) Use of ibuprofen and tramadol for acute pain management

Appropriate pain management is a key component in the treatment of BJI, especially because most patients undergo surgical treatment. Both ibuprofen [6-8] and tramadol [9] can be used up to 5 days for the treatment of acute pain, at labeled doses. See Section 8.7.3.4. for clarification.

1.9 Protocol V13.0, amendment 10

The rationale for the changes introduced by the current amendment is summarized below:

1) Assessment of biomarkers related to the gut microbiota as a new exploratory endpoint

Afabicin is designed to target specifically staphylococci. *In vivo* and preliminary clinical data suggest that afabicin is active against staphylococci but not against other bacteria, thus, with potential microbiome-sparing properties [4]. Therefore, in the current amendment, stool sampling from a subset of patients is included to assess various biomarkers of the microbiota, including the relative abundance of microbial taxa, the prevalence of antibiotic-resistance genes, and various metabolites linked to gut health (including short chain fatty acids and bile acids). These data will help to further evaluate the microbiota-sparing potential of afabicin in patients (See sections 5.3, 9.1.4.3.2, 9.2.8.1, 12.4.2.8, and 14 – Part B).

2) Correction of listed clinical signs and symptoms

As part of secondary efficacy endpoints, presence or absence of 16 clinical signs and symptoms are assessed at i) Day 8, ii) Day 28, (for Cohorts 2, 2B, 2C & 3, 3B, 3C only), iii) Day 42, (for Cohorts 2, 2B, 2C& 3, 3B, 3C only), iv) at EOT, v) at 4 weeks post-EOT, and vi) at 12 weeks post-EOT. This amendment would rectify some identified inconsistencies in listing of these 16 clinical signs and symptoms in different sections of the protocol (see sections: 9.1.3, 9.2.3, and 14 - Part B).

In addition to the main points described above, further corrections, clarifications, and minor typographical changes have been made throughout the protocol.

2 INTRODUCTION

Staphylococcus aureus is the most common causative pathogen implicated in osteoarticular infections. It has been identified in 30 to 60% of osteomyelitis cases and accounts for 39 to 76% of septic arthritis cases.[10] *S. aureus* and coagulase-negative staphylococci (CoNS) also contribute to between 50 and 60% of prosthetic joint infection (PJI) cases.[11] The overall incidence in adults in high resource countries is estimated at 4-10/100 000 patient-years for septic arthritis and 2-10/100 000 patient-years for osteomyelitis.[10] The annual rate of PJIs is estimated at around 2% of hip or knee arthroplasties.[11]

Despite the availability of broad-spectrum antibiotics and advances in diagnostic and surgical techniques, osteoarticular infections continue to be associated with significant morbidity and mortality. Septic arthritis is considered to be a medical and surgical emergency, associated with a mortality rate of around 11%.[12] More than 10% of patients experience a recurrent arthritis and 10-30% of patients with septic arthritis suffer long-term decreased joint function or mobility.[10]

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Osteomyelitis results in inflammatory bone destruction, bone necrosis, and new bone formation. The short-term mortality rates for osteomyelitis are 2.8-7.7% for nonvertebral osteomyelitis and 6-16% for vertebral osteomyelitis. The mortality rate due to PJI has been reported between 0% and 7% for PJI due to *S. aureus*.[11]

The current treatment recommendations for osteoarticular infections involve long-term treatment with broad-spectrum antibiotics. The agent most frequently used for treating osteoarticular infections due to methicillin-resistant *S. aureus* (MRSA) is vancomycin. However, it is associated with significant toxicity (including leukopenia, ototoxicity, and, rarely, nephrotoxicity), low clinical cure rates, therapeutic drug monitoring requirements, emerging problems of nonsusceptibility, poor bone penetration, allergy and intolerance, and the requirement for IV administration, all of which diminish the utility of vancomycin. Thus, other antimicrobial agents have been increasingly used for MRSA osteoarticular infections; these include linezolid and daptomycin. These newer treatment options are also associated with safety risks; linezolid has been associated with cytopenias, peripheral neuropathy, optic neuritis, and severe anemia, while daptomycin therapy requires monitoring for toxicity such as rhabdomyolysis, neuropathy, and eosinophilic pneumonia. Co-administration with statins is not recommended while on daptomycin, which may diminish its utility in certain patient populations. In addition, emergence of daptomycin resistance on therapy has been reported.

The agents most frequently used for treating osteoarticular infections due to methicillin-susceptible *S. aureus* (MSSA) include nafcillin, clindamycin, flucloxacillin, or fluoroquinolones. Common toxicities with these agents include gastrointestinal and central nervous system (CNS) disturbances, and skin rashes. In addition, the use of fluoroquinolones has been associated with a prolonged QTc interval and tendinopathy.

The use of broad-spectrum antibiotics has been implicated in the disturbance of commensal gut microbiota leading to a spread of antibiotic resistance and increased colonization by various gut pathogens, such as *Clostridium difficile* and *Salmonella typhimurium*.[13-15]

In order to avoid the overuse of broad-spectrum antibiotics, rapid diagnostic tools for detection of bacterial pathogens, and especially of MRSA, have been successfully implemented in clinical microbiology practice and are undergoing continuous improvement.[16,17] Wide use of such rapid diagnostic tools will facilitate the use of narrow-spectrum targeted antibiotic therapy.

Afabicin (Debio 1450) is a potent anti-staphylococcal antibiotic with a unique mechanism of action and a narrow spectrum of activity. Afabicin, through its active moiety Debio 1452, targets bacterial fatty acid biosynthesis by inhibiting the enzyme FabI, which is essential for bacterial growth and survival. The FabI target of afabicin/Debio 1452 activity is conserved across all staphylococcal species and a few gram-negative pathogens.

The narrow spectrum of activity of afabicin makes it a promising candidate to meet the growing need for agents effective against antibiotic-susceptible and -resistant staphylococcal isolates associated with human disease. Unlike the broad-spectrum anti-staphylococcal agents in use today, therapy with a narrow-spectrum agent such as afabicin is unlikely to produce significant change in normal gut flora, thus reducing the spread of antibiotic resistance and the incidence of antibiotic-induced colitis, including *C. difficile* enterocolitis.[18,19]

To date, the efficacy and safety of afabicin/Debio 1452 have been demonstrated in patients with ABSSSI in two phase 2 clinical trials. Afabicin and its active moiety have been shown to be effective against MRSA and MSSA, and well tolerated.[2, 20,21]

Afabicin could fill an unmet need given its potential advantages over broad-spectrum antibiotics for the treatment of staphylococcal BJIs, however, to date there are no data generated in a population of patients with osteoarticular infections. The current proposed study will investigate the safety and efficacy of afabicin in adult patients diagnosed with staphylococcal osteoarticular infections, namely septic arthritis, osteomyelitis, and PJI (once the prosthesis is removed or with planned removal).

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3 PHARMACEUTICAL AND BACKGROUND INFORMATION

Afabicin is a small molecule prodrug which is converted *in vivo* to the active free base Debio 1452. The phosphate prodrug afabicin differs from Debio 1452 by the presence of a methylene phosphate.

3.1 Chemical structure, formula, and molecular weight

Chemical name:	(E)-6-[(N-methyl-((3-methylbenzofuran-2-yl) methyl)amino)-3-oxoprop-1-en-1-yl)-2-oxo-3,4-dihydro- 1,8-naphthyridin-1(2H)-yl]methyl phosphate, bis ethanolamine salt.
Drug substance:	Afabicin olamine (Debio 1450 bis-ethanolamine salt (BES), Debio 1450-BES)
Empirical or Molecular Formula:	$C_{23}H_{22}N_3O_7P$ $(C_2H_8NO)_2$
	(Combined: $C_{27}H_{38}N_5O_9P$)
Molecular weight:	607.59

3.2 International non-proprietary name, brand name, and code name

INN:	afabicin
Brand name:	Not applicable
Code names:	Debio 1450

3.3 Mechanism of action

The mechanism of action of Debio 1452 involves an interference with bacterial-specific fatty acid biosynthesis through inhibition of enoyl-acyl carrier protein (ACP) reductase FabI, an enzyme essential for bacterial growth and survival. In the bacterial fatty acid biosynthesis pathway, the FabI enzyme catalyses the final step in the chain elongation process, reducing enoyl-ACP to acyl-ACP. Inhibition of FabI prevents growth of the acyl chain, disrupting both saturated and unsaturated fatty acid biosynthesis, thus preventing bacterial growth.

3.4 Brief summary of nonclinical and clinical data

Please refer to the current version of the afabicin Investigator's Drug Brochure (IDB) for a comprehensive presentation of the nonclinical and clinical data currently available with afabicin.

3.4.1 Nonclinical data

Antimicrobial spectrum of afabicin/Debio 1452 and its efficacy in osteomyelitis model is discussed in Section 4.1, while the mechanism of action is outlined in Section 3.3. This section will focus on the mechanism of resistance and nonclinical safety findings. A detailed presentation of nonclinical data is provided in the current version of the IDB, Section 5.

Mechanism of resistance

Low frequency of spontaneous mutation and low level of resistance due to point mutations in the target FabI enzyme were observed *in vitro* for Debio 1452. Emergence of resistance has not been observed in various animal infection experiments and in the phase 2 ABSSSI study. [redacted]

Nonclinical safety

A core battery of safety pharmacology studies of afabicin was conducted, including effects on human ether-a-go-go-related gene (hERG) and various ion channels *in vitro*; effects on blood pressure,

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heart rate, and ECG parameters in conscious telemetered dogs; as well as CNS and respiratory safety pharmacology studies in rats. Debio 1452 (the active moiety of afabicin, but not the prodrug itself), was found to be a potent inhibitor of PDE3A and PDE3B (IC_{50} 0.67 µM and 0.64 µM, respectively) and a moderate inhibitor of hERG (IC_{50} ~11 µM). Although afabicin showed no effects on ECG parameters in conscious dogs, tachycardia and tremors induced at higher doses may have interfered with QT analysis. In rats, afabicin treatment caused decreased locomotor activity and/or decreased body temperature at ≥ 80 mg/kg.

The main target organs of toxicity were adrenal gland (cortical hypertrophy of the zona fasciculata and vacuolation), cardiovascular system (decrease in blood pressure and increase in heart rate), reproductive organs (decrease in corpora lutea and increase in atretic follicles, higher percentage in pre-implantation loss at very high dose), and infusion sites (IV dosing only). Similar safety profiles and exposure were obtained with both IV and PO dosing.

When Debio 1452 exposures are compared between toxicology species and humans, the area under the concentration vs time curve (AUC) at no-observed-adverse-effect level (NOAEL) in toxicology species was over 2-fold higher than at the proposed human dose in Part A of the current study. In humans, Debio 1452 exposures were 37,930 ng•h/mL after 5 days dosing at 160 mg BID IV and 35,000 ng•h/mL after 5 days dosing at 240 mg BID PO (the initial - maximal - dose regimen of afabicin IV 160 mg BID/240 mg PO BID in the current study).

[redacted]

3.4.2 Clinical data

To date, afabicin has been administered to [redacted] n a series of 11 phase 1 studies to assess PK following single and repeated IV and PO doses, bioavailability and food effect, bone penetration, mass balance, pharmacokinetic drug-drug interactions (perpetrator and victim), injection sites reactions (ISRs) and effects on QTc prolongation (thorough QT [TQT] study).

Additionally, 217 patients received afabicin at one of two dose levels (160 mg IV/240 mg PO BID or 80 mg IV/120 mg PO BID) in a multicenter, randomized, active controlled phase 2 study to assess the efficacy, safety and tolerability of afabicin compared with standard antibiotic therapy (vancomycin IV/linezolid PO) for treatment of ABSSSI due to *Staphylococcus* species (Spp). Clinical efficacy was demonstrated with non-inferiority confirmed for both the afabicin treatment groups compared to the control group. The primary efficacy endpoint of early clinical response (ECR), defined as the proportion of patients with ≥ 20% reduction in lesion size at 48 to 72 hours post-randomization, was achieved by 94.6% (87/92) in the low-dose group, 90.1% (82/91) in the high-dose group, and 91.1% (92/101) in the comparator group.

These findings were consistent with the previously published results of a phase 2a, open-label, non-controlled, ABSSSI study with Debio 1452 (active moiety of afabicin) (study AFN-12520000-010). In that study, patients were treated with 200 mg Debio 1452 PO BID (equivalent to 260 mg afabicin PO BID based on molecular weight). In the microbiologically evaluable population, overall ECR was achieved by 97.3% and “clinical cure” at 7-14 days after EOT by 93.4%.[20]

Treatment with afabicin was generally safe and well-tolerated across phase 1 and phase 2 studies. The main dose-limiting effects were headache, which was dose-proportional, nausea and vomiting.

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There were no deaths in phase 1 trials and 1 death due to heroin overdose in a phase 2 trial (Debio 1450-ABSSSI-201), please refer to IDB (Version 7.0). This patient was a 53-year-old white male with a 10-year history of drug abuse. He was on diamorphine at the time of randomization. He presented with a wound due to MSSA. This patient received 2 doses of afabicin IV 160 mg and 1 dose of afabicin 240 mg PO (total exposure of 560 mg). On Day 3 of the study, he was found dead of heroin overdose. Limited information was provided from the Investigator site on this event and, furthermore, no autopsy was performed. The event was considered by the Investigator as not related to study medication.

[redacted]

The effect of afabicin on QT was assessed during a dedicated TQT study in healthy volunteers. The study reported a dose-dependent risk of QT prolongation. A supratherapeutic dose [redacted] of afabicin caused a mild QTc prolongation of approximately the same magnitude as a therapeutic dose of moxifloxacin. However, no clinically significant QT prolongation (i.e., < 10 ms threshold) was observed following a lower 160 mg IV dose of afabicin with the largest upper 90% confidence interval (CI) limit of 7.7 ms, at approx. 2 hours after infusion start. The observed time course of the QTc prolongation in this study was almost simultaneous with the PK profile of Debio 1452. As PK assessments showed that Debio 1452 does not accumulate with repeated administrations, no further QTc prolongation is expected at steady state. Based on concentration-QTc (C-QTc) modeling, no clinically significant QTc prolongation is anticipated at any dose levels used in the current study. Nevertheless, QT monitoring and cardiac specific exclusion criteria are implemented in the study.

A summary of phase 2 clinical data [redacted] is presented below. [redacted]

Hepatic transaminase elevations in ABSSSI phase 2 trials

1. Debio 1450-ABSSSI-201: In the low-dose group (80 mg IV/120 mg oral), 3 patients (out of 110) had ALT and/or aspartate aminotransferase (AST) elevations >3 x ULN; there were with no associated increases in bilirubin. [redacted]

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- [redacted]

[redacted]

[redacted]

In the high-dose group (160 mg IV/240 mg oral), 1 patient (out of 107) had AST elevations >3 x ULN in this study:

- [redacted]

2. Study AFN-12520000-010: In a previous phase 2, open-label study conducted with Debio 1452 (afabicin's active moiety) in 103 patients with ABSSSI, 1 patient had a shift in both ALT and AST concentrations from normal at baseline to > 3 x ULN. Bilirubin remained within normal range. This patient's concurrent health issues included IV drug abuse and severe infections.

QT prolongation in ABSSSI phase 2 trials

[redacted]

1. [redacted]

2. Study AFN-12520000-010: Mean changes in ECG parameters were small with relatively few shifts in the measured parameters. [redacted] There was no relationship between pre-dose QTc interval and post-dose QTc intervals nor was there a relationship between QTc and AUC or maximum (peak) serum concentration (C_{max}) for Debio 1452.

Serious adverse events in healthy volunteer studies and in ABSSSI phase 2 trials

In the 2 phase 2 studies in patients with ABSSSI, 7 patients reported serious adverse events (SAEs):

1. Debio 1450-ABSSSI-201: There were 3 treatment-emergent SAEs reported:

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- 2 SAEs of skin infection (exacerbation) in patients with ABSSSI treated with low-dose afabicin. One of the cases was considered as treatment related.
- 1 SAE of heroin overdose leading to death in a patient with ABSSSI treated with high-dose afabicin, as described above.

2. Study AFN-12520000-010: In this open-label trial with Debio 1452, 4 patients had serious adverse reactions: opioid drug withdrawal syndrome in 1 patient, neck abscess (due to ongoing heroin injections) in 1 patient, and progression of cellulitis in 2 patients (each had cellulitis at baseline). None of the SAEs were considered to be drug related.

[redacted]

3.5 Risk mitigation plan

The following safety measures are implemented in this trial to ensure patient safety, as described in detail in subsequent sections.

Part A:

1. [redacted]
2. [redacted]
3. Monitoring of liver transaminase values and QT interval [redacted] during afabicin treatment, [redacted] ections 6.4.1).
4. Stepwise (staggered) approach to increase treatment duration (Section 6.1).
5. Safety data review by IDMC at regular intervals (Section 11.2.1).
6. [redacted]
7. Prompt communication of relevant safety data to Investigators, study staff and patients.
8. The Investigator will instruct the patients to refrain from consuming alcohol while in the study and to contact the Investigator before taking any concomitant medications including Over the Counter (OtC) medications and herbal therapies (see Section 8.7). The Investigator and/or the dedicated study physician in charge of home visits will inquire regularly about alcohol consumption and concomitant medications, including OtC and herbal therapies.

Part B:

1. [redacted]
2. Exclusion of immunocompromised and neutropenic patients in the study, since the antimicrobial effect of afabicin may be partly mediated by immune cells (Section 7.2).
3. [redacted]
4. Monitoring of liver transaminase will be performed during afabicin treatment [redacted] (Sections 6.4.1).

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5. Monitoring QT interval through ECGs performed at screening, baseline (Day 1 pre-dose and 3.5 hours post-infusion) and Day 28 or at the EOT visit if treatment < 28 days (pre-dose and 5.5 hours post-dose) (Sections 6.4.1).
6. Stepwise approach to test a longer treatment duration (Section 6.1).
7. Safety data review by IDMC at regular intervals (Section 11.2.1).
8. [redacted]
9. Once a cohort is completed, the data will be reviewed by IDMC, [redacted] and the relevant Health Authorities (when necessary) before initiation of subsequent cohorts. Subsequent cohorts will be also reviewed by the IDMC [redacted] and, if necessary, by the concerned Health Authorities, before the next cohort is open. (Section 6.1.2).
10. Prompt communication of relevant safety data to Investigators, study staff and patients.
11. The Investigator will instruct the patients to refrain from consuming alcohol while in the study and to contact the Investigator before taking any concomitant medications including OtC medications and herbal therapies (see Section 8.7). The Investigator and/or the dedicated study physician in charge of home visits will inquire regularly about alcohol consumption and concomitant medications, including OtC and herbal therapies.

3.6 Benefit-risk assessment

S. aureus and CoNS are the most common causative pathogen implicated in osteoarticular infections. Despite the availability of broad-spectrum antibiotics and advances in diagnostic and surgical techniques, osteoarticular infections continue to be associated with significant morbidity.

Afabicin offers a new class of antibiotics with a high potency, unique mechanism of action and a narrow spectrum of activity, providing significant benefits for treatment of infections caused by *Staphylococci*, such as i) lack of cross-resistance with other antibiotics, ii) low potential for development of resistance, iii) preservation of gut microbiota and therefore reducing the risk of antibiotic-associated diarrhea, *C. difficile* infections, or candidiasis, as well as decreasing potential for antibiotic resistance selection and spread in intestinal microbiota; iv) dual formulation allows treatment with IV followed by a highly bioavailable oral therapy; v) good penetration into the bone; and vi) demonstrated efficacy in patients with ABSSSI comparable with SoC treatment.

In clinical studies to date, involving [redacted] and 217 patients with ABSSSI, afabicin demonstrated a favorable safety profile. In the phase 2 ABSSSI study, the most frequently reported AEs were headache, nausea, and vomiting. Patients treated with afabicin had a lower incidence of diarrhea compared with the comparator group. [redacted] as discussed in Section 3.5. Importantly, recent safety and C-QT modeling data suggest that the current afabicin dosing regimen (55mg IV BID/80 mg PO BID) is not associated with risk of QTc prolongation. [redacted]

Considering the benefits of offering a first-in-class highly potent antibiotic with a unique mechanism of action and a narrow spectrum of activity targeted against *Staphylococci* and risks of alternative therapies for osteoarticular infections, the data generated so far support a potential positive benefit:risk balance for afabicin, [redacted]

The totality of data, including the extensive new mechanistic studies conducted, strongly suggest that the lower dose levels in Part B will provide adequate safety and efficacy in the BJI setting. In addition, several measures have been introduced in this study to closely monitor and early identify a potential safety alert and lack of efficacy of the lower doses in Part B.

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4 RATIONALE FOR CLINICAL INDICATION, TREATMENT REGIMEN AND STUDY DESIGN

This is a phase 2a, open-label, randomized, active-controlled, interventional, multicenter study to investigate safety and efficacy of afabicin in the treatment of patients with BJIs due to *S. aureus* sensitive and/or resistant to methicillin, and/or due to CoNS.

4.1 Choice of clinical indication

Patients with the following indications will be included in the current study:

a) Septic arthritis: including acute and chronic forms.

b) Osteomyelitis: including vertebral and long bone osteomyelitis whether hematogenous, contiguous, or associated with trauma, but excluding diabetic foot osteomyelitis.

c) PJI: between removal and re-insertion of prosthesis, with a planned prosthesis removal when the pathogen is known to be *Staphylococcus* only, or other clinical settings where biofilm is not considered to be yet established and/or has been mechanically eradicated.

   Cases where biofilm is considered as an important factor in the bacterial infection are excluded because (1) afabicin is required to be administered in combination to achieve the highest activity on biofilm, and (2) the combination of afabicin with rifampicin is prohibited due to DDIs (see Section 8.7.4).

The choice of afabicin is appropriate given that these infections are predominantly caused by *S. aureus* and/or CoNS. In addition, afabicin has several characteristics which make it suitable a treatment of choice for therapy in these indications:

(1) It has shown *in vitro* high potency against *S. aureus*, particularly MRSA, and CoNS.

(2) It has shown significant efficacy in nonclinical osteomyelitis models.

(3) It has shown penetration into bone and joint that is similar or better than commonly used antibiotics.

(4) It is unlikely to disturb commensal gut microbiota (based on preclinical and human data), thus reducing the common problems encountered with the use of broad-spectrum antibiotics, such as *C. difficile* infections.

(5) It is available in an IV and highly bioavailable oral formulation.

Antimicrobial potency spectrum

Afabicin has been shown effective in eradicating staphylococci, including *S. aureus* susceptible or resistant to methicillin and other classes of antibiotics. Debio 1452 (active moiety of afabicin) was highly active against [redacted] staphylococcal isolates tested to date. Debio 1452 showed global MIC_{90} values of 0.008 µg/mL against MRSA, 0.016 µg/mL against MSSA and *S. lugdunensis*, 0.06 µg/mL for *S. epidermidis*, and 0.12 µg/mL for other CoNS (Table 4-1). Debio 1452 showed little to no activity against non-staphylococcal pathogens tested [redacted] isolates).

As expected from its novel mechanism of action, Debio 1452 showed no cross-resistance to any of the comparator antibiotic classes tested, including antibiotics typically used to treat gram-positive or staphylococcal infections (e.g., linezolid, daptomycin, clindamycin, levofloxacin, gentamicin).

Table 4-1 Activity of Debio 1452 against staphylococcal isolates (selected data from surveillance and clinical studies 2004-2017)

Organism	Type	Strain No.	MIC (µg/mL)		
			MIC Range	MIC_{50}	MIC_{90}
S. aureus	MR	[redacted]	≤ 0.001 to 0.25	≤ 0.008	0.008
	MS		≤ 0.002 to 0.25	≤ 0.008	0.016
S. epidermidis	MR		≤ 0.001 to 0.50	0.016	0.030

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	MS	[redacted]	≤ 0.002 to 0.50	0.008	0.060
S. lugdunensis	MR		0.008	-	-
	MS		0.002 to > 0.25	0.008	0.016
Other CoNS	MR		0.004 to 0.50	0.016	0.120
	MS		0.002 to 0.50	0.030	0.120

MS = methicillin-sensitive; MR = methicillin-resistant; MIC=Minimal inhibitory concentration; CoNS= Coagulase-negative staphylococci

Debio 1452 shows a formally bacteriostatic effect *in vitro* (with a bactericidal effect beyond 24 hours in a subset of strains), is active against intracellular *S. aureus*, and presents no post-antibiotic effect *in vitro*.

Nonclinical efficacy in osteomyelitis model

Debio 1452 was found to be active *in vitro* against [redacted] MRSA bone isolates (collected 2012-2013) with a very narrow MIC range of 0.004-0.015 µg/mL (the mode, MIC_{50} and MIC_{90} were 0.008 µg/mL). The efficacy of its prodrug afabicin (Debio 1450) has also been shown in rat tibia osteomyelitis model and rabbit model of acute osteomyelitis (see IDB, Section 5.1.2.3.2 for further details).

After a 4-day treatment of osteomyelitis in MRSA-infected rabbits, afabicin demonstrated a dose-effect relationship in reducing significantly the bacterial load (Table 4-1), whereas vancomycin (100 mg/kg once a day [QD] IV, not shown in the figure) did not show a statistically significant antibacterial activity compared to the vehicle group. The lack of activity of vancomycin is in line with the literature indicating that it generally performs poorly in preclinical models of bone infection.[22,23] No development of resistance against afabicin was observed.



Penetration into the bone

Penetration of Debio 1452 into bone and joint tissues was evaluated in a dedicated phase 1 study (Debio 1450-108) in 17 patients undergoing hip replacement surgery. The patients received three pre-surgical oral doses of afabicin (240 mg) approximately 12 hours apart, the last dose being

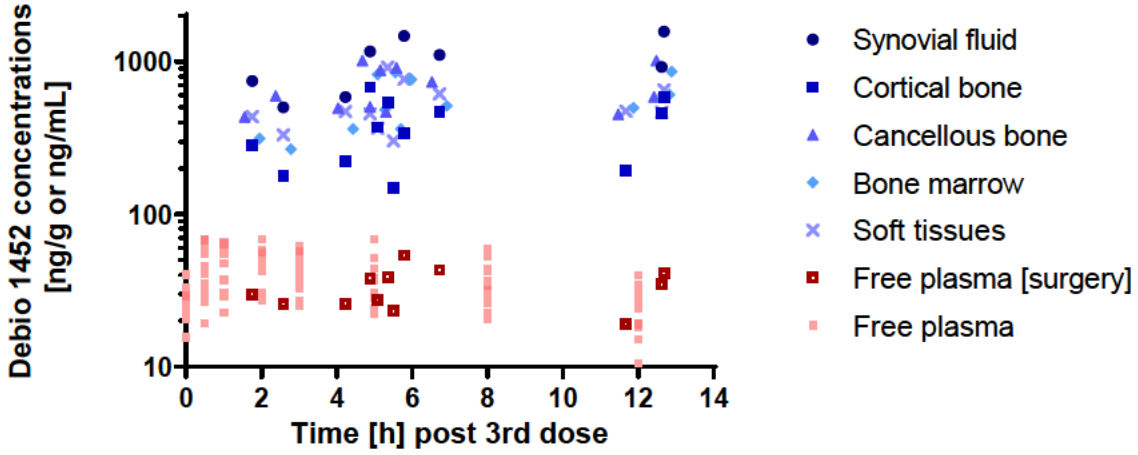
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administered at 2, 4, 6 or 12 hours before surgery. PK was evaluated in bone tissues collected at the time of surgery, and in plasma over the 12-hour dosing interval (see Figure 4-2).

Mean AUC ratios for cortical, cancellous, bone marrow, soft tissue and synovial fluid to total plasma concentrations were 0.21, 0.40, 0.32, 0.35 and 0.61, respectively. These data showed that Debio 1452 has a similar to better penetration into the non-infected bone tissues compared to other anti-staphylococcal antibiotics.[24] In fact, published data in similar study designs (patients undergoing elective surgery and quantification of the drug in bone tissues after homogenization) report mean bone and synovial fluid-to-serum ratios of 0.40 and 0.92 for linezolid; mean cortical and cancellous bone-to-serum ratios of 0.07 and 0.13 for vancomycin; median cortical and cancellous bone-to-serum ratios of 0.13 and 0.19 for ertapenem; and a mean bone-to-plasma AUC ratio of 0.13 for dalbavancin.[25,26] The ratios of tissue-to-free plasma concentrations of Debio 1452 ranged from 14.5 to 26.7 for cancellous bone, 6.3 to 17.9 for cortical bone, 10.4 to 26.2 for bone marrow, 19.5 to 38.5 (~30 on average) for synovial fluid, and 12.0 to 24.9 for soft tissue.

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Figure 4-2 **Study Debio 1450-108: Debio 1452 concentrations in plasma and bone tissues after the third oral dose of afabicin (240 mg, Q12h) in patients undergoing hip replacement surgery.**



The patients received three pre-surgical oral doses of afabicin (240 mg) approximately 12 hours apart, the last dose being administered at 2, 4, 6 or 12 hours before surgery. Debio 1452 concentration was quantified by LC-MS/MS in tissues collected at the time of surgery, and in plasma samples collected over the 12-hour dosing interval. Data are from 14 patients, with the following exceptions: for 1 patient, the plasma sample was missing at the time of resection and the plasma concentration was extrapolated by linear regression between the two adjacent concentration data from the full PK profile in plasma. Synovial fluid was obtained for 8 patients only. For one patient no results except for plasma were reportable at the time of resection, and for another, only plasma, soft tissue, and bone marrow were collected at the time of resection.

Of note, the human bone tissue-to-plasma ratios are comparable to those obtained in non-infected femoral bone marrow and epiphyseal bone marrow collected in the rabbit experimental model of acute osteomyelitis (bone-to-plasma ratios of approx. 0.3). Moreover, a higher bone penetration was observed in infected rabbit tissues (mean ratios usually above 1.0 and individual values ranging from 0.10 up to 11.8). Assuming those data translate into humans, this suggests that bone penetration of Debio 1452 in patients with bone and joint infections may be even higher compared to patients undergoing elective surgery.

Altogether, the non-clinical efficacy data and the human bone penetration data indicate a great potential of afabicin for a high antibacterial activity in bone tissues.

Effect on gut microbiota

The impact of oral afabicin on the fecal microbiota was analyzed by 16S rDNA taxonomical metasequencing in mouse and healthy volunteers. No major changes in gut microbiota composition were detected, confirming the narrow antimicrobial spectrum of activity of afabicin.

Preclinical data: While radical changes in the mouse microbiota composition and abundance were observed in response to three broad-spectrum antibiotics (linezolid, moxifloxacin, clindamycin) over the course of the treatment and post-treatment, there were no statistically significant differences between the afabicin- and the vehicle-treated group.

Clinical data: Stool samples from fifteen healthy subjects who received oral afabicin in an open-label, fixed sequence DDI study Debio 1450-104 were analyzed. In line with the *in vivo* results, the obtained data revealed no radical changes in the human intestinal microbiota composition at the phylum, family and genus level induced by afabicin.

Collectively these results, together with the availability of IV and oral formulation (Section 4.2.1), suggest that afabicin may have therapeutic potential in the treatment of staphylococcal osteoarticular infections, including those resistant to other antibiotics.

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4.2 Choice of dosing regimen

4.2.1 Dose and frequency

The rationale for the selection of the dosing regimens of 160 mg IV BID/240 mg PO BID in Part A, and 55 mg IV BID/80 mg PO BID or 80 mg IV BID/120 mg PO BID in Part B is based on the PK, microbiological findings and safety and efficacy observed in clinical studies with afabicin. The high dose regimen of 160 mg IV BID/240 mg PO BID in Part A was previously assessed in a study of afabicin in patients with ABSSSI. This dosing regimen was also supported by a preliminary PTA calculated using Debio 1452 plasma exposure based on non-clinical targets of efficacy (PK/PD targets) derived from neutropenic mouse thigh infection model.

The lower dose regimens of 55 mg IV BID/80 mg PO BID and 80 mg IV BID/120 mg PO BID in Part B are further supported by:

- [redacted]
- Alternative PTA calculations:
  - Based on ~30-fold higher Debio 1452 concentrations in human synovial fluid and bone tissues compared to plasma (see Section 4.1), as well as in macrophages and monocytes. The rationale for this approach is that tissue concentrations, rather than plasma, are more representative of the bioactive drug levels at the site of infection. This PTA associated with stasis suggests that a dosing regimen ≥ 55 mg IV BID/80 mg PO BID will provide bone tissue exposures that are anticipated to be efficacious in at least 90% BJI patients infected with staphylococci (including *S. aureus* and CoNS) at MIC ≤ 0.06 µg/mL.
  - Based on efficacy data and PK/PD targets obtained in immunocompetent mouse thigh infection model, which are consistent with the PTA calculations using the human synovial fluid. PTA using this approach is 100% for bacterial stasis in patients infected with staphylococci at MIC ≤ 0.06 µg/mL, and 100% for 2-$\log_{10}$ colony-forming units (CFU) reduction in patients infected with staphylococci at MIC ≤ 0.015 µg/mL.

These findings are further described below.

Pharmacokinetics

Afabicin is rapidly converted to the active drug Debio 1452. Debio 1452 has a C_{max} which occurs within 30 minutes after the end of the 2-hour IV infusion or at 3-4 hours after oral dosing in fasted conditions. The plasma half-life of Debio 1452 of approximately 7-12 hours supports a BID dosing regimen.

The bioavailability is approximately 0.7 after oral as compared to IV administration of afabicin and, hence, similar Debio 1452 plasma exposures are achieved with afabicin 160 mg IV versus 240 mg PO, 55 mg IV versus 80 mg PO and 80 mg IV versus 120 mg PO. Moreover, the use of both dosing routes is in line with the current guidelines for osteoarticular infections that recommend treatment with IV antibiotics or highly bioavailable oral antimicrobial therapy.

When afabicin film-coated tablets are administered with food, a similar Debio 1452 AUC but a slightly lower C_{max} (by ca. 25%) and a delayed time to reach maximum plasma concentration following drug administration (t_{max}) (at 8 hours) are observed, as compared to fasted conditions.

The PK-PD index most correlated with antibacterial efficacy according to mouse neutropenic thigh-model data is free-drug plasma $AUC_{0\text{-}24h}$:minimal inhibitory concentration (*f*AUC:MIC). Since efficacy is driven by AUC, and because AUC is not impacted by food, film-coated tablets could be administered without regard to food or timing of meals, with respect to efficacy. However, to minimize

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C_{max} and AEs related to the peak concentration (notably risk of QT prolongation, see Section 3.4.2), afabicin will be administered preferably with meals; except on the day of PK sampling (Day 28 visit) when the film-coated tablets will be administered in the morning in fasted conditions to allow for collecting PK data in standardized conditions.

Probability of PK-PD Target Attainment

Part A

PTA analyses were conducted, based on non-clinical targets of efficacy against *S. aureus* in neutropenic mouse thigh infection model, a population PK model based on clinical plasma exposure, and Monte Carlo simulations. Results of these preliminary analyses predicted that afabicin dose regimens ≥ 160 mg IV BID/240 mg PO BID will provide an adequate target attainment in BJI patients.

Part B

Since tissue concentrations, rather than plasma, are more representative of the bioactive drug levels at the site of infection, an alternative PTA analysis was conducted based on the synovial fluid exposure. This exposure reflects high bone, macrophages and monocytes penetration of the drug. The analyses performed for the afabicin dosing regimen of 80 mg PO BID presented in Figure 4-3 **(A)** showed a [redacted] PTA associated with stasis of staphylococci with [redacted].

[redacted]

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An alternative PTA was also calculated using data of enhanced response observed in immunocompetent vs. neutropenic mice in the thigh infection model. For the afabicin dosing regimen of 80 mg PO BID (Figure 4-3 (**B**)) this analysis showed [redacted] PTA associated with stasis of staphylococci with [redacted], and [redacted] PTA associated with a [redacted]

The enhanced efficacy of afabicin in immunocompetent mice is in line with the rapid Debio 1452 accumulation in monocytes and macrophages observed *in vitro*.[24] This may also contribute to its potential increased concentration at the infection sites due to the recruitment of leukocytes upon infection and inflammation.

The results obtained using both PTA approaches are consistent and support the selection of the 80 mg PO BID dosing regimen.

Clinical safety

In clinical studies to date, involving [redacted] and 217 patients with ABSSSI, afabicin demonstrated a favorable safety profile. The most frequent drug-related adverse effects were headache, nausea and vomiting. As expected, in the phase 2 ABSSSI study (Debio 1450-ABSSSI-201), patients in the 80 mg IV BID/120 mg PO BID dose afabicin group had a lower incidence of headaches and nausea/vomiting compared with the 160 mg IV BID/240 mg PO BID dose group. However, both groups had a lower incidence of diarrhea compared with the comparator group. Afabicin at the initial dose regimen for the current study was well tolerated. Further details on the safety profile of afabicin are provided in Section 3.4.2.

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A favorable hepatic and cardiac safety profile at doses of 55 mg IV BID/80 mg PO BID and 80 mg IV BID/120 mg PO BID is supported by *in silico* and C-QTc models, as presented in Sections 3.4.1 and 3.4.2.

Clinical efficacy

Two afabicin dosing regimens were tested in a phase 2 study in patients with ABSSSI (Study Debio 1450-ABSSSI-201). Both the low-dose afabicin regimen (80 mg IV BID/120 mg PO BID) and the high-dose afabicin regimen (160 mg IV BID/240 mg PO BID) were non-inferior to the SoC comparator (vancomycin IV BID/linezolid PO BID). [redacted]

4.2.2 Treatment duration

Per current practice, treatment of osteoarticular infections usually begins with IV antibiotic therapy, followed by a switch to an appropriate oral formulation after 1 or 2 weeks. However, successful treatment with a shorter duration of IV medication (2-4 days) has been reported.[27-29] A recent study demonstrated that oral therapy is non-inferior to IV therapy when used in the early treatment of bone and joint infection.[5,30,31]

Per the Infectious Diseases Society of America (IDSA) clinical practice guidelines for the treatment of MRSA infections, “clinical response should guide the decision to convert from parenteral to oral therapy” for patients with MRSA-infected bone and/or joints.[32] Thus, in the current protocol, the switch from IV to oral therapy will be made if the acute toxicity of the infection has resolved, the patient is tolerating fluids and a regular diet, and/or the Investigator determines that the patient no longer needs IV antibiotic therapy; however, IV treatment may not exceed 2 weeks. Given afabicin bioavailability of approximately 0.7 after oral as compared to IV administration, an early switch from IV to oral therapy is recommended. In addition, an early switch from IV to oral therapy would reduce risks associated with IV lines, allow early discharge from a hospital, and prove convenient for the patient.

A stepwise approach to lengthening treatment duration with antibiotics (excluding initial empiric therapy) will be implemented in the current study. The afabicin treatment duration for the patients in Cohorts 1, 1B and 1C is a maximum of 3 weeks, in Cohorts 2, 2B and 2C a maximum of 6 weeks and in Cohorts 3, 3B and 3C a maximum of 12 weeks. The maximum treatment duration (up to 12 weeks) with afabicin in the study should not be exceeded.

The proposed treatment durations in this study are aligned with the current treatment recommendations for patients with septic arthritis (3-4 weeks) and osteomyelitis (6-12 weeks).[29,33,34] For patients with PJI following resection arthroplasty with or without planned staged reimplantation, the current IDSA recommendations call for 4 to 6 weeks of pathogen-specific IV or highly bioavailable oral antimicrobial therapy.[35,36]

4.3 Rationale for study design

This is a phase 2a, open-label, randomized, active-controlled, interventional, multicenter study to investigate the safety and efficacy of afabicin in patients with BJIs due to *Staphylococcus*.

The rationale for each aspect of the study design is provided below.

Open-label: The primary objective of this study is to determine the safety and tolerability of afabicin treatment [redacted] and, thus, an open-label design is sufficient to achieve this objective.

Stepwise recruitment: To date, afabicin has been administered up to 32 days in patients and up to 20 days in healthy volunteers. The overall aim of the stepwise approach is to ensure the safety of afabicin administration for longer periods than previously tested and to optimize monitoring

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frequency. Thus, both in Part A and Part B of the study, patients will be recruited into cohorts of increasing duration of treatment (see Section 6.1).

Randomized, controlled, two-arm: Patients will be randomized to afabicin or pre-defined SoC at a 4:1 or a 5:1 ratio in Part A and Part B of the study, respectively. This randomization will aid to reduce Investigator's selection bias. The presence of a control arm will provide a reference point to evaluate both the safety and efficacy of afabicin. Pre-specifying the choice of antibiotics will minimize the heterogeneity in the control arm (see Section 6.2.2). As this is an exploratory study, it is not powered to detect any treatment differences between the afabicin and control arm.

Dosing Design in Part B: The starting afabicin dosing regimen in Part B is 55 mg IV BID followed by 80 mg PO BID. If the results of the first cohort, Cohort 1B, indicate that this dose is well tolerated, safe and efficacious as assessed by [redacted] IDMC and the concerned Healthy Authorities, then Cohort 2B can be initiated with the same dosing regimen. However, if the results for Cohort 1B (or 2B and 3B) meet the criteria for futility (i.e., well tolerated and safe but clinical response rate at EOT < 70%), then Cohort 1C (or 2C and 3C, respectively) could be initiated with an increased dose of 80 mg IV BID and 120 mg PO BID. The increase of afabicin dose will be decided upon approval of [redacted] IDMC and, when necessary, by the concerned Health Authorities.

Maximum treatment duration: The maximum treatment duration of 12 weeks is in line with the guidelines for the treatment of patients with the type of osteoarticular infections included in this study, as described in Section 4.2.2. Also, the treatment cannot exceed 12 weeks as there is currently no preclinical data past 13 weeks to support a longer treatment duration.

Follow-up of 3 months: The proposed follow-up period is deemed sufficient to provide data to investigate the initial microbiological and clinical responses to afabicin treatment. Although, the current study is not designed to determine recurrence rates, it is expected that approximately 50% of recurrences will occur within this follow-up period.[37]

Subsequent trials in this indication will investigate sustainability of the clinical response, and determine the relapse rate following afabicin treatment.

5 STUDY OBJECTIVES

5.1 Primary objective

To assess the safety and tolerability of afabicin in the treatment of patients with BJI (septic arthritis, osteomyelitis, PJI) due to *S. aureus* (both MSSA and MRSA) and/or CoNS and to compare it to SoC.

5.2 Secondary objective

To assess the efficacy of afabicin in the treatment of patients with BJI due to *S. aureus* (both MSSA and MRSA) and/or CoNS.

5.3 Exploratory objectives

To determine the microbiological outcome. In afabicin-treated patients, to describe the PK profile, to explore biomarkers linked with response, toxicity, microbiome sparing features, and PK, and to assess the potential for DDI towards CYPs using endogenous biomarker(s).

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6 STUDY DESIGN AND TREATMENT

6.1 Study design

6.1.1 Part A

Patients will be recruited in 3 cohorts (Figure 6-1), with treatment duration lengthened for each subsequent cohort, as outlined below. The afabicin regimen tested in Part A is 160 mg IV BID/240 mg PO BID.

Cohort 1

This cohort will recruit patients who require treatment with an antibiotic for 2 to 3 weeks (as judged by the Investigator).

Initially, 8 patients will be recruited, randomized at a 3:1 ratio (6 to afabicin, 2 to SoC) and dosed. Additional patients may be enrolled in case of premature treatment withdrawal as outlined in Section 7.3. After the EOT, all available safety and efficacy data for these 8 evaluable patients (including a minimum of 2-week post-treatment follow-up data) will be reviewed by the IDMC [redacted] (thick arrows, Figure 6-1).

The IDMC [redacted] will recommend whether to: (i) initiate recruitment for the subsequent Cohort 2 with a maximum duration of treatment up to 6 weeks, (ii) request to continue recruitment in Cohort 1 in order to generate more data before making a decision on initiating recruitment into Cohort 2, or (iii) amend or terminate the study.

If Cohort 2 is initiated, Cohort 1 will continue to recruit and randomize an additional 12 patients at a 5:1 ratio (10 to afabicin, 2 to SoC), resulting in an overall ratio of 4:1 (total 20; 16 treated with afabicin and 4 treated with SoC) within the cohort at the end of the study.

Cohort 2

This cohort will recruit patients who require treatment with an antibiotic for 3 to 6 weeks (as judged by the Investigator).

Initially, 8 patients will be recruited and randomized at a 3:1 ratio (6 to afabicin, 2 to SoC) and dosed. Additional patients may be enrolled in case of premature treatment withdrawal as outlined in Section 7.3. After the EOT, all available safety and efficacy data for these 8 evaluable patients (including a minimum of 2-week post-treatment follow-up data) will be reviewed by the IDMC [redacted] (thick arrows, Figure 6-1).

The IDMC [redacted] will then recommend whether to: (i) initiate recruitment for the subsequent Cohort 3 with a maximum duration of treatment up to 12 weeks, (ii) request to continue recruitment in Cohorts 1 and/or 2 in order to generate more data before making a decision on initiating recruitment into Cohort 3, or (iii) amend or terminate the study.

If Cohort 3 is initiated, each of Cohorts 1 and 2 will continue to recruit and randomize an additional 12 patients at a 5:1 ratio (10 to afabicin, 2 to SoC). This would result in an overall randomization ratio of 4:1 (16 to afabicin, 4 to SoC) within Cohort 1 and Cohort 2 at the end of the study.

Cohort 3

This cohort will recruit patients who require treatment with an antibiotic for 6 to 12 weeks (as judged by the Investigator).

Initially, 8 patients will be recruited and randomized at a 3:1 ratio (6 to afabicin, 2 to SoC) and dosed. Additional patients may be enrolled in case of premature treatment withdrawal as outlined in Section 7.3. After the EOT, all available safety and efficacy data for these 8 evaluable patients (including a minimum of 2-week post-treatment follow-up data) will be reviewed by the IDMC [redacted] (thick arrows, Figure 6-1).

The IDMC [redacted] will then recommend whether to: (i) continue recruitment into this cohort only to generate further safety data before making a final recommendation on this duration of treatment,

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(ii) open recruitment into all 3 cohorts, (iii) continue recruiting into Cohorts 1 and/or 2 to generate more safety data in shorter durations of treatment, or (iv) amend or terminate the study.

If Cohort 3 is continuing, all cohorts will continue to recruit and randomize an additional 12 patients at a 5:1 ratio (10 to afabicin, 2 to SoC). This would result in an overall randomization ratio of 4:1 (16 to afabicin, 4 to SoC) within each cohort at the end of the study.

6.1.2 Part B

Patients will be recruited in the Cohorts B (1B, 2B and 3B) with a stepwise approach (Figure 6-1 and Figure 6-2). The afabicin regimen tested in Cohorts B is 55 mg IV BID/80 mg PO BID.

Initiation of Cohorts C can only take place if pre-defined futility criteria are met in any of the Cohorts B and if recommended by [redacted] IDMC and when necessary, the concerned Health Authorities. The afabicin regimen tested in Cohorts C is 80 mg IV BID/120 mg PO BID.

Cohort 1B

This cohort will recruit patients who require treatment with an antibiotic for 2 to 3 weeks (as judged by the Investigator).

Patients will be randomized at a 5:1 ratio (20 to afabicin, 4 to SoC). Additional patients may be enrolled in case of premature treatment withdrawal as outlined in Section 7.3. Upon completion of this cohort, the study will be paused and both IDMC [redacted] will review available safety and efficacy data for evaluable patients including a minimum of 2-week post-treatment follow-up data (thick arrows, Figure 6-1). This information will also be shared with the relevant Health Authorities, when necessary. If a determination is made that it is safe to proceed, the next cohort of the study will be initiated. Additionally, continuous futility analysis will be carried out and if the response rate in the cohort fulfils the futility criteria (i.e., EOT clinical response rate < 70%), then Cohort 1C could be initiated if recommended by [redacted] IDMC and the Health Authorities.

Cohort 2B

This cohort will recruit patients who require treatment with an antibiotic for 3 to 6 weeks (as judged by the Investigator).

Patients will be recruited and randomized at a 5:1 ratio (20 to afabicin, 4 to SoC). Additional patients may be enrolled in case of premature treatment withdrawal as outlined in Section 7.3. The IDMC [redacted] will review all available safety and efficacy data for evaluable patients including a minimum of 2-week post-treatment follow-up data (Figure 6-1).

A futility analysis will be carried out and if the response rate in the cohort fulfills the futility criteria (i.e., EOT clinical response rate < 70%), then Cohort 2C will be initiated if recommended by [redacted] and IDMC, and if necessary, by concerned Health Authorities.

If the futility criteria are not met, the IDMC [redacted] will recommend whether to initiate recruitment for the subsequent Cohort 3B, to amend the protocol or terminate the study.

Cohort 3B

This cohort will recruit patients who require treatment with an antibiotic for 6 to 12 weeks (as judged by the Investigator).

Patients will be recruited and randomized at a 5:1 ratio (20 to afabicin, 4 to SoC). Additional patients may be enrolled in case of premature treatment withdrawal as outlined in Section 7.3. The IDMC [redacted] will review all available safety and efficacy data for these patients including a minimum of 2-week post-treatment follow-up data (thick arrows, Figure 6-1).

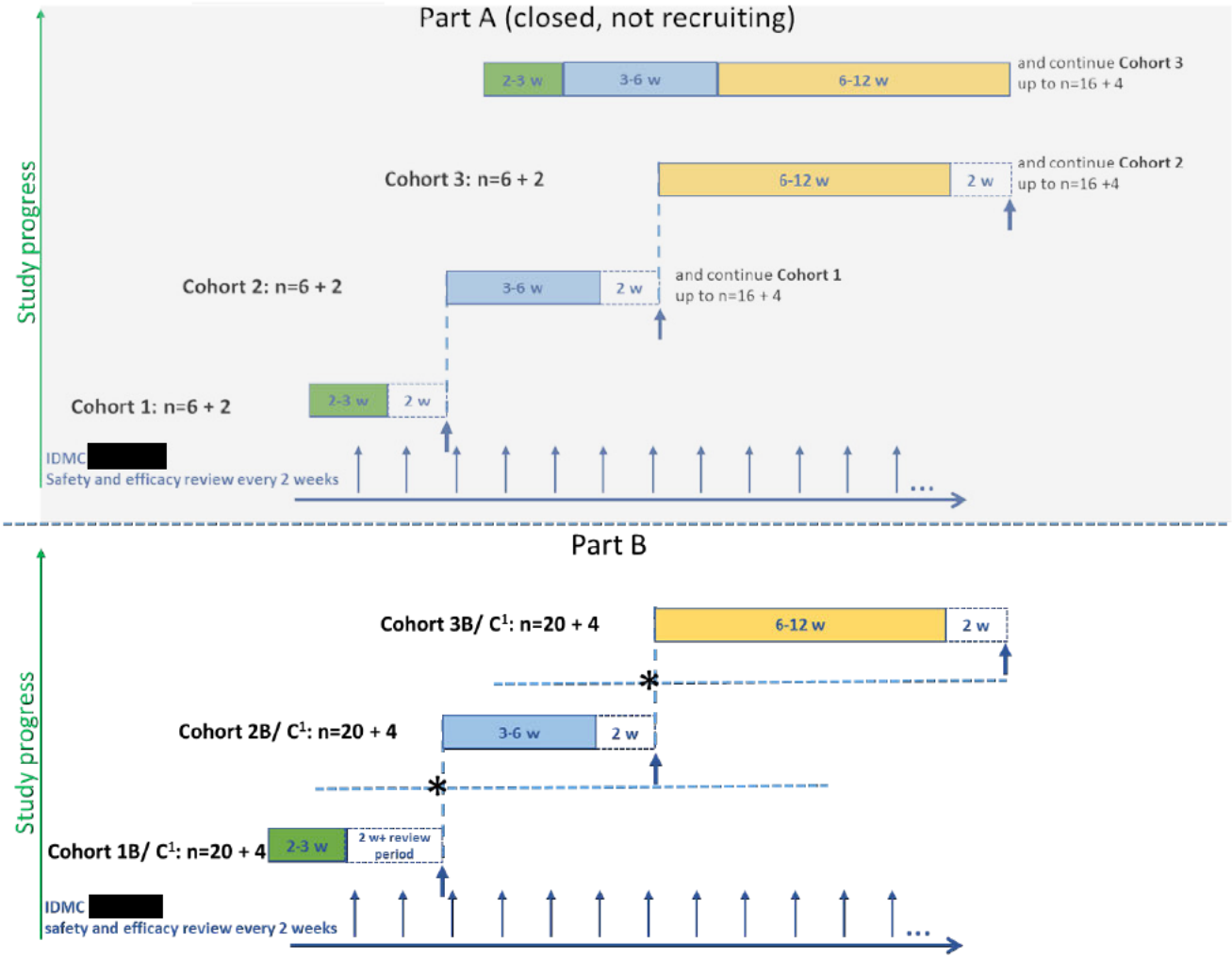
A futility analysis will be carried out and if patients' response rate in Cohort 3B fulfills the futility criteria (i.e., EOT clinical response rate < 70%), then Cohort 3C will be, if recommended by [redacted] IDMC, and if necessary, by concerned Health Authorities.

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Safety reviews by the IDMC (all safety) [redacted] will be conducted once every two weeks across all cohorts and will include cumulative safety data from all patients, as shown below (thin arrows, Figure 6-1). Ad-hoc safety reviews by the IDMC [redacted] may be performed more often than indicated, on an as-needed basis.

IDMC will consider the assessment and recommendation [redacted] in order to make the decision on initiating the next cohort.

Figure 6-1 Study diagram

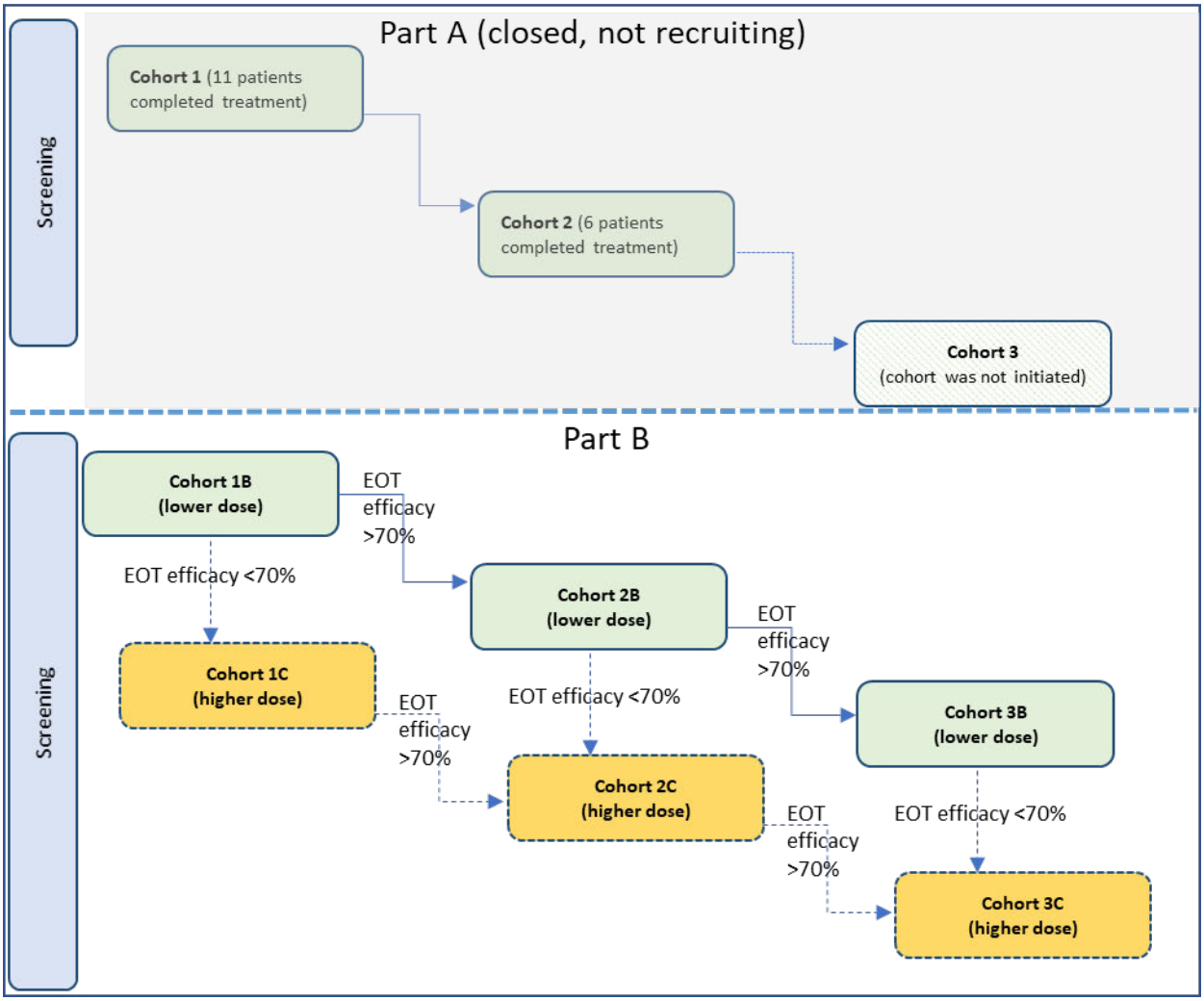


Efficacy and safety data review by the IDMC (all safety) [redacted] are indicated as: thin arrows for regular (i.e., biweekly) data review, and thick arrows for review of data from the whole cohort (24 evaluable patients: 20 in afabicin arm and 4 in SoC arm).

[1] For Cohort 1B, upon completion this cohort, the study should be paused and both IDMC [redacted] should provide assessment. This information will be also shared with the Health Authorities. Based upon this information, a determination will be made regarding the safety of proceeding to the next cohort in the study. If the criteria for futility analysis in a cohort with the lower dose of afabicin is fulfilled (i.e., EOT clinical response rate < 70%) then a subsequent cohort with a higher afabicin dosing regimen will be initiated (i.e., 1C, 2C, or 3C) following recommendation from IDMC, [redacted] and/ or the Health Authorities.

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Figure 6-2 Study design



Study design includes Part A (top part, shaded) and Part B (lower part). Part B: A continuous futility analysis will be carried out and if any of the cohorts with the lower afabicin dose (i.e., 1B, 2B, 3B) fulfils the futility criteria (i.e., EOT clinical response rate < 70%) while meeting safety criteria, then higher afabicin dose will be initiated (i.e., 1C, 2C, 3C). If futility criteria are fulfilled in any of the higher dose cohorts the study would be terminated. In addition to futility analysis, if stopping rules (as described in Section 6.6) from a safety point of view are met, the study would also be terminated.

Confirmation of staphylococcal infection and empiric treatment

If not already confirmed, blood, bone, synovial fluid, or soft tissue will be collected prior to study treatment to confirm the presence of staphylococci. If in the Investigator's opinion the isolated bacteria should not be considered as a pathogen (e.g., colonization, contamination of specimen), this decision will be documented and the isolate will not be considered as a pathogen for the purpose of inclusion of a patient in the study.

During screening, patients may be treated with an Investigator-selected short half-life antibiotic agent for up to 7 days (see Section 8.7.1). The maximum treatment duration with empiric therapy of 7 days should not be exceeded, and where possible treatment with study drug should start after 3 to 5 days of empiric therapy.

If the aerobic culture grows *Staphylococcus* only before Day 7 of screening (in the absence of growth in an anaerobic culture), the patient will begin treatment with the study medication, as randomized. However, the anaerobic culture will be continued (the total time depends on site's practice) and if non-staphylococcus bacteria are isolated, the patient will be withdrawn from study medication and will be replaced (Section 7.3).

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Patients will be followed up for 12 weeks post-EOT. The proposed follow-up period is deemed sufficient to provide data to investigate the efficacy of afabicin.

6.2 Study treatment

6.2.1 Afabicin

Patients will be treated with open label afabicin IV at a dose of 160 mg BID in Part A and 55 mg (or 80 mg) BID in Part B for a minimum of 1 day (at least 1 dose) and up to a maximum of 14 days (2 weeks), followed by a switch to oral afabicin at a dose of 240 mg BID in Part A and 80 mg (or 120 mg) BID in Part B for the remaining treatment duration. The switch from IV to oral therapy will be made if the acute toxicity of the infection has resolved, the patient is tolerating fluids and a regular diet, and/or the Investigator determines that the patient no longer needs IV antibiotic therapy. The total treatment durations with afabicin during the different stages of this study are summarized below.

Table 6-1 Study treatment duration

The study treatment duration for Part A of the study.

	Cohort 1	Cohort 2	Cohort 3	Total during the study
Treatment duration	2 to 3 wks	3 to 6 wks	6 to 12 wks	2 to 12 wks
Maximum number of patients	N=20	N=20	N=20	N=60

[redacted]

The study treatment duration for Part B of the study:

	Cohort 1B	Cohort 2B	Cohort 3B	Cohorts 1C, 2C, or 3C*	Total during the study
Treatment duration	2 to 3 wks	3 to 6 wks	6 to 12 wks	2 to 3 wks, 3 to 6 wks, or 6 to 12 wks	2 to 12 wks
Maximum number of patients	N=24	N=24	N=24	N=24	N=96

* Higher dose of afabicin in Cohorts C will only be tested if the lower dose in the respective Cohort B will not show sufficient activity as per the futility assessment.

In this study, no recommendation has been made regarding dose adjustment for individual patients. However, as this is an open-label trial, patients' data will be reviewed at regular intervals by the IDMC [redacted] (Sections 11.2.1 and 11.2.2, respectively) and dose regimen modifications (without jeopardizing safety) may be recommended by the IDMC [redacted]

6.2.2 Comparator: standard of care

The following points were considered in proposing a choice of SoC:

- Recommendations by the clinical guidelines (e.g., IDSA);
- Single agent (no multiple drug combinations);
- Coverage for oxacillin-/methicillin-susceptible and –resistant staphylococci;
- Availability in IV and/or oral formulation;
- Lack of overlapping toxicities with afabicin;
- The licensed use of the product and the licensed dosage (as per product label).

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All the antibiotics recommended by clinical guidelines for the treatment of bone and joint staphylococcal infections (methicillin-susceptible and -resistant) are reviewed in accordance with the above criteria (Section 16.1). The SoC should be administered in accordance with the approved regional labelling, without exceeding the maximum dosing schedule.

Overall, for oxacillin-/methicillin-susceptible staphylococci, the recommended SoC for the comparator arm are, as appropriate for the indication:

- IV - Cefazolin or vancomycin or linezolid or clindamycin;
- Oral - Linezolid or clindamycin.

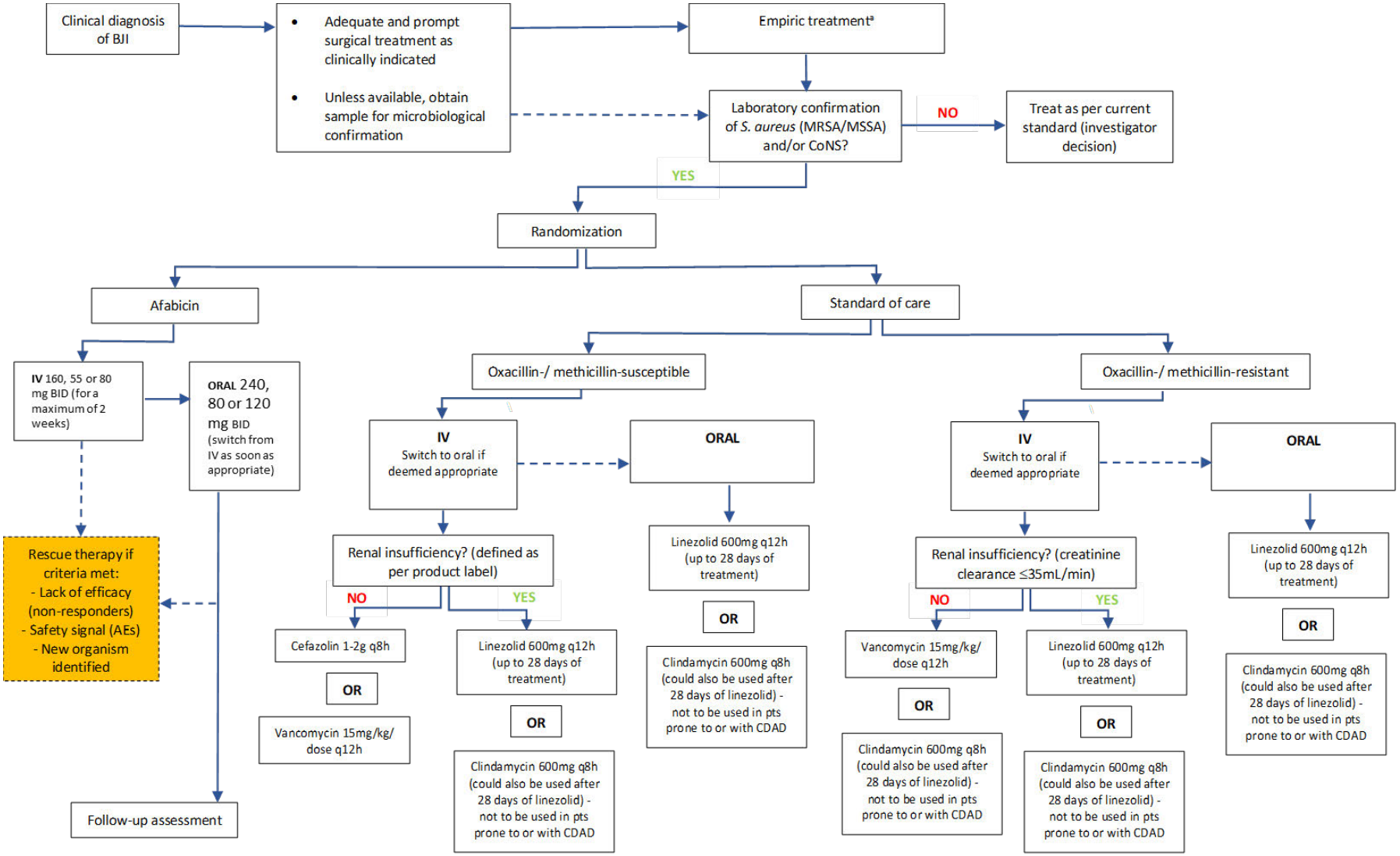
For oxacillin-/methicillin-resistant staphylococci, the recommended SoC for the comparator arm are:

- IV - Vancomycin or clindamycin or linezolid;
- Oral - Linezolid or clindamycin.

The management of patients including the choice of the SoC comparator are presented in the algorithm below (Figure 6-3).

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Figure 6-3 Algorithm for selection of SoC for the comparator arm and as rescue therapy



[a] As per Table 8-1. CDAD = *C. difficile* associated diarrhea; pts = patients

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6.2.3 Rescue treatment

Rescue therapy will be considered under the following conditions:

1. For patients who will be discontinued from afabicin due to AEs.
2. Treatment failure (i.e., non-responders, Section 9.1.2).
3. Isolation of a new, non-susceptible pathogen in patient treated with:
    - Afabicin – patient with newly isolated non-staphylococcal pathogen will be switched to SoC aligned with the recommended selection (Figure 6-3) and the susceptibility profile of the pathogen,
    - Comparator – patient with newly isolated non-susceptible pathogen will be switched to another SoC aligned with the recommended selection (Figure 6-3) and the susceptibility profile of the pathogen.

For patients who meet any of the above criteria, a rescue treatment will be instituted. The rescue therapy is aligned with the recommended SoC (Figure 6-3). If for a given patient, the proposed choice of antibiotic is not suitable, the Investigator should determine the best choice of an alternative treatment, while ensuring no overlapping toxicities.

At each EOT study visit, the status of the patients will be re-assessed thoroughly by the Investigator (i.e., clinical signs and symptoms, inflammatory markers, imaging, microbiological response) who will determine whether there is a need for further antibiotic therapy.

Part A:

The Investigator may then determine if it is necessary to (i) institute a rescue treatment for patients not responding to therapy, or (ii) prolong treatment even though the patient is not exhibiting a lack of response. All patients, where treatment has been extended due to confirmed or presumed lack of response will be counted as treatment failures at the time of receiving additional or new antibiotics.

In the Investigator's judgement, there may be a need to prolong antibiotic therapy beyond the cohort-specified duration of treatment with afabicin for patients who are responding (Section 9.1.2). In this situation, extending the duration of treatment with afabicin may only be carried out under the following conditions:

a) If the patient is being treated within the first cohort (up to 3 weeks), treatment with afabicin can only be extended if safety data is available from Cohort 2 and/or 3 to show that treatment with afabicin up to 6 and 12 weeks is acceptable, respectively, otherwise the patient will need to be treated with the SoC (Figure 6-3). The treatment cannot be extended beyond the duration of available data.

b) If the patient is being treated within Cohort 2 (up to 6 weeks), treatment with afabicin can only be extended if safety data is available from Cohort 3 to show that treatment with afabicin up to 12 weeks is acceptable, otherwise the patient will need to be treated with the SoC (Figure 6-3). The treatment cannot be extended beyond the duration of available data.

c) If the patient is being treated within Cohort 3 (up to 12 weeks), then treatment with afabicin cannot be extended, and the patient will need to be treated with the SoC (Figure 6-3).

Part B:

The Investigator may determine if it is necessary to institute a rescue treatment for patients not responding to afabicin. All patients requiring rescue antibiotic due to confirmed or presumed lack of response will be counted as treatment failures (Figure 6-3).

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6.3 Study duration

The total study duration for an individual patient will be approximately 25 weeks, as follows.

- Screening of up to 10 days.
- Depending on the cohort recruited, treatment will last between 2 weeks and 12 weeks.
- Follow-up of 12 weeks.

6.3.1 Definition of the end of the trial

The end of trial will be defined as the last patient's last visit in the study.

6.4 Criteria for patient withdrawal

6.4.1 Criteria for withdrawing patient from treatment

The Investigator will consider discontinuing patient from treatment under the following circumstances:

1. [redacted]

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- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

2. [redacted]

- [redacted]
- [redacted]
- [redacted]

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3. **SAE assessed as having a reasonable causal relationship** to study drug and unlikely to abate with continuation of treatment.
4. Clinical and/or microbiological **evidence of lack of efficacy.**
5. If the patient concomitantly takes **prohibited medication**, a decision should be made by the Investigator to either discontinue study treatment or the prohibited drug. Please consult Section 8.7.4 for prohibited medications with afabicin and local labelling for SoC.
6. **Presence of a** pathogen that requires additional antimicrobial therapy (e.g., if positive culture results for non-staphylococcal pathogen are available after the initiation of afabicin treatment or if a non-susceptible pathogen is isolated after treatment with SoC has been initiated).
7. **Pregnancy.**

For patients withdrawn from the afabicin treatment at any point during the study due to: (i) QT prolongation, (ii) lack of efficacy, and/or (iii) an SAE possibly related to afabicin, blood samples will be drawn for additional investigations, which may include pharmacogenomic profiling, PK, biomarker analyses.

6.4.2 Criteria for withdrawing patient from the study

A patient may withdraw consent (or the Investigator may withdraw the patient from the study) at any time without penalty and for any reason without prejudice to his or her future medical care.

The Investigator should consider withdrawing the patient from the study under the following circumstances:

- Non-compliance with study procedures or study drug administration
- Complicated bacteremia characterized by at least one of the following:
    i. Positive follow-up blood cultures at 48 to 96 hours. Patients who have a positive culture at 48 hours but negative at 72 and 96 hours can be included or continue in the study.
    ii. Persistent fever ≥ 38°C at 72 hours from presentation.
    iii. Skin findings suggesting an acute systemic infection (petechiae, vasculitis, infarcts, ecchymoses, or pustules).
    iv. Significant presence of other comorbidities, or immune-compromised patients.
    v. Infective endocarditis.
    vi. Evidence of sepsis (Sequential Organ Failure Assessment [SOFA] score ≥ 2) (see SOFA score calculation in Section 16.2).

In all cases, the date and reason(s) for withdrawal (including the primary reason) must be recorded in the electronic case report form (eCRF). If a patient is prematurely withdrawn from the study for any reason, the Investigator must make every effort to perform the evaluations described for the EOT visit. Every effort will be made to follow-up patients who prematurely discontinue from the study to determine final outcome.

If a patient withdraws consent, during the study, and still agrees to undergo a final examination, this will be documented on the eCRF and the Investigator's copy of the informed consent form (ICF), which will be countersigned and dated by the patient.

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6.5 Futility analysis (Part B only)

Since the control response rate (efficacy endpoint) is expected to be 70%, a continuous futility analysis (monitoring of efficacy) will be carried out to ensure that patients are not under-exposed to afabicin. The futility criterion is defined as < 70% of patients with clinical response rate at EOT. The cohort will be stopped if 4 out of the first 9 evaluable patients are non-responders. The data of the Cohort 1B will be reviewed by [redacted] IDMC and Health Authority before proceeding to the next cohorts. Data of the subsequent cohorts will continue to be reviewed by [redacted] IDMC and, if warranted, by Health Authority. In case futility is met in Cohorts 1B, 2B or 3B, Cohorts 1C, 2C or 3C could be initiated, unless there is a safety concern (see also 6.1.2). If the futility is met for any of the Cohorts C, the study will be terminated.

Based on up to 20 evaluable patients treated with afabicin, the cohort would be stopped for futility as follows:

Number of evaluable afabicin patients	Stop cohort B if the number of responses is	Continue if the number of responses is
9*	0-5	6-9
10	0-5	6-10
11	0-6	7-11
12	0-7	8-12
13	0-7	8-13
14	0-8	9-14
15	0-9	10-15
16	0-9	10-16
17	0-10	11-17
18	0-11	12-18
19	0-11	12-19
20	0-12	13-20

* A cohort will be stopped if 5 out of the first 9 evaluable patients are non-responders.

If the futility analysis is performed only once, the conditional probability to stop for futility, according to the experimental arm response rate (p1), are as follows:

p1=70%	p1=80%	p1=85%	p1=90%	p1=95%
0.42	0.128	0.048	0.010	<0.001

6.6 Stopping rules for the study

The IDMC [redacted] may recommend at any time to terminate the study to ensure patient safety, with a [redacted]

[redacted]

[redacted]

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[redacted]

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[redacted]

[redacted]

[redacted]

At any point in the study, the recommendations of the IDMC [redacted] will be implemented immediately and may include:

a) Continuing the study with no modifications;
b) Continuing the study but modify study assessments or monitoring frequency;
c) Increasing the number of patients in any given cohort;
d) Suspending further extension of study duration;
e) Exploring a lower drug exposure by adjusting the dosing regimen;
f) Stopping the study.

The stopping rule for lack of efficacy is described above and in Section 6.5.

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7 STUDY POPULATION

Study population consist of adult patients with a confirmed bone or joint staphylococcal infection, including septic arthritis, osteomyelitis and subset of PJI. Sixty evaluable patients are planned to be enrolled at several centers. However, more patients may be enrolled to confirm safety or early efficacy, per the recommendations from IDMC [redacted].

7.1 Inclusion criteria

Unless otherwise specified, patients who fulfil the following inclusion criteria at the screening visit (within 10 days prior to first afabicin administration) will be included:

1. Able to provide written informed consent and to comply with study procedures.
2. Adult male and female patients (≥ 18 years of age).
3. Diagnosis of septic arthritis, osteomyelitis, or PJI which fulfils the following conditions:
   a. Infection is due to *S. aureus* (MSSA or MRSA) and/or CoNS only; **and**
   b. Patient had received no more than 7 days of empiric antibiotics prior to initiating treatment with study drug unless the pathogen isolated was resistant to the administered empiric antibiotics; **and**
   c. Biofilm is not considered to be yet established and/or has been mechanically eradicated. Therefore, orthopedic hardware associated with the primary site of bone infection should be removed before randomization (e.g., in cases of implant-associated osteomyelitis or PJI with explantation in a 2-stage strategy); **and**
   d. Infection is not associated with an ischiatic or a sacral osteomyelitis; **and**
   e. Infection can involve periosteal or soft tissue.
4. All female patients who are of childbearing potential (*defined as not postmenopausal for at least 12 months or not surgically sterile for at least 7 months*), must have a negative pregnancy test at screening and agree to use a highly effective contraception method until at least 60 days after dosing.

   An acceptable method of contraception includes a double-barrier method (diaphragm, condoms, spermicides) or mechanical products such as an intrauterine device along with at least a single-barrier method (diaphragm, condoms, spermicides).
5. Able to tolerate at least one of the proposed SoC treatments, as appropriate for the indication.
6. Anticipated duration of treatment does not exceed the maximum treatment duration for the enrolling cohort (i.e., 3 weeks for Cohorts 1, 1B or 1C, 6 weeks for Cohorts 2, 2B or 2C, and 12 weeks for Cohorts 3, 3B or 3C).
7. Patient with controlled HIV infection on stable ART can be included (undetectable viral load for at least 10 months [HIV RNA < 50 copies/ mL], stable ART for more than 11 months, CD4 ≥ 200 cells/ mm^3, stable weight and no opportunistic infections) – Criterion only applicable in South Africa and Argentina according to local regulatory requirement.

7.2 Exclusion criteria

Any of the following would render a patient ineligible for inclusion:

1. Presence of co-infection with non-staphylococcal bacteria at the affected joint or bone site, or in the blood.
2. Patients at an increased risk of developing liver injury, such as:

[redacted]

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[redacted]

d. Obesity (elevated BMI ≥ 30) or poorly controlled diabetes mellitus (i.e., blood levels of Glycosylated Haemoglobin HbA1C ≥ 8.0%), or hypertriglyceridemia CTCAE ≥ grade 2 (serum triglycerides >300 mg/dL), or concomitant CTCAE grade 1 hypertriglyceridemia (150-300 mg/dL) and abnormally low HDL levels, or

e. Metabolic syndrome – according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition, metabolic syndrome is present if 3 or more of the following five criteria are met: waist circumference over 40 inches [101 cm] (men) or 35 inches [89 cm] (women), blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dL, fasting HDL cholesterol level less than 40 mg/dL (men) or 50 mg/dL (women) and fasting blood sugar over 100 mg/dL.

3. [redacted].

4. Patients who have any of the following medical conditions that increase the risk of QT prolongation:

   a. Prolonged QTcF interval (> 450 ms in men and > 470 ms in women using Fridericia formula at screening).

   b. Heart rate (on ECG) ≤ 40 beats/min (bpm) or > 100 bpm.

   c. Congenital long QT syndrome or family history of sudden death.

   d. Hypokalemia, hypocalcemia and/or hypomagnesemia CTCAE grade ≥ 2. Correction of electrolytes levels with supplements to meet eligibility criterion is allowed.

5. Medical history within the previous 3 months of: myocardial infarction, unstable angina pectoris, coronary artery or cerebral revascularization procedure or stroke, ventricular tachycardia, multifocal ventricular ectopics requiring treatment, or any other clinically relevant symptomatic ventricular arrhythmias.

6. Any of the following comorbidities:

   a. Clinical or laboratory signs of sepsis: score of ≥ 2 on the SOFA [38] scale at screening. Note that patients with uncomplicated bacteremia (defined as bacteremia that does not meet the criteria for complicated bacteremia as described in Section 6.4.2) may enter the study.

   b. Heart failure with reduced left ventricular function and those patients meeting New York Heart Association (NYHA) class III or IV.

   c. Severe and frequent migraine headaches (recurring weekly).

   d. Immunosuppression or immune deficiency or immunotherapy (steroid therapy is allowed if judged not to be associated with immunosuppression by the Investigator).

   e. Measured or estimated creatinine clearance (CL) < 30 mL/min.

7. Prothrombin time prolongation or partial thromboplastin time prolongation > 1.5 x ULN or platelets < 100 000/µL.

8. Patients who are treated or have been treated with prohibited medications within a period less than 5 half-lives of the drugs (this applies to the following drugs which have the potential for PK or PD interactions):

   a. PDE3 inhibitors.

   b. More than one antiplatelet/anticoagulant agent

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c. Drugs or herbal products that are known to be moderate or strong inhibitors of CYP 3A4.

d. [redacted]

9. Patient who are treated or have been treated with drugs or herbal products that are known inducers of CYP 3A4 within a period less than 5 half-lives of the drugs or 2 weeks (whichever is longer).
10. Documented history of alcohol or drug abuse within the previous 12 months.
11. Known or suspected allergies or hypersensitivities to any of the components of the study drugs (refer to the afabicin Investigator's Brochure and local labelling for the SoC treatments).
12. Received any investigational medication during the last month (30 days or 5 half-lives, whichever is longer) prior to enrolment in the current study or previously received afabicin.
13. Any condition that, in the view of the Investigator, renders the patient unlikely to benefit from treatment or place him/her at a high risk of unwarranted side effects or prevent him/her from completing the study.
14. Pregnant or breast-feeding women.
15. Any contraindications to each of the proposed SoC treatments, based on the local labelling for each SoC, such that none of the proposed SoC therapies could be administered.

For Part B only:

16. Neutrophil counts < 1000 cells/mm^3.
17. Signs of clinically relevant abnormalities of the liver, pancreas, gall bladder and bile ducts, as assessed by ultrasound examination.
18. Circulatory shock or any medical condition associated with acute risk of death.
19. Life expectancy of less than 1 year.
20. For patients with DFO:
    a. Severe peripheral arterial disease (PAD) requiring revascularization; however, patients with peripheral artery disease are eligible for inclusion, provided they have undergone successful revascularization or it has been deemed unnecessary by a vascular surgeon
    b. Necrotizing fasciitis or gangrene requiring complete lower extremity amputation (of all infected bone and soft tissue).
    c. Patients with Charcot foot (suspected neuro-osteoarthropathy according to Investigator's judgment).
    d. Need for digital amputation.

7.3 Inclusion of additional patients

Additional patients will be included if patients withdraw (or are withdrawn) from treatment before completing the minimum mandated treatment duration (i.e., < 2 weeks for Cohort 1, < 3 weeks for Cohort 2, and < 6 weeks for Cohort 3) and their number will equal to the number of patients who are not contributing sufficient data for safety assessment.

These additional patients will not be randomized but will be allocated to the same treatment (i.e., either afabicin or SoC) and cohort as the patient who was withdrawn.

Patients who withdrew (or were withdrawn) from treatment for the reasons below, regardless of duration, will not be replaced:

[redacted]

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d) SAE considered as possibly related to study treatment, and/or

e) Lack of efficacy.

Additional patients will substitute for **all patients in all cohorts** who dropped out of the study (withdrew or were withdrawn) before completing the minimum treatment duration (based on the cohort to which they were randomized), unless withdrawn for the reasons above.

8 CLINICAL SUPPLIES

8.1 Investigational Medicinal Product

Afabicin vials (powder for solution for infusion) contain the equivalent of 160 mg of afabicin + excipient: sucrose and potassium phosphate.

Afabicin film-coated tablets contain the equivalent of 80, 120 or 240 mg afabicin + excipients: histidine, sodium lauryl sulfate, isomalt, povidone, crospovidone, colloidal silica, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, glycerylmonostearate and coloring agent.

Afabicin vials containing powder for solution for infusion as well as afabicin film-coated tablets will be provided by Debiopharm International SA.

8.2 Packaging and storage of Investigational Medicinal Product

8.2.1 Packaging

Afabicin 160 mg powder for solution for infusion vials are provided in boxes of 24 vials.

Afabicin film-coated tablets will be provided in blisters of 14 tablets sufficient to cover patient's treatment duration.

8.2.2 Labelling

Labels will comply with health authority requirements in each participating country.

8.2.3 Storage

Afabicin 160 mg powder for solution for infusion should be stored at room temperature. The vials should be maintained in a low humidity environment and protected from light.

Afabicin 80, 120 and 240 mg film-coated tablets must be stored at 2°C to 8°C. They should not be frozen.

Storage of the SoC should be in accordance with local labelling.

8.3 Method of administration and compliance

Afabicin doses (IV or oral) will be administered BID, 12 hours apart (+/- 30 min).

The IV or oral administration of SoC should be in accordance with local labelling.

8.3.1 Intravenous administration

IV infusions of afabicin will be administered over a 2-hour period (+/- 10 min). There will be a 10-hour window between the end of one infusion and the start of the next infusion.

Peripheral or central catheter lines may be used. Use a 0.2 µm polyethersulfone (PES) inline filter during the administration.

The IV solution will be prepared at each study site prior to use and administered as soon after preparation as feasible. However, a maximum of 15 hours between vial reconstitution in the infusion bag and the end of infusion will be allowed. It is recommended to minimize the time between the IV solution preparation and its administration.

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Part A:

Vial (powder for solution for infusion) will be reconstituted with 10 mL of 5% dextrose in water (D5W) and then diluted into a 250 mL D5W bag for administration (160 mg dose). This IV solution must be protected from light (i.e., using an amber bag to obscure the infusion bag). Complete reconstitution instructions will be available in the pharmacy manual.

Part B:

Vial (powder for solution for infusion) will be reconstituted with 16.0 mL of D5W. After gently mixing until complete dissolution, 5.5 mL (55 mg dose) or 8.0 mL (80 mg dose) will be withdrawn and then diluted into a 200 or 250 mL D5W bag for administration. This IV solution must be protected from light (i.e., using an amber bag to obscure the infusion bag). Complete reconstitution instructions will be available in the pharmacy manual.

Please note that the vials are single use vials, the remaining solution must not be used.

8.3.2 Oral administration

Afabicin will be administered preferably with meals, except at Day 28 visit (or EOT, if treatment lasts < 28 days) when the drug will be administered orally in the morning in fasted conditions (from at least 4 hours before until at least 4 hours after dosing) on the day of PK sampling. The exact dose and time/date of drug intake (from Day 1 up to Day 28 visit inclusive) and the exact time/date of PK sample collection will be recorded.

In case a dose is missed, the patient should be instructed to take the next scheduled dose and leave the missed dose intact in the blister.

8.3.3 Treatment compliance

While patients are treated with IV study drug, the staff will record the time and date of the start and end of each infusion.

A ‘’Patient diary’’ (either for ‘’Afabicin’’ or for ’’SoC/Comparator’’) will be provided to the patient at the time of the switch from IV to oral treatment. Patients will be instructed on the use of the diary by study staff.

The patient will record the time and date of each oral dose (afabicin or SoC), the number of oral doses taken (afabicin or SoC), and whether it was taken with food. The patient will record the reasons for any missed dose(s). The patient will also record any accompanying side effect/AEs, the start and end times for each side effect, any medication taken for the side effect, and the duration that these medications were taken. In addition, the patient will record any other medication taken concomitantly with the study treatment.

The Patient diary will be reviewed with the patient at on-site visit(s) or by the study physician at home visits. All used and unused/unopened study drug containers will be returned to the study site and inventoried at EOT or early withdrawal.

8.3.4 Dose modification

As this is an open-label trial, patients’ data will be reviewed at regular intervals by the IDMC [redacted] and dose regimen modifications may be recommended by these committees (Sections 11.2.1 and 11.2.2). However, any dose regimen modification must ensure patient safety and avoid compromising efficacy.

8.4 Dispensing and accountability of Investigational Medicinal Product

8.4.1 Study drug dispensation

IV treatment can be administered for up to 14 days. It is recommended that the patient remains hospitalized during the IV treatment period. Depending on local practice, the Investigator may opt to administer IV treatment on an outpatient basis provided that all scheduled assessments can be

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completed and close safety monitoring can be maintained. The timing of the switch from IV to oral study drugs will be at the Investigator's discretion and can occur anytime within the first 14 days of treatment. The switch to oral treatment may occur at any point during the day, as the next scheduled dose of study drug (every 12 hours [q12h]).

At the switch to oral treatment, the patient can be discharged (if previously hospitalized) or stay at the hospital, according to the local practice.

Daily treatment with oral study drugs will continue from the time of the switch (from IV to oral) until the Investigator deems the treatment as completed based on his/her clinical assessment. Total treatment duration with afabicin will not exceed 12 weeks.

Afabicin film-coated tablets will be supplied in 14-tablet blisters and dispensed at the time of the IV-to-oral switch. Dispensing will occur according to the dispensing schedule defined in the Interactive Web Response System (IWRS). Dispensing will be automatically recorded in the IWRS/eCRF including date and quantity of the IMP, as well as IMP identification numbers.

8.4.2 Accountability for IMP

The IMP and certificates of analysis (CoAs) will be provided to the Investigators by and under the responsibility of the Sponsor, who will also ensure release of the IMP as per current Good Manufacturing Practice (GMP) guidelines. Any documentation required by local health authorities for import of the IMP will be appropriately submitted.

The Investigator/Pharmacist at each study site will inventory and acknowledge receipt of all shipments of IMP. The IMP accompanied by analytical reports when appropriate, must be kept in a locked area with access restricted to designated study personnel, and must be stored in accordance with the manufacturer's instructions.

The Investigator/Pharmacist at each study site will keep accurate records of the IMP (and other study-related drugs) dispensed. These records will specify dates and amounts dispensed, to and by whom (drug dispensing list), and report any IMP accidentally or deliberately destroyed.

At study closure, unused IMP will be counted and returned to the Sponsor, or destroyed with their written permission. Any discrepancies between the IMP returned and the expected balance must be justified.

Unused IMP must not be discarded or used for any purpose other than the present study. Throughout the study, the Sponsor's monitor/representative will collect the drug accountability forms along with any unused IMP in the original packaging.

8.5 Randomization and Patient Numbering

8.5.1 Randomization method

Patients will be randomized to receive either afabicin or a pre-defined SoC matched for the treatment duration selected by Investigator. Randomization will be performed on Day -1 (i.e., within 24 hours prior to the first dose).

Part A:

- Initially, in each cohort, patients will be recruited and randomized at a 3:1 ratio (afabicin, SoC) until a subsequent cohort is open for enrolment (for Cohorts 1 and 2) or further enrolment is permitted (for Cohort 3) per the decision of the IDMC [redacted]
- Additional patients in each cohort will be randomized at a 5:1 ratio (afabicin, SoC).

At the end of the study, the final allocation ratio of afabicin, SoC will be 4:1 for evaluable patients in each cohort.

Part B:

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- In each cohort, patients will be recruited and randomized at a 5:1 ratio (afabicin, SoC, 20 : 4).

8.5.2 Randomization procedure

The IWRS will be used to randomize patients. The IWRS will assign patients to treatment group based on a pre-defined randomization lists specific for each site. Within lists, treatment allocation will be varied by permuted block sizes of size 4 and 6 reflecting the respective randomization ratio and allowing for a balanced allocation.

8.5.3 Screening number

At the screening visit (between Day -10 to Day -1), each patient will receive via the IWRS a unique screening number which will not be replicated.

The screening number for each patient will be a unique 4-digit identifier. The first 2 digits identify the site number and digits 3 and 4 identify the screening chronological order of the patient at the site. The first patient screened at site 01 will be given the screening number 01**01**, the second patient screened at that site will be 01**02**, and the third patient screened at that site will be 01**03**.

8.5.4 Patient number

If a screened patient fulfils all eligibility criteria and none of the exclusion criteria, the Investigator or designated study coordinator will enroll the patient via the IWRS.

The IWRS automatically generates the patient number. The patient number identifies the patient's enrolment order within the site (starting at 01). Allocation of patient numbers at the study sites is automatically tracked by the audit trail of eCRF.

The randomization number is an extension of the screening number and consists of 2 digits added to the screening number: e.g., Patient # 0201**01** identifies the first patient randomized in site 02.

8.6 Blinding and Unblinding Methods

Not applicable. This is an open-label, exploratory study.

8.7 Concomitant Therapy

At screening, patients will be asked about prior and concomitant medications they had taken during the previous 30 days. At each subsequent study visit, patients will be asked about medications they are currently taking.

During the study treatment period, patients should contact the Investigator before taking any concomitant medications including OtC medications and herbal therapies. In case of procedures involving anesthesia, the anesthesiologist must be informed of the patient's participation in the study and the possible interactions of study treatment with anesthetic agents.

Administration of concomitant medications and concomitant therapies by the patient during the study period must be reported on the concomitant medications page of the eCRF. A medication or therapy is defined as concomitant when administered between the date of signature of informed consent and the last visit (including follow-up). Information to be reported on the eCRF includes: i) international non-proprietary name and trade name, ii) dosage information (dose, unit, frequency, route), iii) dates of administration/discontinuation, and iv) reasons for use.

8.7.1 Antibiotics

During the screening period, treatment with non-study antibiotics, provided they have short half-lives, may be administered for up to 7 days. The choice of antibiotics will be at the Investigator's discretion. Examples of permitted short-acting antibiotics and of prohibited antibiotics (either longer-acting or prohibited due to DDIs with afabicin) are listed Table 8-1. Please refer to local labelling for DDI of SoC.

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Table 8-1 Permitted and prohibited antibiotics during the screening period

Permitted Antibiotics (Short-Acting)	Prohibited Antibiotics
Cephalosporins	
Cefaclor, Cefadroxil, Cefazolin, Cefdinir, Cefepime, Cefixime (200 mg), Cefotaxime, Cefpodoxime, Cefprozil, Ceftazidime, Ceftibuten, Ceftizoxime, Cefditoren, Cefuroxime, Cephalexin, Loracarbef, Ceftaroline	Cefixime (400 mg), Ceftriaxone
Fluoroquinolones	
	Ciprofloxacin, Gatifloxacin, Gemifloxacin, Grepafloxacin, Levofloxacin, Moxifloxacin, Ofloxacin, Norfloxacin, Sparfloxacin
Macrolides and Ketolides	
	Azithromycin, Clarithromycin, Dirithromycin, Erythromycin, Roxithromycin, Telithromycin
Penicillins and Carbapenems	
Amoxicillin, Ampicillin, Ampicillin/sulbactam, Dicloxacillin, Imipenem, Meropenem, Nafcillin, Oxacillin, Penicillin-G, Penicillin-V, Piperacillin, Piperacillin/tazobactam, Ticarcillin/clavulanate	Ertapenem, Penicillin-G (Benzathine/Procaine)
Tetracyclines	
Doxycycline (100 mg), Minocycline, Tetracycline	Doxycycline (200 mg), Minocycline Extended Release, Tigecycline
Glycopeptides	
Vancomycin	Telavancin, Dalbavancin, Oritavancin
Other Antibiotics	
Clindamycin, Linezolid	Lincomycin, Quinupristin/dalfopristin, Rifampin, Tedizolid, Trimethoprim/sulfamethoxazole

In case of a surgical intervention during screening or treatment period of the study, antibiotic prophylaxis will be allowed, when clinically indicated, if administered for fewer than 7 days.

In the afabicin arm, any systemic antibiotics with anti-staphylococcal activity are prohibited during the study. The exception will be antibiotic prophylaxis prior to surgery as described above.

8.7.2 Permitted non-drug therapies

The following surgical procedures are allowed during the study:

- Debridement for osteomyelitis
- Lavage of infected arthritis
- Removal and debridement of infected prosthesis

The following treatment modalities are allowed during the study:

- Hyperbaric oxygen chamber use
- Vacuum-assisted closure

Application of local antibiotics (e.g., antibiotic-impregnated cement, spacers, beads) are allowed if deemed necessary by the Investigator.

8.7.3 Medications to be used with caution with afabicin

8.7.3.1 Medicines that are substrates of CYP450 enzymes

Pharmacology studies with afabicin have demonstrated that afabicin is a weak inducer of CYP 2C9 and CYP 3A4. Thus, any concomitant drugs which are substrates of these enzymes may be

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metabolized faster, leading to their decreased exposure and efficacy. Examples include: celecoxib, glicazide, glyburide, everolimus, alfentanil, methadone, simvastatin.

Afabicin is a moderate inducer of CYP 2B6 and CYP 2C19, thus, any concomitant drugs which are substrates of these enzymes may be metabolized faster, leading to their decreased exposure and efficacy. Examples include bupropion, lansoprazole.

Please refer to label's recommendations for drugs that are sensitive or narrow-therapeutic-range substrates of CYP 2C9, CYP 3A4, CYP 2B6, and CYP 2C19; a comprehensive listing can also be consulted in: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007) (http://medicine.iupui.edu/clinpharm/ddis/); and on the FDA website at:

Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers | FDA

8.7.3.2 Anti-platelet and anti-coagulant agents

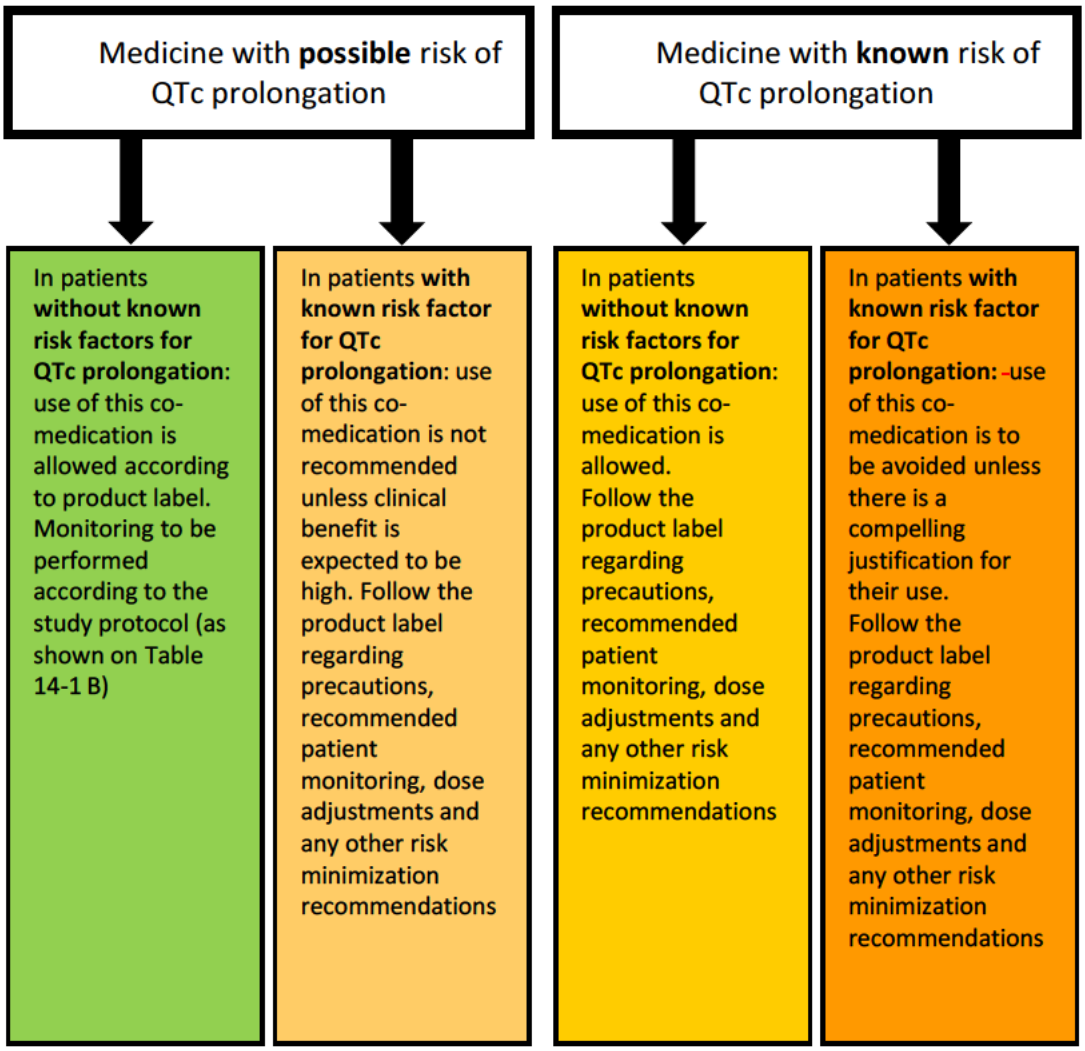
In vitro data indicate that Debio 1452 inhibits PDE3 therefore a pharmacodynamic effect of afabicin on platelet aggregation cannot be excluded and there is risk of pharmacodynamic synergism with platelet aggregation inhibitors. Thus, only one antiplatelet/anticoagulant agent may be used during afabicin treatment. Some examples include aspirin, clopidogrel, bivalirudin, ticlopidine.

8.7.3.3 Medicines associated with a risk of TdP

Clinical and C-QT modeling data suggest that afabicin prolongs the QT interval in a concentration-dependent manner. While a supratherapeutic dose of [redacted] IV afabicin induces a mild QTc prolongation, the current therapeutic regimen (55 mg IV BID/80 mg PO BID) is not predicted to be associated with a risk of clinically relevant QT prolongation. Therefore, medicines associated with a risk of TdP can be co-administered with caution with afabicin 55 mg IV BID/80 mg PO BID, according to the following recommendations:

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Figure 8-1 Recommendations concerning concomitant use of afabicin, and drugs associated with risk of TdP [39]



Please refer to product label or to databases such as https://crediblemeds.org/ for the most up to date listing of medications with a known or possible risk of TdP.

8.7.3.4 Other medicines

- Gastric mucosal protective agents, such as sucralfate, magnesium salts, calcium carbonate, could physically interfere with oral absorption and should be administered at least 2 hours before or at least 2 hours after oral afabicin. Note that pH modifying agents such as PPIs can be used (e.g., rabeprazole, lansoprazole, dexlansoprazole, pantoprazole), exception made to omeprazole which is under the prohibited list of medications with afabicin (see Section 8.7.4).
- Ibuprofen, although listed in the Livertox database category A, is considered as one of the safest nonsteroidal anti-inflammatory drugs (NSAIDs) and is generally well tolerated in the management of acute pain across patient populations. Therefore, the use of ibuprofen for up to 5 days is allowed for pain management in the study, if needed, according to the Investigator's opinion. Investigators are kindly asked to follow the approved local label. The Sponsor recommends the usage of the following anti-inflammatory, analgesic, or antipyretic drugs (if deemed appropriate and approved by the Investigator): acetaminophen, indomethacin, etodolac, fenoprofen. Although tramadol is associated with possible risk of QTc prolongation, use of tramadol up to 5 days can be considered for acute pain management after surgery, according to the approved local label.

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8.7.4 Prohibited medications with afabicin

This section aims to give an overview on prohibited medication based on their reported toxicity profiles and/or predicted interaction with afabicin. In case of uncertainty at any time, the Investigator should consult the medical monitor and/or Sponsor to determine if the use of a specific concomitant medication is prohibited during the study.

- **PDE3 inhibitors**: Debio 1452 inhibits PDE3 and therefore a pharmacodynamic synergism of afabicin with other PDE3 inhibitors (e.g., cilostazol, milrinone) cannot be excluded; thus, PDE3 inhibitors are prohibited during afabicin treatment.
- **CYP 3A4 inducers and inhibitors**: Clinical PK data indicate that the active drug Debio 1452 is metabolized by CYP 3A4. Its plasma exposure is significantly decreased when combined with a known CYP 3A4 inducer (e.g., rifampin, carbamazepine, phenobarbital, efavirenz), and increased in the presence of drugs that are known moderate or strong inhibitors of CYP 3A4 (e.g., diltiazem, verapamil, cimetidine, boceprevir, itraconazole). Thus, any concomitant drugs or herbal products that are known inducers of CYP 3A4, or are moderate or strong inhibitors of CYP 3A4 (such as St John's wort [*Hypericum perforatum*]) are prohibited during afabicin treatment. In addition, consumption of food and beverages containing grapefruit or Seville oranges is prohibited during the study as these may lead to an undesirable increase in the blood level of Debio 1452. Please refer to product label for drugs that are inducers, moderate or strong inhibitors of CYP 3A4; a comprehensive listing can also be consulted in: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007) (http://medicine.iupui.edu/clinpharm/ddis/); and on the FDA website at:

  Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers | FDA
- [redacted]

Please see Section 16.5 for examples of prohibited drugs in the study, with their minimum wash out periods.

8.7.5 Prohibited medications with SoC

Please refer to local labelling for prohibited medications with SoC.

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9 STUDY ENDPOINTS, ASSESSMENTS, AND PROCEDURES

9.1 Endpoints

9.1.1 Primary endpoint: safety

The primary endpoint is the nature, incidence, severity, seriousness, and outcome of treatment-emergent adverse events (TEAEs), and the incidence of laboratory abnormalities (grades 1, 2, 3, and 4) compared to baseline and the SoC arm, assessed up to 12 weeks post-EOT.

9.1.2 Secondary endpoints: efficacy

The secondary efficacy endpoints are the proportion of patients with clinical response at (1) 8 days, (2) 28 days (for Cohorts 2, 2B, 2C & 3, 3B, 3C only), (3) 42 days from randomization (for Cohorts 2, 2B, 2C& 3, 3B, 3C only), (4) at EOT, (5) at 4 weeks post-EOT, and (6) at 12 weeks post-EOT. Patient status will be classified as responder, non-responder, or indeterminate.

Responders are defined as patients meeting all the following criteria:

- Improvement of disease-specific signs and symptoms and no new signs, symptoms or complications attributable to the initial infection.
- No evidence of drainage, sinus tract formation or infection-related bone instability.
- No requirement for subsequent antibiotics with activity against Staphylococcus to treat the initial infection after the start of study treatment.
- Microbiological eradication of the baseline pathogen (if post-baseline sample[s] are available).
- Imaging test at 12 weeks post-EOT showing no worsening of baseline pathology or presence of signs indicating resolution or healing of the infection. This will only be assessed if baseline and 12 weeks post-EOT imaging is available using the same modality, otherwise the imaging will not be considered for the criteria of response. Imaging indicating a worsening of the condition will be considered as clinical failure. For each patient, the same method of imaging should be used throughout the study. The type of imaging (magnetic resonance imaging [MRI], computed tomography [CT]-Scan, etc.) and additional imaging assessments between screening and 12 weeks post-EOT are at the Investigator's discretion.

Non-responders will be defined as patients with available follow-up assessment(s) who do not meet at least one of the criteria for clinical response.

Indeterminate status will be applied in cases where the patient is lost to follow-up or had an amputation at the site of the initial infection due to vascular pathology without sign of infection.

Improvement of disease-specific signs and symptoms is defined as:

- No new sign, symptoms, or complications post baseline and attributable to the initial infection,
- Reduction of the number of disease-specific signs and symptoms compared to baseline and
- Resolution of infection-related fever (< 38°C).

9.1.3 Criteria for efficacy response evaluation

This section expands on the above criteria used to define clinical response.

Response to afabicin treatment will be evaluated based on clinical signs and symptoms, requirement for rescue antibiotics, and microbiological outcome (if available), radiological evidence

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(if available). These criteria will be evaluated at Day 8, Day 28, Day 42, EOT and each post-EOT follow-up assessment.

Clinical signs and symptoms

- The clinical symptoms associated with osteoarticular infections include pain (at rest or during weight-bearing, as assessed using the Pain Intensity Numerical Rating Scale (PI-NRS), see Section 16.4 [40], localized warmth, restricted active/ passive movement, lymphadenopathy, extremity weakness/ numbness, tenderness, erythema, swelling, draining sinuses, bone/ joint instability.
- Clinical signs include fever, irritability, nausea, fatigue, weight loss.

Rescue antibiotics:

- Requirement for subsequent antibiotics with activity against staphylococci to treat the initial infection after the start of study treatment.

Microbiological assessment:

- All patients should have a microbiological assessment to document presence of *S. aureus* and/or CoNS prior to starting afabicin therapy. Any of the following specimens can be used for microbiological assessment: bone, tissue, synovial fluid, or blood.
- During the study treatment and follow-up period, where clinically possible, a follow-up specimen from bone, tissue, synovial fluid or blood should be obtained to assess for microbiological eradication of the baseline pathogen (using molecular typing tests if the same staphylococcal species as the baseline one is isolated from the follow-up samples).

Radiological evidence:

- Various imaging modalities are used in patients with osteoarticular infections. These are X-rays, MRI scans, CT scans, isotope and labelled white blood cell (WBC) scanning, and ultrasonography. The choice of the method is dictated by the clinical scenario, Investigator preference, and availability of the imaging technique. Each of these methods has its own merits and for the purpose of this study, wherever possible and appropriate, the same method should be repeated during and after the completion of treatment to assess for evidence indicative of resolution of infection.

9.1.4 Exploratory endpoints

9.1.4.1 PK – only for patients who are treated with afabicin

The PK parameters will be derived by non-compartmental analysis or by population PK data analysis using a nonlinear mixed-effects modelling approach and will include the following parameters:

- PK after first IV dose (Day 1): $AUC_{0\text{-}12h}$ and, if applicable, C_{max}, t_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $t_{½}$, mean residence time (MRT), CL or CL/F, V_z or V_z/F for afabicin and/or its active moiety Debio 1452, as applicable.
- PK at steady-state (ss) (after oral morning dose in fasted conditions, at Day 28 visit or EOT): AUC_{τ} and, if applicable, $t_{max,ss}$, $C_{max,ss}$, CL_{ss}/F, C_{trough}, C_{av}, peak trough fluctuation (PTF) for Debio 1452,

In addition, the following PK/PD index will be calculated:

- PK-PD index on Day 1 and at steady-state: Debio 1452 *f*AUC:MIC.

If deemed appropriate the PK concentrations may be pooled with data from other studies for a subsequent population PK data analysis. This will be described in a separate analysis plan and reported separately.

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Furthermore, potential factors (demographic, pathophysiological, pharmacogenetic or other covariates) affecting afabicin and Debio 1452 disposition, safety and efficacy will be investigated.

9.1.4.2 Microbiological outcome – for all patients

An exploratory endpoint will be the microbiological outcome at each visit where the microbiological sample can be collected, based on culture results (if available). Microbiological outcome will be evaluated as follows:

- Documented Eradication: absence of baseline pathogen(s) in post-baseline cultures.
- Presumed Eradication: no material available for culture and successful clinical response.
- Documented Persistence: presence of at least one baseline pathogen in post-baseline cultures of the original site of infection.
- Presumed Persistence: no material available for culture and clinical non-response.
- Recurrence: presence of at least one baseline pathogen in post-EOT cultures of the original site of infection after documented or presumed eradication.
- Super-infection: a new pathogen cultured from the original site of infection during the treatment period, in the presence of signs and/or symptoms of infection.
- New Infection: a new pathogen cultured from the original site of infection after therapy (EOT), in the presence of signs and/or symptoms of infection.
- Unknown: outcome assessment is not possible (e.g., patient is lost to follow-up).

In Part B only, if in the Investigator's opinion the isolated bacteria should not be considered as a pathogen (e.g., colonization, contamination of specimen), this decision will be documented and the isolate will not be considered as a pathogen in analysis of microbiological outcome. In case the IDMC considers that the isolated bacterium – from a randomized patient - is a clinically relevant pathogen, this assessment will be used for the final microbiological outcome in the study.

9.1.4.3 Biomarker exploration

9.1.4.3.1 Biomarkers related to response, toxicity and PK

An explorative research in order to identify biomarkers related to response, toxicity, and PK will be conducted on in afabicin-treated patients. Notably, the following points will be explored:

- Relation of toxicity, [redacted] but also others, with [redacted]. In order to establish the predictive value of a potential biomarker, this analysis could be conducted in all patients, including those who did not experience any toxicity.
- Relation of toxicity, PK, and response to treatment with [redacted] gene variants.
- Relation of toxicity, [redacted] but also others, with plasma biomarkers such as, but not limited to, [redacted] Since the baseline levels of such biomarkers are not well defined, samples will be taken from all afabicin-treated patients at baseline (before afabicin treatment), and then again in case of AEs justifying such an investigation. These biomarkers will only be analyzed in case the Sponsor deems necessary in view of the toxicities observed, but the Sponsor reserves the right in such a case to analyze also baseline samples of patients with no related toxicities in order to obtain a baseline value for the study population.
- [redacted]

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9.1.4.3.2 Biomarkers related to the gut microbiota

Explorative research to identify biomarkers related to the impact of treatment on the gut microbiota will be conducted in afabicin and standard of care treated patients. This will be performed at selected sites and only in a subset of patients who have agreed to participate in this exploratory and optional assessment. Notably, the following points will be assessed:

- Changes compared to baseline in relative abundance of microbial taxa and antimicrobial resistance (AMR) genes in the stool of patients at EOT and 4 weeks post-EOT.
- Quantification of key metabolites in the stool including but not limited to bile acids and short chain fatty acids (SCFA) at baseline, and temporal within-patient metabolic changes during the study (baseline, EOT, and 4 weeks post-EOT).

9.1.4.4 Drug-drug interaction potential – only for patients who are treated with afabicin

- The DDI potential of afabicin towards CYPs will be assessed using the following parameter: Change from baseline in 4-β-OH-cholesterol plasma concentrations and/or 4-β-OH-cholesterol/cholesterol ratio (and other endogenous DDI biomarkers if applicable) after repeated administration of afabicin.

9.1.4.5 Improvement of inflammation

As exploratory endpoint C-reactive protein (CRP) will be assessed to better understand patient's overall improvement of inflammation. CRP levels are checked as part of full panel laboratory assessment (see Table 14-1).

Inflammation would be considered improved when the baseline CRP level is over the normal range and it decreases at the EOT visits and 12 weeks post-EOT (excluding other causes of inflammation). The CRP analysis is considered as an exploratory endpoint as it has a low specificity in BJI as an inflammatory biomarker.

9.2 Study assessments and procedures

9.2.1 Study plan

Schedule of assessments (Table 14-1) outlines all of the tests and evaluations to be performed during the study. Study procedures must be performed according to the planned time schedule with strict adherence to visit intervals. All patients enrolled in the study must attend the study visits as indicated in the study plan. Additional safety assessments during study treatment and post-EOT will be performed by the dedicated study physician during hospital or home visits. For complete Schedule of Assessment please see Table 14-1.

Prior to conducting any of the screening tests, the Investigator or designee will explain the study fully to the prospective patient and provide him/her with a copy of the Patient Information Leaflet/ICF. If the patient is willing to participate in the study, s/he and the Investigator or designee will each sign two copies of the ICF, one of which will be provided to the patient. Patients will attend the screening visit(s) within 10 days prior to the start of study treatment. The patient's eligibility for the study will be confirmed by the inclusion/exclusion criteria (see Section 7).

Previous results obtained using invasive procedures, e.g., bone/synovial fluid/tissue microbiological diagnostics, imaging tests, performed as a component of routine patient care through the local laboratory before screening period can be used to determine patient eligibility, unless there had been a change in the clinical scenario as determined by the Investigator that may impact previously obtained results. Study specific informed consent must be obtained before performing any other study-specific screening procedures (Section 9.2.3).

The efficacy will be assessed at fixed time points from randomization (at Day 8, Day 28, and Day 42), which will allow for a clearer comparison of the 2 treatment arms. In addition, all patients will be assessed for efficacy at the following time points: EOT, 4 weeks post-EOT, and 12 weeks post-

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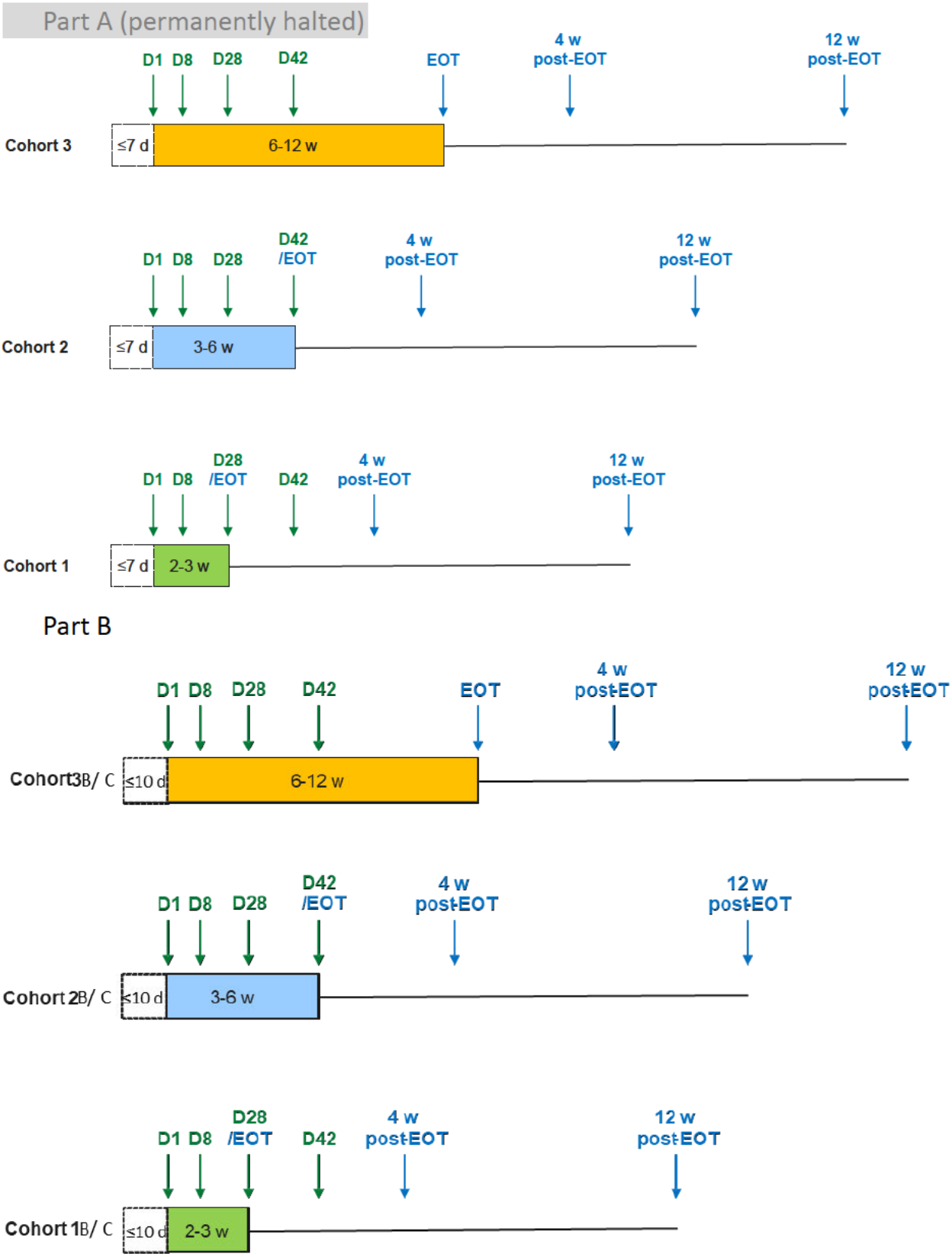
EOT. Due to the varying treatment duration of these patients (from 2-12 weeks) some of these assessment time points may coincide and will be counted once (Figure 9-1).

The following on-site visits are planned during the study:

- Screening visit: to take place between Day -10 and Day -1. During this visit, a culture will be taken for microbiological assessment of the pathogen. The pathogen must be identified prior to the start of study medication.
- Day 1 visit: start of IV study medication. The first infusion will be administered in the morning in order to facilitate Day 1 assessments.
- Day 8 visit (±1 day): a visit to assess the safety and efficacy of treatment.
- Day 28 visit (±1 day) (if the patient is still on study medication): a visit to assess the safety and efficacy of treatment. The patient will attend the visit prior to the morning oral dose in order to facilitate PK sample collection.
- Day 42 visit (±1 day) (if the patient is still on study medication): a visit to assess the safety and efficacy of treatment.
- EOT visit (+1 day): treatment duration will depend on the patient's diagnosis (i.e., septic arthritis, osteomyelitis, or PJI) and will be at the Investigator's discretion but no longer than 12 weeks (3 months).
- Follow-up visit: 4 weeks post-EOT (±2 days)
- Follow-up visit: 12 weeks post-EOT (±7 days)

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Figure 9-1 Study assessment time points



Fixed time points from randomization are indicated by green arrows; time points based on EOT are indicated by blue arrows.

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Each study site will have a dedicated study physician to oversee the safety of the patients when out of hospital and to ensure a timely follow-up of any events. On Day 3 or Day 4, weekly thereafter (starting at Day 8) during study treatment (when the patient is not hospitalized or scheduled for an on-site visit) and weekly for the first 6 weeks post-EOT, a dedicated study physician will visit the patient to assess safety, obtain a blood sample for a laboratory safety panel (Section 9.2.5.2), and review the diary card. The timing of assessments is shown in Table 14-1 and this section will provide more information on the data that need to be collected as part of each assessment/procedure.

If necessary, additional visit(s) should be planned at the discretion of the Investigator.

9.2.2 Patient monitoring: operational set up

Given the complex study design and frequent monitoring of patients mandated by this protocol, a study support structure outlined in this section will be set up to assist the Investigator and ensure an immediate response to any concerns with patient safety.

The Investigator will have access to a preselected [redacted] at the study site for any consultations, as needed. The Sponsor/Contract Research Organization (CRO) will be available to the Investigator for any guidance regarding prohibited medications throughout the study.

A physician will be identified at the site to support the Primary Investigator and assume the duties of the sub-investigator in case the Investigator is unavailable for immediate consultation.

Dedicated study physician(s) will be assigned to each site to oversee patient safety when the patient is out of hospital. The physician must be qualified, experienced in infectious diseases, and well-trained in study procedures, including phlebotomy, ECG administration, and patient diary review. The dedicated study physician will visit each patient on Day 3 or Day 4, weekly thereafter (starting at Day 8) during treatment administration and weekly for the first 6 weeks post-EOT to collect a blood sample for a laboratory safety panel (Section 9.2.5.2) and review the patient diary, unless there is a scheduled visit where a full panel (which includes a safety panel) is performed. In case any concerns are raised upon review of the patient diary or if the patient shows any signs or symptoms (e.g., appearance of fatigue, nausea, vomiting, jaundice, right upper quadrant pain or tenderness, fever, rash), the physician will relay the information in an expedited manner to the Investigator or sub-investigator for further follow-up.

9.2.3 Baseline assessments

Study specific ICF must be obtained before performing any other study-specific screening procedures.

Patient demographics will include: age at screening, race, gender, height, weight.

The following characteristics of the osteoarticular infection will be recorded at screening:

- Type of infection (e.g., septic arthritis, osteomyelitis, PJI) and localization (e.g., knee, hip, shoulder), imaging, and microbiology investigations that support the diagnosis, including a previous confirmation (see Section 9.2.1) of the infecting pathogen causing the current infection to be treated
- Onset and duration of the condition
- Origin of the infection (e.g., hematogenous, arthrocentesis or arthroplasty)
- Clinical signs and symptoms at the site of infection of the disease (e.g., pain, localized warmth, tenderness, restricted active/passive movement, lymphadenopathy, extremity weakness/ numbness, erythema, swelling, draining sinuses, bone/ joint instability)
- General clinical signs: (e.g., fever, irritability, nausea, fatigue, weight loss)
- Any surgical procedures related to the disease performed prior to study treatment

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For documentation of medical history, any relevant or active medical conditions within the last 5 years prior to screening will be recorded. In addition to general medical history, the following information must be assessed:

- History of alcohol, IV drug, or other drug abuse
- History of HIV, hepatitis B virus (HBV), hepatitis C virus (HCV) infections
- History of lymphedema
- History of recurrent staphylococcal infections
- Any significant prior surgical procedures (a surgery which requires total anesthesia or involves treatment of an internal organ)

The medical history will be obtained by interviewing the patient or by inspecting his/her medical records.

Prior and concomitant medication will be documented at screening to determine patient eligibility, particularly the use of antibiotics. Prohibited concomitant medications are described in Section 8.7.4.

A blood sample will be collected at baseline to allow analyses of biomarkers such as [redacted] These samples will be analyzed only in cases of any emergent safety events.

9.2.4 Study drug administration and treatment compliance

Study drug administration and compliance are described in Section 8.3.

9.2.5 Safety assessments

This section expands on the nature of the safety assessments in Table 9-1, however, the frequency of monitoring may be adapted based on the safety signals reported as the study progresses. In addition, any safety assessments may be performed more frequently per the Investigator's judgement.

9.2.5.1 Adverse events

The procedures for the collection, reporting, and assessment of AEs are outlined in Section 10. Adverse events of special interest (AESI) are described in Section 10.1.5. AEs will be collected at screening and at all study visits.

9.2.5.2 Laboratory assessments

Blood specimens for all laboratory assessments will be drawn and tested by the local hospital laboratory. Laboratory tests included in the full panel are shown in Table 9-1.

Serology tests will be performed only at screening. All other laboratory assessments (hematology, clinical chemistry, electrolytes, coagulation tests, urinalysis, and pregnancy tests) will be performed at every Investigator site visit up to and including the visit at 4 and 12 weeks post-EOT, as indicated in Table 14-1; however, they should be performed more frequently whenever clinically indicated per the Investigator's judgement.

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Table 9-1 Laboratory assessments: full panel

Hematology	White blood cell (WBC) count Neutrophils (absolute and %) Eosinophils (absolute and %) Basophils (absolute and %) Lymphocytes (absolute and %) Monocytes (absolute and %)	Platelet count Hemoglobin Hematocrit
Clinical chemistry	C-reactive protein (CRP) Creatinine Calculated glomerular filtration rate Glucose Blood urea nitrogen Uric acid Total protein	Bilirubin (total, direct, indirect) Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Gamma glutamyl transferase (GGT) Creatine phosphokinase (CPK) Creatine kinase-MB (CKMB), if CPK is elevated
Electrolytes	Sodium Potassium Magnesium	Bicarbonate Chloride Calcium (ionized or total - corrected for albumin)
Coagulation tests	Prothrombin time Activated partial thromboplastin time (aPTT)	International normalized ratio (INR)
Serology	hepatitis B surface antigen (HBsAg)[a] hepatitis C virus antibody (anti-HCV)[a,c]	anti-nuclear antibody[a] human immunodeficiency virus (HIV)[b]
Urinalysis	Dipstick	
Pregnancy test	Urine test in women of childbearing potential only	

a: At screening only; [redacted]

b: At screening and only applicable in South Africa and Argentina according to local regulatory requirement. If HIV serology testing is positive, HIV RNA PCR and CD4 cell counts will be conducted.

c: At screening only; If HCV serology is positive, HCV PCR should be performed during the screening period.

In between on-site visits, [redacted] (while hospitalized and after discharge) and weekly for the first 6 weeks post-EOT, as indicated in Table 14-1. Any patient exhibiting any abnormality will be followed up until resolution. Laboratory tests included in this more frequently monitored safety laboratory panel are shown in Table 9-2. Liver enzyme elevations are considered as AESIs (Section 10.1.5) and recommendations for follow-up and intervention are discussed in Section 6.4.1.

Table 9-2 Laboratory tests included in a safety panel

[redacted]

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9.2.5.3 [redacted]

[redacted]

9.2.5.4 Electrocardiograms

Cohorts 1A, 2A and 1B

A standard 12-lead ECG will be performed for all patients at a minimum:

a) At the screening visit;

b) Daily during hospitalization or on an outpatient basis, depending on local practice on Days 1, 2, and 3. ECGs will be linked to PK assessments as follows:

- Part A: On Day 1: the ECG should be performed pre-dose and then just prior to drawing blood for PK: at 15 minutes (±5 min) and 5.5 hours (±0.5 hour) after the end of the first IV infusion.
- Part B: On Day 1, the timing of ECG relative to PK sampling is shown in Figure 9-3.
- On Day 2 and Day 3: ECG should be performed within 3 hours after the end of study drug infusion,

c) After discharge from hospital, or continuing on an outpatient basis per local practice, while on study treatment: ECG will be performed every 3 to 4 days,

d) At Day 28 or EOT (if study treatment is < 4 weeks) on-site visit: ECG should be performed pre-morning dose and just prior to drawing blood for PK at 5.5 hours (±0.5 hour) after the morning oral intake, as shown in Figure 9-4.

e) Follow-up ECGs at 2- and 4-week post-EOT will be performed only if ECG tracing indicates abnormalities at the EOT.

Cohorts 2B and 3B

a) At the screening visit;

b) On Day 1, the ECG should be performed pre-dose and just prior to drawing blood for PK at 3.5 hours (±0.5 hour) after the end of the infusion;

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c) At Day 28 or EOT (if study treatment < 28 days) on-site visit: ECG should be performed pre-morning dose and just prior to drawing blood for PK at 5.5 hours (±0.5 hour) after the morning oral intake.

In addition to the above time points, an ECG will be recorded at any point during treatment if clinically indicated and on any patient who experiences an AE of sustained tachycardia, chest pain, palpitations, or arrhythmia while on study drug.

Patients should rest comfortably in a semi-recumbent position for at least 10 minutes prior to recording.

All ECGs will be recorded in triplicate at intervals of 2 to 3 minutes between tracings. All tracings will be read locally at study site.

During home visits, a dedicated study physician will perform ECGs in triplicate using a portable ECG device. The same device should be used at each home visit for a given patient to allow comparisons in between visits. The dedicated study physician will scan the ECG tracing and send it in an expedited manner to the Investigator. In case of abnormal ECG readings, the Investigator may decide whether it is appropriate to continue treatment with study medication and may hospitalize the patient for further evaluation. In all cases, the Investigator will have access to a cardiologist (pre-selected at each study site) for advice and interpretation, if needed.

9.2.5.5 Physical examination

The examination will include general appearance, sclera, cardiovascular system, pulmonary system, neurologic system, skin and gastrointestinal system.

9.2.5.6 Vital signs

Vital signs will include blood pressure, heart rate, respiratory rate, and temperature will be measured per schedule in Table 14-1. On Day 1, these will be measured prior to the administration of the first dose of the study drug, at the time of completion of the first dose of study drug, and 1 hour after the completion of the first dose of study drug. While the patient is hospitalized (or on an outpatient basis, depending on local practice), on Day 2 and Day 3, vital signs will be checked within 3 hours of completing the study drug infusion.

9.2.5.7 Concomitant medications

Prior and concomitant medication will be documented at the time points shown in Table 14-1. The details of allowed and prohibited concomitant medications are outlined in Section 8.7.

9.2.6 Efficacy assessments

Efficacy will be evaluated at the time points outlined in Table 14-1. The criteria for efficacy assessments are outlined in Section 9.1.2.

9.2.6.1 Microbiological assessments: bone, synovial fluid, and blood cultures

The clinical microbiology laboratory manual will include detailed description of microbiological methods and procedures. At any time point in the study, the Investigator can decide that the isolated bacteria should not be considered as a pathogen (e.g., colonization, contamination of specimen). This decision will be documented and the isolate will not be considered as a pathogen for the purpose of e.g., patient inclusion or analysis of microbiological outcome. In case the IDMC considers that the isolated bacterium – from a randomized patient - is a clinically relevant pathogen, this assessment will be used for the final microbiological outcome in the study. Baseline samples for microbiological assessment are defined as all samples that have been collected at screening, ideally prior to the start of any empiric antibiotic treatment. For all patients, baseline samples from the primary site of infection (bone, synovial fluid, or soft tissue biopsy) should be taken and blood samples are mandatory for identification of baseline pathogens.

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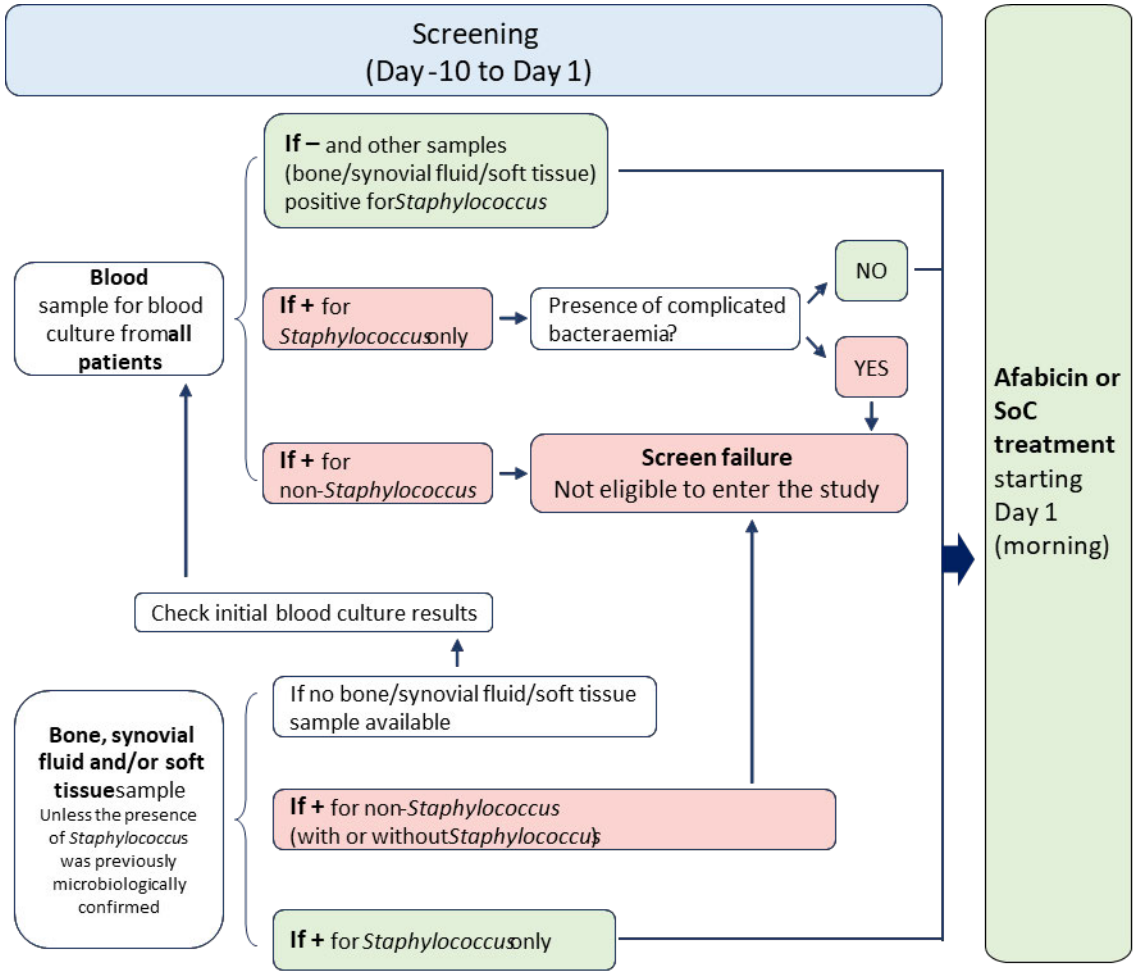
The microbiological assessments needed to enroll the patient in the study are shown in Figure 9-2. Patients with only staphylococcal species as baseline pathogens can be enrolled in the study.

Patients who have a positive blood culture for Staphylococcus aureus at screening, in the absence of other complicating clinical factors, can be enrolled and start treatment with afabicin. However, in these cases it is mandatory to repeat blood cultures to document two consecutive negative results in order to continue afabicin treatment (e.g., negative blood cultures at 48 and 72 hours after start of treatment). If there are signs of complicated bacteremia, as discussed in Section 6.4.2, patients will be withdrawn from the study (Figure 9-2).

During the treatment and follow-up periods, follow-up synovial fluid or bone/tissue biopsy samples should be taken where clinically appropriate to assess the clinical response to the study drug and to establish the presence or absence of other pathogens. All synovial fluid samples or bone/tissue biopsy samples (debridement, needle aspiration, arthroscopic lavage, synovial fluid examination or bone biopsy) obtained during study treatment should be used when possible for microbiological assessment.

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Figure 9-2 Microbiological assessments during screening and treatment period



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The responsibility for the primary bacterial culture from all blood, bone, and synovial fluid samples, isolation, identification, and susceptibility testing to routine medication, including selected SoC, will fall on the local hospital microbiology laboratory. These analyses will be carried out according to local supplies and routine procedures and used for the determination of eligibility for enrolment in this study.

To identify the patients who have an infection with staphylococcal species as the only pathogen prior to the treatment with afabicin, the following tests can be included and combined: Gram staining, pathogen identification by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, culture on selective medium or validated polymerase chain reaction (PCR) assay. Susceptibility testing to routine medication could also be performed to further characterize isolates.

If non-staphylococcal pathogen(s) are identified after the start of the treatment with afabicin, patients should be withdrawn from the study treatment, as discussed in Section 6.4.1. All clinically relevant bacterial isolates (from synovial fluid, bone, blood or soft tissues) from randomized patients at all visits will be sent (isolated in a pure 24-hours culture) to the central laboratory after isolation and identification.

The central laboratory will confirm their identification, perform susceptibility testing with Debio 1452 and routine medication, including selected SoC, and carry out molecular test for further characterization when required. These molecular tests include but are not limited to, virulence and resistance factor testing (mecA gene conferring methicillin resistance, Panton-Valentine Leukocidin [PVL]), and other bacterial characteristics of interest. Bacterial cultures taken post baseline that are positive for staphylococci and of the same species will be compared with the baseline pathogen using molecular typing (e.g., pulsed-field gel electrophoresis [PFGE]) and/or whole genome sequencing techniques by the central laboratory). Data from the susceptibility testing will be used in conjunction with the clinical efficacy data after completing the trial to provide additional information to determine the breakpoint for afabicin.

Local laboratory will retain a frozen copy of the isolate for backup purposes for the duration of the study (not to be destroyed without Sponsor’s approval). These backup isolates will be requested by the central laboratory if required.

If results from the central and local laboratories are incongruent, the identification of the bacterial isolates and antibiotic sensitivity results of the central laboratory will be utilized. The local laboratory results will be used for analysis only if an isolate is not received by the central laboratory (i.e., lost or non-viable).

All isolates will be stored at the central laboratory for further analyses that may include afabicin susceptibility and genetic characterization.

9.2.7 Exploratory assessments

9.2.7.1 Pharmacokinetic and DDI potential assessments

PK sampling, only in patients treated with afabicin, will occur on two days during the study: Day 1 and at Day 28 or EOT (if treatment < 28 days). The aim of this PK collection is to provide pharmacokinetic profiles and assess variability after single and multiple doses of afabicin in BJI patients. Furthermore, any correlation between plasma exposure and change in the ECG parameters and correlation between exposure and efficacy (PK/PD) will be explored.

In case synovial fluid samples or bone/tissue biopsy samples are taken during study treatment if clinically indicated, these samples may also be used to determine Debio 1452 concentration. In addition, a PK sample may be collected in case of safety events as described in Section 6.4.1.

PK sampling (Part A)

Sparse PK samples will be collected as follows:

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- On Day 1: at 15 minutes (±5 min), 3.5 hours (±0.5 hour) and 5.5 hours (±0.5 hour) after the end of the first IV infusion. The infusion will be administered on one arm, blood for PK will be collected from the other arm; the exact date/time of infusion start, infusion end and PK sample collection will be recorded.
- At Day 28 (or at EOT if the treatment < 28 days): at pre-morning dose; then at 5.5 hours (±0.5 hour) after morning oral intake. On that morning, afabicin will be administered in fasted conditions (from 4 hours before to 4 hours after drug intake); the exact date/time of PK sample collection will be recorded. In case fasting is not possible for the patient, the time and type of the meal (i.e., high-fat vs low-fat) should be recorded.

The exact dose and date/time of each drug intake from Day 1 to Day 28 visit (included) will be recorded.

For patients with septic arthritis who may finish treatment prior to Day 28 visit, the sampling will be conducted at their EOT visit. In such cases, patients should take their last dose at the EOT visit and be in a fasted state from 4 hours prior to the visit until 4 hours after dosing. In case fasting is not possible for the patient, the time and type of the meal (i.e., high-fat vs low-fat) should be recorded.

When ECG are to be collected at the same time point(s) as the PK, the ECG should be performed just prior to drawing blood for PK as described in Section 9.2.5.4 for sparse PK sampling.

PK sampling (Part B)

PK sampling time points are as follows:

- On Day 1: at the end of the first IV infusion (30 minutes to 10 minutes before the end of the infusion); then at 15 minutes (±5 minutes), 1 hour (±10 minutes), 3.5 hours (±0.5 hour), 5.5 hours (±0.5 hour), 8 hours (±0.5 hour), and 10 hours (±0.5 hour) (i.e., just before the second dose) after the end of the first IV infusion. Only patients for whom a second venous access can be obtained to insert a catheter line for PK sampling will be included. The line used for drug infusion should not be used for PK sampling. The infusion will be administered on one arm, blood for PK will be collected from a catheter placed on the other arm. The exact date/time of infusion start, infusion end, infusion arm and collection arm, and PK sample collection will be recorded.
- At Day 28 (or at EOT if the treatment < 28 days): at pre-morning dose and then at 1 hour (±10 minutes), 2.5 hours (±0.5 hour), 4.5 hours (±0.5 hour), 5.5 hours (±0.5 hour), 8.5 hours (±0.5 hour), and 10.5 hours (±1 hour) after morning oral intake.

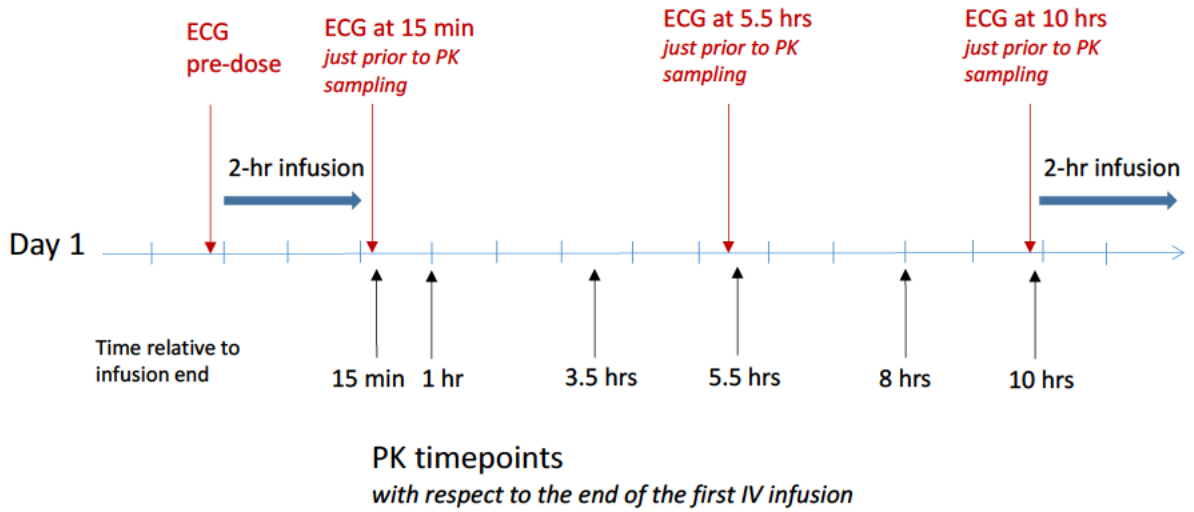
  On that morning, afabicin will be administered in fasted conditions (from 4 hours before to 4 hours after drug intake). In case fasting is not possible for the patient, the time and type of the meal (i.e., high-fat vs low-fat) should be recorded. The exact date/time of PK sample collection will be recorded. In addition, the exact dose and date/time of each drug intake from Day 1 to Day 28 visit (included) will be recorded.

When ECG are to be collected at the same time point(s) as the PK, the ECG should be performed just prior to drawing blood for PK. The relative timing of PK sampling and ECG recording is shown in Figure 9-3 (Day 1) and Figure 9-4 (Day 28 visit/EOT).

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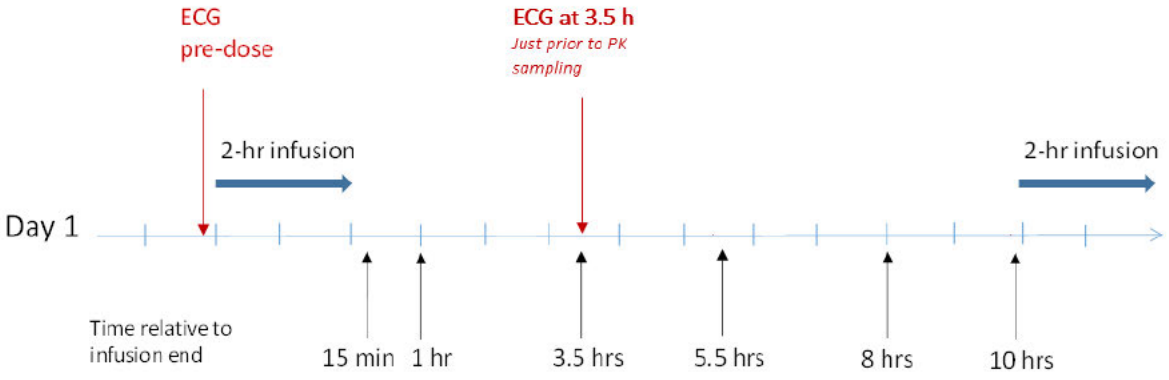
Figure 9-3 Timing of PK sampling (Cohort 1B, Cohorts 2Band 3B) and ECG reading on Day 1

Cohort 1B



PK timepoints
with respect to the end of the first IV infusion

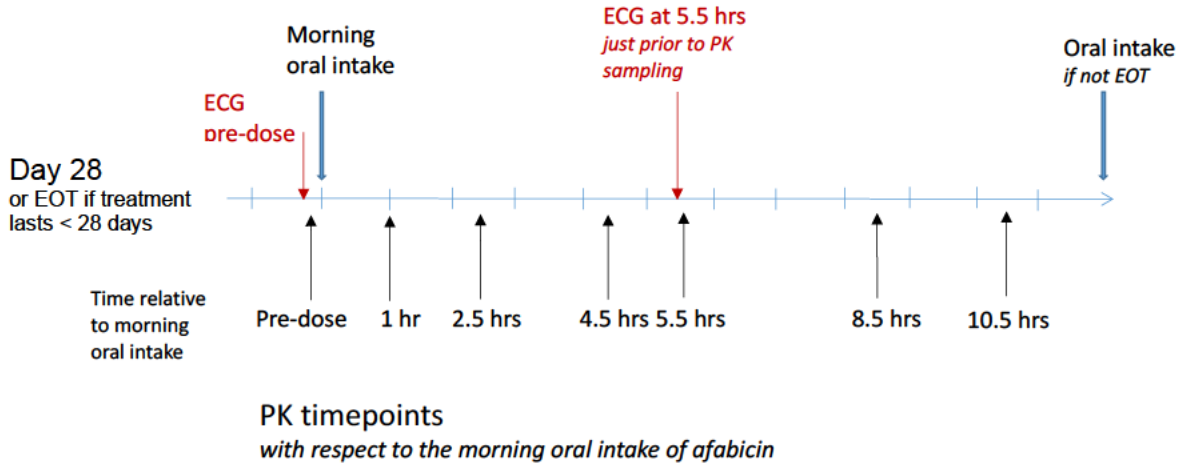
Cohorts 2B and 3B



PK timepoints
with respect to the end of the first IV infusion

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Figure 9-4 Timing of intense PK sampling (Part B) and ECG reading on Day 28



All samples must be protected from sun and artificial light exposure during collection and processing. Samples will be processed and analyzed for concentrations of afabicin and Debio 1452 by a validated method. Blood sample collection, processing and shipping details will be outlined in a separate laboratory manual. PK samples will also be used for quantification of 4β-OH-cholesterol and/or 4β-OH-cholesterol/cholesterol ratios and potentially of other DDI biomakers, see Section 9.1.4.3.

After completion of the analysis, the remaining PK samples may be stored for up to a maximum of 10 years after the end of the study and, if required, may be used for a retrospective examination of safety laboratory tests, of proteins involved in the metabolism or the pharmacological effects of afabicin, for metabolic profiling, for determination of the unbound fraction, or for further bioanalytical investigations (such as method cross-validation and protein binding) to validate data for the development of afabicin. Analyses will be restricted to parameters necessary for this purpose only.

9.2.8 Other exploratory assessments

9.2.8.1 Biomarker samples

Blood. A blood sample (2 mL blood, for plasma isolation) will be collected on Day 1 prior to afabicin dosing from all patients randomized to afabicin treatment, to allow analyses of biomarkers such as [redacted] Other sample(s) will be collected in case of an AE(s) deemed of interest for the same purpose. These samples will be analyzed in an exploratory manner. The baseline samples of patients who did not have AEs may also be analyzed to establish a baseline range in this population.

Stool. Stool samples will be collected at baseline, EOT, and 4 weeks post-EOT. Patients will receive either a scoop (one scoop for solid material) or a plastic bulb pipette (approximately 1-2 mL of liquid material). Stool will be collected into two separate tubes (one for metagenomic sequencing analysis and the other for metabolomic quantification studies) according to the instructions.

9.2.8.2 Pharmacogenomics samples

A blood sample (whole blood, 5 mL) will be collected from all afabicin-treated patients on Day 8 (or later in case of a missed visit), and may be analyzed notably for [redacted], to explore the possibility of a connection between variants in [redacted] genes and toxicities and/or efficacy and/or PK. Samples of patients who did not experience AEs may also be analyzed to help establish the positive and negative predictive values of any identified potential biomarkers.

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9.2.9 Total volume of blood collected

For each patient enrolled, the amount of blood collected during the study for all procedures will be up to 350 mL.

10 ADVERSE EVENTS

The Investigator is responsible for detection and documentation of events meeting the criteria and definition of an AE/SAE as provided in this protocol. At each safety evaluation during the study, the Investigator or designee will collect information on unusual manifestations or AEs and SAEs, and will record them on the AE page of the eCRF. Their nature, severity, duration, treatment, and relationship with the IMP as assessed by the Investigator will be recorded. The Investigator will also indicate whether study treatment was discontinued and how the event evolved.

10.1 Definitions and Assessment Criteria

10.1.1 Adverse Event

Per the International Council for Harmonization (ICH), an AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. AEs can be serious or non-serious. They may or may not lead to the withdrawal of the patient from the study.

A TEAE is any undesirable event either not present prior to medical treatment or worsening (in intensity or frequency) following treatment. Any such AE which occurs once treatment has started will be considered as treatment emergent.

10.1.2 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life threatening (i.e., puts the patient at immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect, or
- Is otherwise medically significant: Important medical events that may not immediately be life threatening or result in death or hospitalization, but that jeopardize the patient or require intervention to prevent one of the outcomes listed in the definitions above shall also be considered as serious.

[redacted]

Non-serious: All AEs that do not correspond to the definition of SAE are considered as non-serious.

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10.1.3 Severity of Adverse Events

AEs will be graded by the Investigator or designee as mild, moderate or severe according to the following definitions:

Mild:

Transient, non-progressive, and does not influence performance of daily activities. Medical intervention is not usually necessary.

Moderate:

Marked symptoms, sufficient to cause discomfort. Interferes with the performance of daily activities, but is not incapacitating. Medical intervention may be necessary.

Severe:

Symptoms cause considerable discomfort. Substantial influence on daily activities and may be totally incapacitating. Medical intervention is usually required.

In addition, CTCAE version 4.03 will be used to grade laboratory abnormalities. For QTc-related AEs, CTCAE version 3.0 will be used which is consistent with guidance E14 (*Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*).[41,42]

10.1.4 Relationship with the Investigational Medicinal Product

The causal relationship of the AE to study drug will be determined by the Investigator or designee and described by one of the following terms.

AE related:

- Follows a reasonable temporal sequence from administration of the study drug.
- Cannot be reasonably explained by the patient's clinical state, environmental or toxic factors or other therapies administrated to the patient.
- Disappears or decreases on cessation or reduction in dose of the study drug.
- Follows a known pattern of response to the study drug.
- Reappears or worsens upon rechallenge.

AE not related:

- The AE does not meet criteria for relatedness.
- There is sufficient information to determine that the etiology of the AE is not related to the study drug or study procedure.

10.1.5 AEs of Special Interest

[redacted]

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All of the above listed events require appropriate reporting within 24 hours of becoming aware of the event. The procedure for AESI reporting is outlined in Section 10.4.

10.2 Reporting of Serious Adverse Events to the CRO

10.2.1 Reporting during the study

All SAEs occurring during treatment and within 12 weeks of the last study drug administration will be reported within 24 hours of SAE awareness. The Investigator must notify the CRO **of all SAEs within 24 hours** of awareness by fax or e-mail using the Sponsor's SAE Report form.

- When reported by fax, the SAE Report form will be filled in and sent with the provided fax cover page entitled Serious Adverse Event Report transmittal form to country-specific toll-free fax number indicated on the fax cover page.
- When reported by e-mail, the SAE Report form will be sent to CRO's Safety Desk at the following e-mail address: safetydesk@psi-cro.com.

Notification of SAEs does not depend on their relationship with the IMPs. All SAEs regardless of their relationship with the study drugs and occurring until the last study visit will be reported as described above.

10.2.2 Follow-up of Serious Adverse Events

All SAEs, regardless of severity, must be followed up:

- To resolution (the patient's health has returned to the baseline status or all variables have returned to normal), or
- Until stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event), or
- Until the event is otherwise explained regardless of whether the patient is still participating in the study.

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Some events are often ongoing; however, once these events have been determined by the Investigator to be stable or chronic, s/he may consider the event to be resolved or resolved with sequelae.

The Investigator will notify the Sponsor/CRO of any follow-up information by fax or e-mail within 24 hours of new information awareness (see Section 10.2.1 above).

10.3 Procedure for Serious Adverse Event Notification to Independent Ethics Committees

If required by applicable local regulations, the Investigator will promptly notify the relevant Independent Ethics Committee (IEC) or Institutional Review Board (IRB) (in addition to the Sponsor/CRO) of any SAE (including post-study SAEs and follow-up information) that occurred at their site or was brought to their attention by the Sponsor/CRO. The Investigator will verify that the IEC/IRB acknowledges receipt of the notification.

10.4 Procedure for reporting an Adverse Event of Special Interest

For any AESI (as defined in Section 10.1.5) occurring during the period of the clinical trial, whether related to the treatment or not, and whether expected or not, the Investigator must notify the CRO within 24 hours of awareness by fax or e-mail using the AESI form.

All AESIs, regardless of severity, must be followed up:

- To resolution (the patient's health has returned to the baseline status or all variables have returned to normal), or
- Until stabilization of the event has occurred (the Investigator does not expect any further improvement or worsening of the event), or
- Until the event is otherwise explained regardless of whether the patient is still participating in the study.

Some events are often ongoing; however, once these events have been determined by the Investigator to be stable or chronic, s/he may consider the event to be resolved or resolved with sequelae.

The Investigator will notify the Sponsor/CRO of any follow-up information by fax or e-mail within 24 hours of new information awareness as described above.

10.5 Pregnancies

If the trial patient becomes pregnant, the Investigator must withdraw the patient from the trial.

The Investigator has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the study drug and to inform the Sponsor about this outcome.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication.

If the pregnancy leads to an abortion (voluntary abortion, spontaneous abortion or therapeutic abortion), in utero death or congenital anomaly, the procedure for declaration of a SAE should be followed (see Section 10.2.1). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

All pregnancies must be reported within 24 hours from the Investigational site to the CRO using the Sponsor's *Pregnancy Report Form*.

In case of serious pregnancy outcome experienced by the parent and/or the fetus/child, the serious parent or fetus/child events should be reported as SAEs by the Investigational site to the Sponsor using the SAE Report Form and/or the Pregnancy Report Form and according to the same processes and timelines (within 24 hours) as defined for SAE reporting (Section 10.2).

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10.6 Overdose of study drug

In case of an accidental afabicin overdose, the patient should be closely monitored for AEs, particularly QT prolongation and hepatic function.

The symptoms of afabicin overdose are expected to be an extension of the effects seen at the therapeutic dose, i.e., headache, nausea, vomiting, tachycardia, hypotension, and dizziness. In addition, other symptoms may be tremors and convulsions which have been observed in dogs at very high doses.

There is no known antidote for afabicin overdose. In cases of suspected overdose, patients should be supported by medical professionals utilizing standard medical practice. Study treatment will be discontinued if persistent or unacceptable treatment-related toxicity is observed.

Any overdose must be reported in the eCRF. Any overdose of study drug, if associated with an SAE must be reported by following the same process as for all other SAEs (Section 10.2).

11 MONITORING AND STUDY COMMITTEES

11.1 Study Monitoring

The study Sponsor is Debiopharm International S.A., Lausanne, Switzerland.

At mutually convenient times during the study, the Investigator will let Sponsor or its representative review all eCRFs and related source documentation, i.e., patient's medical chart, hospital, clinic, and laboratory records.

At timely intervals, and at the closing of the study, all IMPs will be accounted for and dispensing records made available to the Sponsor or its representative (see also Sections 8.4 and 8.3).

In case eCRFs require support information, the Sponsor may request copies of patient records or other source documents. All the necessary steps will then be taken to anonymize these documents and protect patient identity. Adherence to local and national laws governing protection of patient identity will be ensured.

11.2 Monitoring of Patient Data

Patients will be monitored intensively during this study. All data will be collected and analyzed in a timely manner.

The Sponsor will review data on an ongoing basis. In addition, [redacted] (IDMC [redacted] will also review the data and assess its implication on patient safety. The Health Authority will be informed regularly of pertinent data reviewed and evaluated [redacted].

Summary of the reporting timelines and potential actions to be taken in relation primarily to safety data are described in Table 11-1. The role of each committee is discussed in the subsequent sections.

11.2.1 Independent Data Monitoring Committee

An IDMC will be assembled prior to study start to review accumulating safety data on a regular basis (and ad-hoc in case of unexpected safety issues) throughout the study in order to ensure patient safety. The IDMC will consist of independent experts external to the study, and will include [redacted], as well as at least one infectious disease specialist with particular interest in BJIs.

Part A:

The review of accumulating data will be conducted once every 2 weeks and at EOT of the initial evaluable 8 patients (6 in afabicin and 2 in SoC arm), and including a minimum of 2-week post-

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treatment follow-up, for each cohort (see Figure 6-1). For this purpose, the IDMC will be provided all of the available safety, efficacy and pharmacokinetic data. In addition, the IDMC will perform expedited review of urgent safety issues such as AESIs and SAEs (Table 9-2).

Part B:

The review of accumulating data will be conducted once every two weeks and at the end of each cohort which includes 24 evaluable patients (20 in afabicin and 4 in SoC arm), and including a minimum of 2-week post-treatment follow-up (Figure 6-1). For this purpose, the IDMC will be provided all available safety, efficacy and pharmacokinetic data. In addition, the IDMC will perform expedited review of urgent safety issues such as AESIs and SAEs (Table 9-2).

The IDMC may also recommend the study to be modified (e.g., number of patients, monitoring frequency, afabicin dose) or the study to be terminated to ensure patient safety. The roles and responsibilities of the IDMC will be defined in the IDMC charter.

11.2.2 [redacted]

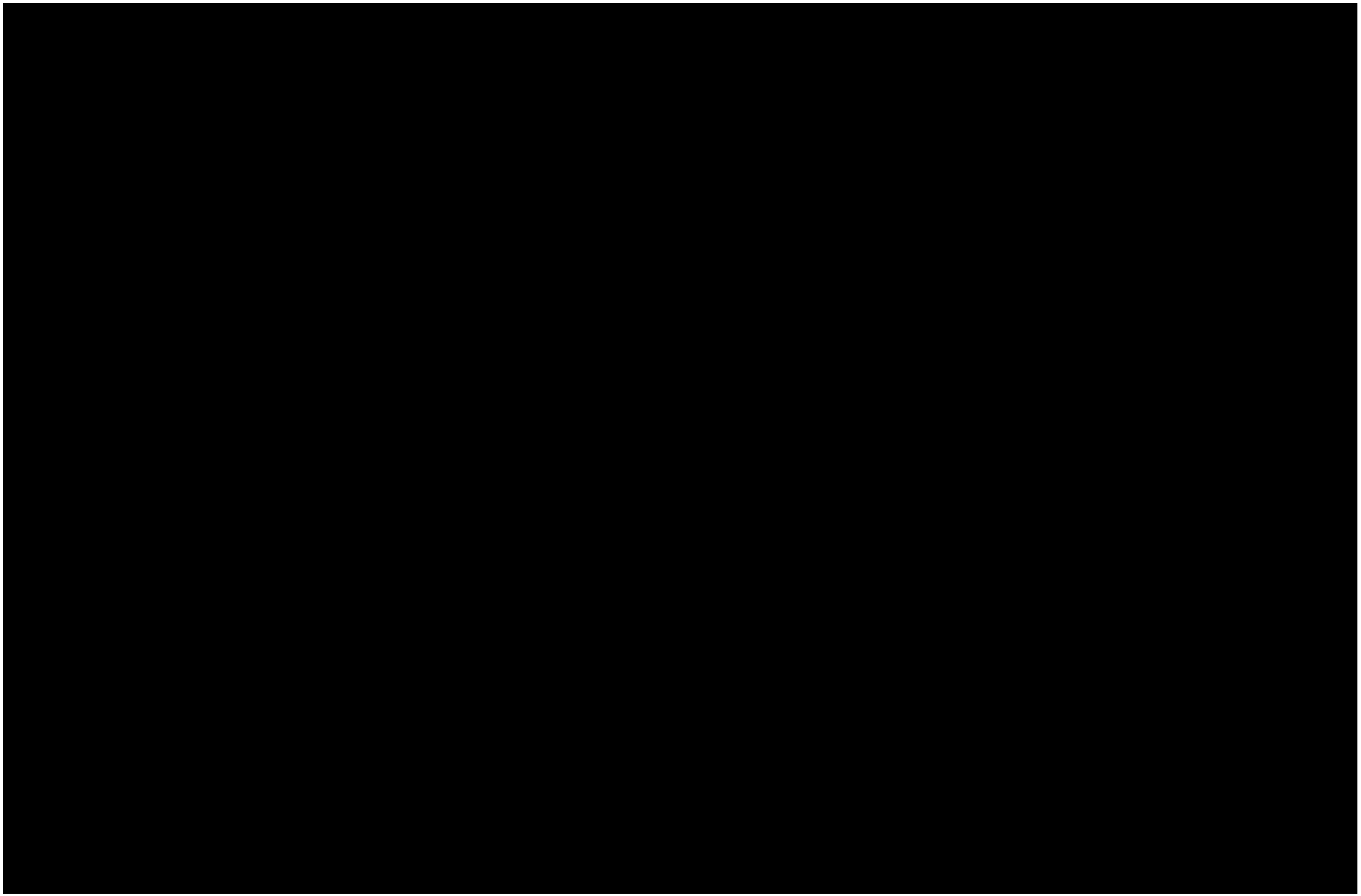
[redacted]

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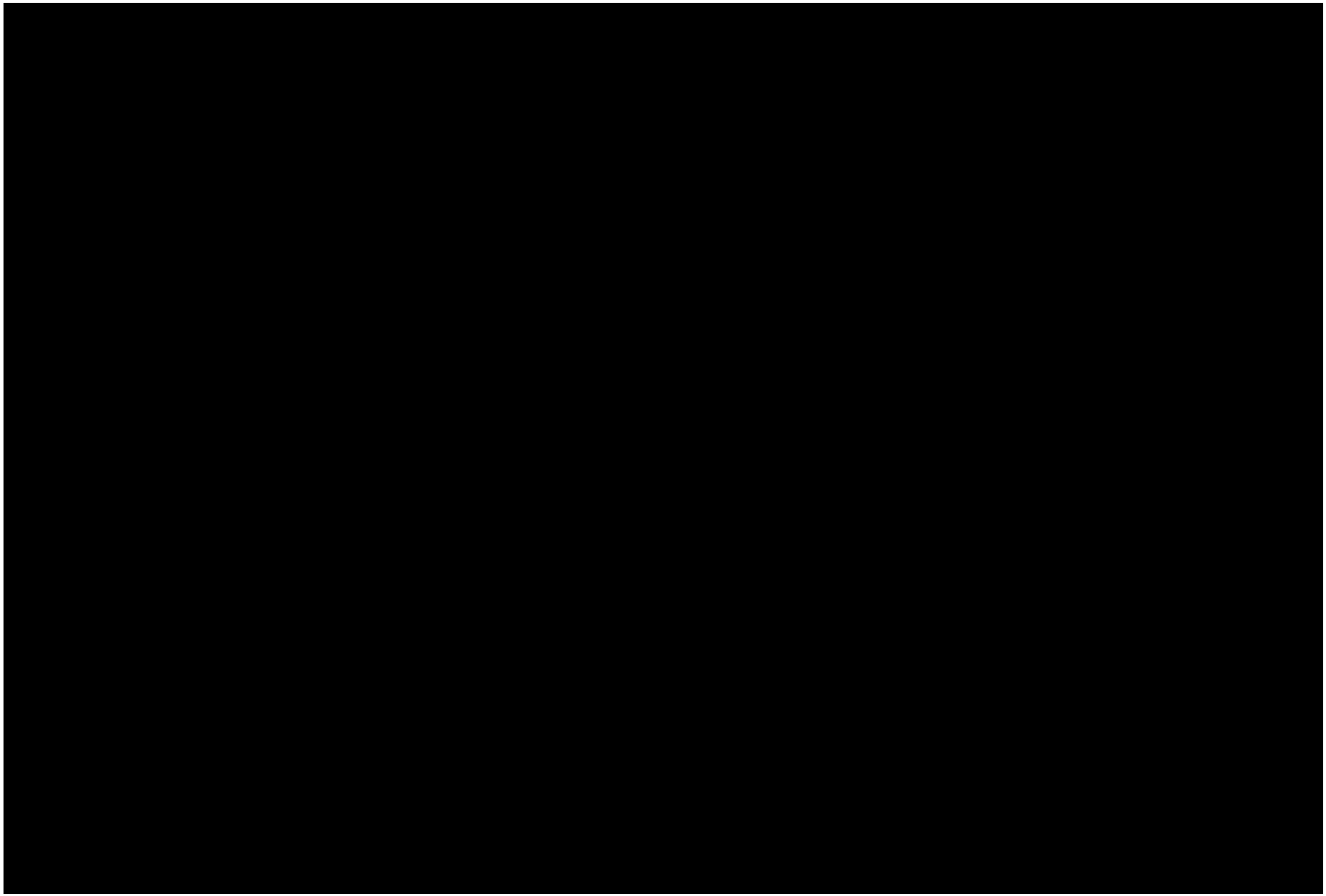
[redacted]

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Table 11-1 Reporting of adverse events and action to be taken



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12 DATA MANAGEMENT AND STATISTICAL ANALYSIS

12.1 Sample size

No formal sample size calculation was performed. This is an exploratory study with a planned recruitment of initially up to 60 in Part A and up to 96 evaluable patients in Part B with sufficient exposure to assigned treatment unless withdrawn due to liver-related AEs, increases in liver parameters, QT prolongation, SAEs related to study treatment, or lack of efficacy. The number of patients may be increased if deemed necessary to assess any emerging safety signal(s).
The statistical analysis outlined below will apply for both study Part A and Part B and will be performed for each cohort. The sample size is shared as follows:

- Part A is divided in 3 cohorts of at least 8 evaluable patients (6 in the afabicin arm and 2 in the control arm) and at most 20 evaluable patients (16 in the afabicin arm and 4 in the control arm), leading to 60 evaluable patients at most in the first stage of the study. [redacted]
  This number of patients is expected to be sufficient to detect any safety signals with afabicin treatment in patients with BJI. [redacted]

- Part B is divided in 3 cohorts of 24 evaluable patients (20 in afabicin arm and 4 in the control arm). A fourth cohort of 24 evaluable patients may be requested to switch from the lower to the higher afabicin dose, leading to up to 96 evaluable patients (Figure 6-2).
  In 80 patients, [redacted]

12.2 Data management and handling

12.2.1 Data capture, verification and validation

All data generated by the site personnel will be captured electronically at each study site using eCRFs. Corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the electronic data capture (EDC) application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query, and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the eCRF page.

The site will be trained on the specific procedures to be used for data entry and query resolution using the eCRF.

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12.2.2 Missing data handling for statistical analysis

For the secondary efficacy endpoint analyses, patients with missing data contributing to determination of the endpoint will be defined as having indeterminate status.

12.2.3 Derived parameters and endpoints

12.2.3.1 Efficacy

Not applicable.

12.2.3.2 Pharmacokinetics

Refer to Section 9.1.4.1.

12.2.3.3 Coding

Medical history, AEs, concomitant procedures, and surgeries will be coded per system organ class (SOC) and preferred term (PT) using the last available version of the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded per anatomical therapeutic chemical (ATC) class levels 2 and 4 using the last available World Health Organization Drug Dictionary (WHO-DD).

12.3 Analysis populations

Screened population: All screened patients.

Intent-to-Treat (ITT) population: All randomized patients.

Safety population: All randomized patients who received at least one dose of the study drug. This population will be used for the primary analysis.

Microbiological Intent-to-Treat (mITT) population: All randomized patients who received at least one dose of the study drug and have a positive staphylococcal only culture or PCR. This population will be used for the secondary analysis.

Per Protocol (PP) population: All mITT patients who have completed treatment without any major protocol deviations.

PK population: All patients who received at least one dose of afabicin and have a valid PK assessment.

Reporting in the ITT and mITT populations will be according to randomized treatment assignment. Reporting in the safety, PP and PK populations will be according to the actual treatment received.

12.4 Statistical analysis

12.4.1 Interim analysis

No interim analysis is planned. However, during the study the Sponsor will decide - based on the IDMC [redacted] recommendation – whether to proceed or terminate the study. The safety stopping rules are outlined in Section 6.6.

12.4.2 Final analysis

The statistical analyses planned to be performed will be described in detail in a Statistical Analysis Plan (SAP). Any deviations from the SAP, reasons for such deviations, and all alternative or additional statistical analyses that may be performed, will be clearly described as such in the final clinical study report (CSR).

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12.4.2.1 Disposition of patients, demographic and baseline data

The number and percentage of patients entering and completing the study will be presented. Reasons for withdrawal before and after initiation of afabicin treatment will also be summarized. The disposition of patients will also include information on the number and percentage of patients who:

- Complete study drug and follow-up,
- Withdraw from study drug but complete follow-up,
- Withdraw from study drug and from follow-up.

Demographic data, medical history, concomitant disease, and prior and concomitant medications will be summarized by means of descriptive statistics (number of non-missing values, mean, standard deviation, median, minimum, and maximum) or frequency tables. Demographic and baseline characteristics will be summarized for the ITT, mITT, and the PP populations.

12.4.2.2 Investigational and control medicinal products, concomitant medication and illnesses

Extent of exposure to afabicin (Debio 1450) and SoC will be summarized by descriptive statistics based on duration (IV and/or oral), number of doses, and total amount (mg).

Medical history, concomitant medications, surgeries, and medical procedures, as well as illnesses will be summarized per cohort and study drug.

12.4.2.3 Efficacy

The proportion of patients with clinical response at Day 8, Day 28, Day 42, EOT, at 4 weeks post-EOT, and at 12 weeks post-EOT will be described by summary frequencies along with 95% CI.

12.4.2.4 Safety

TEAEs and SAEs will be summarized using number and percentage of patients with at least one event by SOC, PT and grade.

Shift tables based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grading will be presented for laboratory parameters between baseline and worst case on-treatment including the follow-up period. CTCAE version 4.03 will be used to grade laboratory abnormalities. For QTc-related AEs, CTCAE version 3.0 will be used. [41,42]

12.4.2.5 Pharmacokinetics/Pharmacodynamics

Plasma concentrations of afabicin and its active moiety (Debio 1452) will be listed and summarized by time point of collection. Summary statistics in the tabulation will include n, mean, standard deviation, coefficient of variation (CV%), median, minimum, maximum, geometric mean and geometric CV%.

As applicable, PK parameters will be calculated by non-compartmental analysis and/or derived by population PK data analysis using a nonlinear mixed-effects modelling approach, and summarized by descriptive statistics as above.

The PK-PD index *f*AUC:MIC will be derived for Debio 1452 as applicable, and relationships between the MIC, PK-PD index, and observed clinical and microbiologic outcomes will be evaluated.

12.4.2.6 Microbiological outcome analysis

Microbiological outcome categories Documented Eradication, Presumed Eradication, Documented Persistence, Presumed Persistence, Recurrence, Super-infection, New Infection,

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and Unknown (as defined in Section 9.1.4.2) will be summarized by visit, including unscheduled visits (if any), on a patient level.

12.4.2.7 DDI potential with CYP endogenous biomarkers

Individual plasma concentrations of 4β-OH-cholesterol and 4β-OH-cholesterol/Cholesterol ratio will be listed by timepoint and by dosing regimen. The absolute and percentage change from baseline of 4β-OH-cholesterol and of 4β-OH-cholesterol/Cholesterol ratio will be calculated for each patient, and summary statistics will be presented by dosing regimen.

If applicable, data from other CYP endogenous biomarkers will be presented similarly.

12.4.2.8 Microbiota outcome analysis

Metagenomic and metabolomic data generated from stool samples in a subset of patients will be analyzed descriptively by visit.

13 SPONSOR AND INVESTIGATOR OBLIGATIONS

13.1 Good Clinical Practice and Declaration of Helsinki

This trial will be conducted in accordance with the protocol and in compliance with the ICH Good Clinical Practice (GCP) guidelines, the ethical principles that have their origin in the Declaration of Helsinki and its subsequent amendments, and applicable local laws and regulations. The Investigator will be responsible for the overall conduct at the study site and adherence to the requirements of the ICH guidelines and all other applicable local regulations.

13.2 Independent Ethics Committees and Institutional Review Boards

Prior to initiation of the trial at any site, the trial, including the protocol, ICF, and other trial documents must be approved by an appropriate IEC or IRB. The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites.

A letter documenting IEC/IRB approval (in which the protocol title and protocol number are specifically identified) and a list of IEC/IRB members and affiliations must be received by the Sponsor prior to initiation of the study.

Within 90 days of completion of the study (last patient, last visit) or 15 days of early termination of the study, the IEC/IRB will be informed of the end of the study by the Investigator, Sponsor or designee.

Every serious or unexpected AE that might affect patient safety must be brought to the IEC's or IRB’s attention by the Investigator if required by relevant IEC/IRB regulations.

13.3 Informed consent

The Investigator or designee must ensure that signed ICF in accordance with the Declaration of Helsinki, local laws, and all applicable regulatory requirements, is obtained from each potential patient prior to any study related procedure. The informed consent process must be documented.

Each patient will be given oral and written information in an easily understandable language describing the nature and duration of the study. The ICF will clearly state and inform the patients that there is a possibility that afabicin may not improve their condition and there are other options available to treat their infection. The potential side effects and risks, monitoring requirements will also be highlighted. The Consent process must take place under conditions where the patient has adequate time to consider the risks associated with study participation.

Two originals of the ICF must be signed by the patient (and/or legal authorized representative [guardian, next of kin, or other authorized individual] if applicable) and the Investigator or designee.

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One signed original will be given to the patient and one will be kept in the Investigator file at the study site.

*Exceptions to the above occur, when, for instance, a patient is not able to give consent (e.g., stroke trials, emergency indication). In such cases, the informed consent procedure must be described in detail, including the possibility to obtain delayed consent or consent from a relative or legal guardian. Applicable regulations must be strictly enforced and referred to.

13.4 Patient confidentiality

The Investigator will ensure that patient reports and samples are identified only by an identifier to maintain patient confidentiality. All patient study records will be kept safely in an access controlled area. Identification code lists linking the patient names to identifiers should preferably be stored separately from patient records. Clinical information will not be released without written permission from the patient, except for monitoring by Regulatory Authorities or the study Sponsor.

13.5 Data reporting and electronic Case Report Forms

The Investigator and/or designee will accurately, completely, and in a timely manner enter data resulting from execution of the protocol into eCRFs made available by the Sponsor via an EDC system, i.e., a web-based computerized system designed for the collection of clinical data in electronic format. One eCRF will be completed for each patient and must be electronically signed and dated by the Principal Investigator or the Co-investigator responsible for patient care during the study. Corrections in eCRFs will be recorded in an audit trail. The data will be extracted from the eCRF database after final database lock. At the end of the study, each site will be given a CD-disk with all study data entered in the eCRF plus external data.

13.6 Retention of data

The Investigator will maintain adequate study records including the CD-disk with electronically collected study data, medical records, laboratory reports, ICFs, drug disposition records, safety reports, information regarding participants who discontinued and other pertinent data, such as letters and administrative documents exchanged between the Sponsor and the center. Records can be in paper or electronic format.

All study records must be retained by the Investigator for the maximum period of time authorized by the hospital, institution or clinic but in no case for less than **15 years** after study completion.

To avoid any possible errors, the Investigator must contact the Sponsor prior to the destruction of any study records or if leaving the institution where the study was conducted. The Investigator will notify the Sponsor in the event of accidental loss or destruction of any study records.

13.7 Deviations from the protocol/protocol amendments

The Investigator will not deviate from the protocol without prior written approval from the Sponsor. In case of medical emergencies, the Investigator will use medical judgment and will remove the participant from immediate hazard. The Sponsor and the IEC or IRB will be notified of the type of emergency and course of action taken. Permanent changes to or deviations from the protocol will be formalized in an amendment to the protocol.

The amendment must be approved by the Sponsor and, if substantial as defined in directive 2001/20/EC or other local applicable regulations, submitted for approval to the Health Authorities and IEC/IRB prior to being implemented. If the change implies a modification of treatment or of patient evaluation tests, a new version of the ICF must be prepared and submitted for approval to Health Authorities and the IEC/IRB. The Sponsor will assume any responsibility or liability resulting from a change in the protocol, only if the change has been approved in writing by himself, the Health Authorities, and the IEC/IRB.

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13.8 Investigational Medicinal Product accountability

The Investigator must maintain accurate records of the IMP received from the Sponsor. These records will include receipt and dispensing dates, and dates of return and/or destruction of unused supplies.

At trial termination, clinical supplies must be accounted for and a written clarification provided in case of discrepancies. All unused supplies must be properly destroyed at the study site or returned promptly to the Sponsor; written authorization from the Sponsor must be obtained prior to destruction which must be documented.

When the above tasks are delegated to a Pharmacist, the Investigator remains ultimately responsible for the maintenance of accurate drug dispensing records.

13.9 Study monitoring

At agreed upon times during the study and after the study has been completed, the Investigator will let Sponsor representatives periodically review the eCRF and corresponding office, hospital, and laboratory records (source documents) of each study patient. The eCRFs must be completed by the Investigator on a regular basis and prior to each monitoring visit.

Monitoring visits allow the Sponsor or a mandated CRO to evaluate study progress, verify accuracy and completeness of eCRFs, resolve any inconsistencies in the trial records, and ensure that all protocol requirements, applicable local laws, ICH guidelines, and Investigator obligations are fulfilled.

13.10 Sponsor audits

During the study or after the study has been completed, the Investigator will allow Sponsor representatives or external auditors to conduct an audit of the study. The purpose of the audit is to evaluate compliance with GCP guidelines, applicable regulations, the study protocol and the Sponsor's procedures, and to assess accuracy of the study data.

Before the audit, the Investigator will be contacted by the monitor to arrange a convenient time for the visit. Investigator and staff are expected to be present, co-operate with the auditors, and allow access to all patient records supporting the eCRFs, and other study-related documents.

13.11 Regulatory agency inspections

The Investigator may undergo a Regulatory Agency/IEC/IRB inspection during the study or after the study has been completed. The purpose of such an inspection is to conduct an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial.

The Investigator and staff are expected to be available for the inspection and allow access to patient records supporting the eCRFs and other study-related documents. If given advance notice of this inspection, the Investigator must contact the Sponsor immediately.

13.12 Publications

A scientific communication/paper related to this study can be published only if a written agreement to this intent has been reached between the Sponsor and the Investigator and after review of the final draft by the Sponsor.

13.13 Insurance policy

The Sponsor will subscribe a liability insurance covering his and the Investigator's responsibility as well as the responsibility of any person involved in the conduct of the study, provided there is proper adherence to the protocol. An insurance certificate will be provided by the Sponsor to the IEC if required.

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13.14 Premature study termination

The trial may be prematurely terminated by the Sponsor, the Investigator, or the IEC/IRB at any time. If the study is prematurely terminated, the Investigator must promptly inform the study patients and ensure that they receive appropriate therapy and follow-up. All procedures and requirements pertaining to study closure as defined by the Sponsor will be carried out.

If the Investigator terminates the trial, s/he should promptly inform the Sponsor and the IEC/IRB and provide a detailed written explanation of the termination. If the Sponsor terminates the trial, the Investigator should promptly inform the IEC/IRB and provide a detailed written explanation of the termination. If the IEC/IRB terminates the trial or suspends its approval, the Investigator should promptly inform the Sponsor and provide a detailed written explanation of the termination.

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14 SCHEDULE OF ASSESSMENTS

Table 14-1 Schedule of assessments for patients with septic arthritis, osteomyelitis or PJI

Part A:

				TREATMENT (UP TO 12 WEEKS)				FOLLOW-UP		
Visit		Investigator site	Investigator site	*Hospital or home visits*	Investigator site	*Hospital or home visits*	Investigator site	*Hospital or home visit*	Investigator site	
Notes		*Screening (≤ 7 days)*	*Start of treatment*	*Every 3 to 4 days[a]*		*Every 3 to 4 days*	*Within 24 hrs of last dose*			
Day/Week (D/Wk)		D -7 to D -1	D 1 morning	Until D 28 visit	D 8[b], D 28	*Until EOT*	D 42[b], EOT[c]	*2-wks post-EOT*	*4 wks post-EOT*	*12 wks post-EOT*
Visit windows				*Interval between visits: >2 d & <5d*	±1 d	*Interval between visits: >2 d & <5d*	+1d	±1d	±5 d	±7 d
BASELINE	ICF reviewed and signed	X								
	Demographics, disease characteristics, medical history, prior medications	X								
	Inclusion/exclusion criteria	X								
	Randomization	on D -1								
Treatment	Study drug dispensing and administration		*IV for max 2 weeks, followed by switch to oral at Investigator's discretion*							
	Patient Diary *(provided at IV to oral switch)*			*During oral treatment only*						
SAFETY	Adverse event monitoring	X	X	X	X	X	X	X	X	X
	Laboratory assessment (full panel)	X	X		X		X		X	X
	Laboratory assessment (safety panel)[d]			X		X		X		
	[redacted]									
	12-ECG *(in triplicate)*[e]	X	X	X	X	X	X	*If abnormal at EOT*	*If abnormal at EOT*	
	Physical examination	X	X		X		X		X	X
	Vital signs[f]	X	X		X		X		X	X
E	Concomitant medications	X	X	X	X	X	X	X	X	X

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				TREATMENT (UP TO 12 WEEKS)				FOLLOW-UP		
Visit		Investigator site	Investigator site	*Hospital or home visits*	Investigator site	*Hospital or home visits*	Investigator site	*Hospital or home visit*	Investigator site	
Notes		*Screening (≤ 7 days)*	*Start of treatment*	*Every 3 to 4 days[a]*		*Every 3 to 4 days*	*Within 24 hrs of last dose*			
Day/Week (D/Wk)		D -7 to D -1	D 1 morning	Until D 28 visit	D 8[b], D 28	*Until EOT*	D 42[b], EOT[c]	*2-wks post-EOT*	*4 wks post-EOT*	*12 wks post-EOT*
Visit windows				*Interval between visits: >2 d & <5d*	±1 d	*Interval between visits: >2 d & <5d*	+1d	±1d	±5 d	±7 d
	Clinical signs and symptoms of infection[g]	X	X		X		X		X	X
	Imaging *(at Investigator's discretion)*	X			X		X		X	X
	Microbiological assessment[h]	X	*Whenever a sample is available[h]; biopsies/synovial fluid aspirations are not mandated*							
Exploratory	Plasma PK collection[i]		X		X		X			
Exploratory	Plasma biomarker samples for afabicin patients[j]		X	X						
Exploratory	Blood sample for pharmacogenomic analysis for afabicin patients				*At D 8 visit (or later)*					
Exploratory	Blood sample for MetaHeps analysis for afabicin patients			*Only upon Sponsor request*						

Abbreviations: d,D = days; ECG = electrocardiogram; EOT = end of treatment; ICF = informed consent form; IV = intravenous; PK = pharmacokinetics; wks = weeks

a: Every 3 or 4 days unless there is a scheduled Investigator site visit.

b: No PK sampling on Day 8 and Day 42 (unless EOT falls on Day 42 or in case of safety events, see Section 6.4.1).

c: For patients with septic arthritis, EOT is expected between Day 22 and Day 29 (i.e., 3-4 weeks of treatment); if EOT occurs prior to Day 28 visit, the patient should attend the EOT visit in fasted state (from 4 hours before to 4 hours after drug intake) and take the last dose of study drug at the Investigator's site in order to allow for the final PK sample collection. For patients with osteomyelitis or PJI, EOT is expected between Day 43 and Day 85 (i.e., after 6-12 weeks of study treatment). The EOT visit should be scheduled within 24 hours (±4 hours) of the last dose.

d: Blood samples drawn [redacted] for a safety panel unless there is a scheduled visit where a full panel (which includes a safety panel) is performed.

e: On Day 1: pre-dose and just before PK sampling at 15 minutes (±5 minutes) and 5.5 hours (±0.5 hour) after the end of the first IV infusion.
ECG will be performed on Day 2 and Day 3 within 3 hours of study drug infusion. ECG should be performed on a daily basis while the patient is hospitalized; otherwise every 3-4 days while on study treatment.
At Day 28 visit (or at EOT if the treatment < 28 days): pre-dose and just before PK sampling at 5.5 hours (±0.5 hour) after the morning oral intake. ECGs will be performed at follow-up visits only if the ECG tracing indicates abnormalities at EOT.

f: On Day 1, vital signs will be checked prior to first dose administration, at the time of completion of the first dose, and 1 hour after the administration of the first dose was completed. Vital signs will be checked on Day 2 and Day 3 within 3 hours of study drug infusion.

g: Clinical symptoms include pain (at rest or during weight-bearing), restricted movement, fever, extremity weakness/numbness, weight loss, fatigue. Clinical signs include localized warmth and tenderness, swelling (effusion), erythema, draining sinuses, and restricted active/passive movement, bone/joint instability.

h: Debridement, needle aspiration arthroscopic lavage, synovial fluid examination or bone biopsy. These samples may also be retained to determine Debio 1452 concentration. Blood samples at screening are mandatory. Blood sampling for microbiological assessment may be repeated whenever indicated by the Investigator.

i: For all patients sparse PK sampling: (1) on Day 1, at 15 minutes (±5 minutes), 3.5 hours (±0.5 hour) and 5.5 hours (±0.5 hour) after the end of the first IV infusion; the infusion will be administered on one arm, blood for PK will be collected from the other arm; the exact date/time of infusion start, infusion end and PK sample collection will be recorded; and (2) at Day 28 visit (or at EOT if the treatment < 28 days): at pre-morning dose; then at 5.5 hours (±0.5 hour) after morning oral intake. On that morning, Debio 1450 will be administered in fasted conditions (from 4

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hours before to 4 hours after drug intake); the exact date/time of PK sample collection will be recorded. For a subset of patients, intense PK sampling may be performed according to the time points listed in Section 9.2.7.1. An additional blood sample may be collected during the study period in case of safety events see Section 6.4.1.

j: Only in afabicin-treated patients, a blood sample will be collected at baseline pre-dose to allow analyses of biomarkers such as [redacted] In case of any emergent safety event, a post-baseline sample will also be collected and both the baseline and post-baseline samples will be analyzed.

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Part B:

				TREATMENT (UP TO 12 WEEKS)				FOLLOW-UP								
Visit		Investigator site	Investigator site	*Hospital or home visits*	Investigator site	*Hospital or home visits*	Investigator site	Hospital or home visit	Investigator site	*Hospital or home visit*			Investigator site	*Hospital or home visit*		Investigator site
Notes		*Screening (≤ 10 d)*	*Start of treatment*	*D3 or D4*		*Weekly*		Weekly	*Within 24 hrs of last dose*							
Day/Week (D/Wk)		D-10 to D-1	D1 morning	Until D8 visit	D8[a]	*From D8 until D28*	D28	Until EOT	D42[a,b], EOT[b]	*1-wk post-EOT*	*2-wks post-EOT*	*3-wks post-EOT*	*4-wks post-EOT*	*5-wks post-EOT*	*6-wks post-EOT*	*12 wks post-EOT (EOS visit)l*
Visit windows				*From ≥2 d to ≤6 d*	±1 d	*Weekly ± 1d*	±1 d	Weekly ± 1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±7 d
BASELINE	ICF reviewed and signed	X														
	Demographics, disease characteristics, medical history, prior medications	X														
	Inclusion/exclusion criteria	X														
	Randomization[k]	on D-1														
Treatment	Study drug dispensing and administration		*IV for max 2 weeks, followed by switch to oral at Investigator's discretion*													
	Patient Diary *(provided at IV to oral switch)*			*During oral treatment only*												
SAFETY	Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Laboratory assessment (full panel)	X	X		X		X		X				X			X
	Laboratory assessment (safety panel)[c]			X		X		X		X	X	X		X	X	
	[redacted]															
	12-ECG *(in triplicate)*[d]	X	X				X		X[d]							
	Physical examination	X	X		X		X		X				X			X
	Vital signs[e]	X	X		X		X		X				X			X
	Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Assessment of pain	*Daily during the treatment period*								X	X	X	X	X	X	X
EFFICACY	Clinical signs and symptoms of infection[f]	X	X		X		X		X				X			X
	Imaging[j]	X														X
	Microbiological assessment[g]	X	*Whenever clinically indicated*[g]													

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			TREATMENT (UP TO 12 WEEKS)				FOLLOW-UP								
Visit	Investigator site	Investigator site	*Hospital or home visits*	Investigator site	*Hospital or home visits*	Investigator site	Hospital or home visit	Investigator site	*Hospital or home visit*			Investigator site	*Hospital or home visit*		Investigator site
Notes	*Screening (≤ 10 d)*	*Start of treatment*	*D3 or D4*		*Weekly*		Weekly	*Within 24 hrs of last dose*							
Day/Week (D/Wk)	D-10 to D-1	D1 morning	Until D8 visit	D8[a]	*From D8 until D28*	D28	Until EOT	D42[a,b], EOT[b]	*1-wk post-EOT*	*2-wks post-EOT*	*3-wks post-EOT*	*4-wks post-EOT*	*5-wks post-EOT*	*6-wks post-EOT*	*12 wks post-EOT (EOS visit)l*
Visit windows			*From ≥2 d to ≤6 d*	±1 d	*Weekly ± 1d*	±1 d	Weekly ± 1 d	±1 d	±2 d	±2 d	±2 d	±2 d	±2 d	±2 d	±7 d
Exploratory: Plasma PK collection[h]		X				X		(X [m])							
Exploratory: Blood/Plasma biomarker samples for afabicin patients[i]		X			X										
Exploratory: Blood sample for pharmacogenomic analysis for afabicin patients				*At D8 visit (or later)*											
Exploratory: Stool samples for metagenomic analysis and metabolite quantification[n]		X						X				X			

Abbreviations: d, D = days; ECG = electrocardiogram; EOT = end of treatment; hr(s) = hour(s), ICF = informed consent form; IV = intravenous; PK = pharmacokinetics; wks = weeks

a: No PK sampling on Day 8 and Day 42 (unless in case of safety events, see Section 6.4.1).
b: For patients with septic arthritis, EOT is expected between Day 22 and Day 29 (i.e., 3-4 weeks of treatment); if EOT occurs prior to Day 28 visit, the patient should attend the EOT visit in fasted state (from 4 hours before to 4 hours after drug intake) and take the last dose of study drug at the Investigator's site in order to allow for the final PK sample collection. For patients with osteomyelitis or PJI, EOT is expected between Day 43 and Day 85 (i.e., after 6-12 weeks of study treatment). The EOT visit should be scheduled within 24 hours (±4 hours) of the last dose.
c: Blood samples drawn on Day 3 or Day 4, and weekly thereafter (starting at Day 8) for a safety panel unless there is a scheduled visit where a full panel (which includes a safety panel) is performed.
d: On Day 1: pre-dose and just before PK sampling and 3.5 hours (±0.5 hour) after the end of the first IV infusion.
At Day 28 visit (or at EOT if the treatment is shorter than 28 days): pre-dose and just before PK sampling at 5.5 hours (±0.5 hour) after the morning oral intake. All ECGs tracings will be read locally at study site.
e: On Day 1, vital signs will be checked prior to first dose administration, at the time of completion of the first dose, and 1 hour after the administration of the first dose was completed. Vital signs will be checked on Day 2 and Day 3 within 3 hours of study drug infusion.
f: Clinical symptoms include pain (at rest or during weight-bearing), localized warmth, restricted active/ passive movement, lymphadenopathy, extremity weakness/ numbness, tenderness, erythema, swelling, draining sinuses, bone/ joint instability. Clinical signs include fever, irritability, nausea, fatigue, weight loss.
g: Debridement, needle aspiration arthroscopic lavage, synovial fluid examination or bone biopsy. These samples may also be retained to determine Debio 1452 concentration. Blood samples at screening are mandatory. Blood sampling for microbiological assessment may be repeated whenever indicated by the Investigator.
h: PK sampling: (1) on Day 1, at the end of the first IV infusion (30 min to 10 min before the end of the infusion), at 15 minutes (±5 minutes), 1 hour (±10 minutes), 3.5 hours (±0.5 hour), 5.5 hours (±0.5 hour), 8 hours (±0.5 hour), and 10 hours (±0.5 hour) (i.e., just before the second dose) after the end of the first IV infusion; only patients for whom a second venous access can be obtained to insert a catheter line for PK sampling will be included. The line used for drug infusion should not be used for PK sampling. The infusion will be administered on one arm, blood for PK will be collected from the other arm; the exact date/time of infusion start, infusion end, infusion arm and collection arm, and PK sample collection will be recorded; and (2) on Day 28 visit (or at EOT if the treatment < 28 days): at pre-morning dose; then at 1 hour (±10 minutes), 2.5 hours (±0.5 hour), 4.5 hours (±0.5 hour), 5.5 hours (±0.5 hour), 8.5 hours (±0.5 hour), and 10.5 hours (±1 hour)

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after morning oral intake. On that morning, afabicin will be administered in fasted conditions (from 4 hours before to 4 hours after drug intake); in case fasting is not possible for the patient, the time and type of the meal (i.e., high-fat vs low-fat) should be recorded; the exact date/time of PK sample collection will be recorded. An additional blood sample may be collected during the study period in case of safety events see Section 6.4.1.

i: Only in afabicin-treated patients, a blood sample will be collected at baseline pre-dose to allow analyses of biomarkers such as [redacted]. In case of any emergent safety event, a post-baseline sample will also be collected, and both the baseline and post-baseline samples will be analyzed.

j: Additional imaging assessment can be performed at the discretion of the Investigator.

k: [redacted]

l: In case of treatment failure (e.g., lack of efficacy or discontinuation due to AE), the EOS visit will be performed within one week post-EOT (i.e., 7 days, ±2 days).

m: In case Day 28 PK was collected, blood sampling for PK is not needed. However, if EOT takes place before Day 28, PK sampling should be collected as described above (see h).

n: Subjects will be provided with non-invasive stool collection kits and instructions prior to first sampling. Stool samples will be collected either onsite or at home at baseline, EOT, 4 weeks post-EOT. Stool samples are to be collected within 24 hours of the appropriate visit and stored at ambient temperatures prior to delivery to the clinical unit.

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16 APPENDICES

16.1 IDSA guidelines on treatment of MSSA/MRSA

IDSA Guidelines		Agent	Toxicity			Formulation [IV/ Oral]	Dosage/ Schedule	Relevant licensed indications	Restrictions
			Hepatic	Cardio	Specific				
Septic arthritis (SA) (IDSA 2011)[1] [Duration 3-6 weeks]	MSSA	**N/A**	---	---	---	---	---		---
	MRSA	**Vancomycin**	---	---	Nephrotoxicity, ototoxicity, thrombocytopenia, red man syndrome	IV	15mg/kg of body weight q12h	Serious or severe MRSA infections, penicillin-allergic pts, pts who have failed to respond to other drugs including penicillins and cephalosporins. Effectiveness documented in other staph infections, including septicemia, bone/ skin and structure infections	Contraindicated in known hypersensitivity to vancomycin and pts with underlying renal impairment. should be restricted to patients with type I or documented delayed allergy to β-lactams
		Daptomycin	---	---	Rhabdomyolysis, eosinophilic pneumonia	IV	6mg/kg/ dose q24h	Complicated skin and structure infections (cSSSI), *S. aureus* bacteremia	Decreased efficacy in pts with moderate baseline renal impairment. Not recommended as initial therapy for gram-positive infections/ vancomycin-resistance enterococci (VRE) wound infections
		Linezolid	---	---	Thrombocytopenia, anemia, optic neuropathy, peripheral neuropathy	IV or PO	600mg q12h	Infections caused by gram-positive bacteria: cSSSIs including diabetic foot infections	Contraindicated in known hypersensitivity to linezolid, not to be administered for >28 days, monitor blood counts weekly and consider discontinuation in pts who develop or have worsening myelosuppression

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IDSA Guidelines		Agent	Toxicity			Formulation [IV/ Oral]	Dosage/ Schedule	Relevant licensed indications	Restrictions
			Hepatic	Cardio	Specific				
		Clindamycin	IDSA 2004 OPAT[2]: 0% hepatic AEs (2-year registry)	---	Diarrhea, nausea, vomiting, anorexia, rash	IV or PO	600mg q8h	Serious infections caused by susceptible anaerobic bacteria, streptococci, pneumococci and staphylococci (respiratory tract, serious SSSIs)	*Clostridium difficile*/ severe colitis. Consider nature of infection and suitability of less toxic alternatives (e.g., erythromycin). Contraindicated in pts with hypersensitivity to clindamycin
Osteomyelitis (IDSA 2015)[3] [Duration 4-12 weeks]	MSSA	*Preferred:*							
		Nafcillin (flucloxacillin may be used in EU) or **oxacillin**	Elevation of liver transaminases/ cholestasis at higher doses	---	Local reactions/ neurotoxic reactions similar to penicillin G	IV	1.5g q4-6h or continuous infusion	Susceptible penicillinase-producing staphylococci.	Contraindicated in any penicillin hypersensitivity/ pts with concomitant hepatic insufficiency and renal dysfunction. Not to be used in infections susceptible to penicillin G or when MRSA identified
		Cefazolin	---	---	Phlebitis, rash, fever, eosinophilia	IV	1-2g q8h	Preoperative prophylaxis	Caution of use in pts with renal impairment (as drug mainly eliminated via renal mechanisms). Use only in pts whose creatinine clearance is greater than or equal to 35 mL/min, who require entire dose and not in any fraction of it.
		Ceftriaxone	Cases of moderate to severe hepatic abnormalities	---	Pseudocholelithiasis, phlebitis, rash, fever	IV	2g q24h	SSSIs, bone and joint infections caused by *S. aureus* and other bacteria, surgical prophylaxis	Contraindicated in pts with known hypersensitivity to cephalosporins, pts with impaired vitamin K synthesis or low vitamin K stores (hepatic disease and malnutrition) may require monitoring of prothrombin time)
		Alternative:							
		Vancomycin/ daptomycin/ linezolid/ clindamycin							
	MRSA	*Preferred:*							

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IDSA Guidelines		Agent	Toxicity			Formulation [IV/ Oral]	Dosage/ Schedule	Relevant licensed indications	Restrictions
			Hepatic	Cardio	Specific				
		Vancomycin							
		Alternative:							
		Daptomycin/ linezolid							
Resection arthroplasty (IDSA 2013)[4] [Duration 4-6 weeks]	MSSA	*Preferred:*							
		Nafcillin/ cefazolin/ ceftriaxone (no consensus on use of ceftriaxone)							
		Alternative:							
		Vancomycin/ daptomycin/ linezolid							
	MRSA	*Preferred:*							
		Vancomycin							
		Alternative:							
		Daptomycin/ linezolid							

OPAT = Outpatient Parenteral Antimicrobial Therapy; Pts = patients; SSSI = skin and skin structure infection

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16.2 SOFA score calculation

Sequential [Sepsis-Related] Organ Failure Assessment Score

	Score				
System	**0**	**1**	**2**	**3**	**4**
Respiration					
PaO_2/FIO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, x $10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular					
	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[a]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[a]
Central nervous system					
Glasgow Coma Scale score[b]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (µmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: FIO_2 = fraction of inspired oxygen; MAP = mean arterial pressure; PaO_2 = partial pressure of oxygen
a: Catecholoamine doses are provided in µg/kg/min for at least 1 hour.
b: Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Reproduced from:

Singer et al, The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 2016. 315(8): p. 801-10.

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16.3 [redacted]

[redacted]

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16.4 Assessment of pain

The Pain Intensity Numerical Rating Scale (PI-NRS) is an 11-point scale for self-report of pain [40]. It is the most commonly used unidimensional pain scale. The patient will select a whole number (integers 0–10) that best reflects the intensity of the patient's pain. The anchors are 0 = no pain and 10 = extreme pain/worst possible pain. The patient will be asked to make three pain ratings, corresponding to current, least and worst pain experienced over the past 24 hours. The average of the 3 ratings will represent the patient's level of pain over the previous 24 hours.

The following reduction would be considered clinically significant on the PI-NRS scale: i) at least two scale points between two time-points of an assessment, ii) reduction to at least 3 at EOT.

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16.5 Examples of prohibited drugs in the study, with their minimum wash out period.

If a prohibited medication is present at screening, it can be temporarily stopped or replaced by another permitted medication, provided this will not put the patient at increased risk, as per Investigator's judgment. Examples of minimum wash-out period required for potential common concomitant medications are presented in the table below. Please note that this is not an exhaustive list. For other prohibited drugs, the label should be consulted to inform about the half-life to define the washout period. Potential permitted alternatives for pain management and acid reducing agents are described in Section 8.7.3.4.

	Therapeutic class	Prohibited Drug	Minimum wash out (days)
CYP 3A inducers	Central Nervous System	Carbamazepine	14
		Phenytoin	14
CYP 3A4 inhibitors	Calcium Channel Blockers	Amlodipine	11
	Antifungal	Ketoconazole	3
	Antiviral	Ritonavir	2
[redacted]			

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