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

NCT ID: NCT03723551

Document Version and Date: Version 4.0 and 26 September 2025

Debiopharm International S.A.

STATISTICAL ANALYSIS PLAN

PROTOCOL *Debio 1450-BJI-205*

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*

Protocol Code:	Debio 1450-BJI-205
SAP Version:	Final v4.0
SAP Date:	26-SEP-2025
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DOCUMENT HISTORY

VERSION HISTORY

Version #	Version Date
1	05-DEC-2019
2	18-OCT-2021
3	26-MAR-2025
4	26-SEP-2025

REVISION HISTORY

Version #	Chapter	Revision Summary	Reason(s) for Revision
2	NA	SAP author and reviewers were updated	To reflect updates in the study team
	NA	'Subjects' are changed to 'patients' throughout	To be consistent with other study documents
	NA	Editorial and clarification updates throughout the document	To make planned analysis description clearer and unambiguous
	1	List of abbreviations updated	To reflect updates to SAP text
	2	Study protocol and CRF version updated	To reflect latest study documents
	4.1, 4.2.1 4.2.3 5, 6	Part A and Part B descriptions are added	To reflect changes to the study design in the protocol
	4.3	Part A and Part B descriptions are added as well as futility analysis	To reflect changes to the study design in the protocol
	4.4	Section added	To provide more details on safety monitoring of the data performed by sponsor
	7.3.4	Section added	To be consistent with protocol
	9	Clarification about inclusion of patients who are replaced to mITT and Safety populations	To clarify protocol language defining the populations
	10.1 10.5	Clarification how data from Part A and Part B will be presented	To reflect changes to the study design in the protocol
	10.2	Treatment groups and cohorts according to which data will be presented in the tables are updated	To make content clearer and unambiguous

	10.4.3. 10.8.1	Updates to definition of clinical responder and non-responder are made	To comply with protocol section 9
	10.7.5	Graphical presentation of micro-data added	To better present the results
	10.8.1	Summaries of patients enrolled before and after mid-cohort review was removed Additional tables for clinical response were added	To reflect changes to the study design in the protocol To provide more information on resistance profile of afabicin
	10.10.1	PK section was added	To have all analysis specified in one place as per sponsor request
3	NA	SAP author and reviewers were updated	To reflect updates in the study team
	1	List of abbreviations updated	To reflect updates to SAP text
	2	Study protocol and CRF version updated	To reflect latest study documents
	3.3	Exploratory objectives updated	To comply with protocol 7.0 (amendment 4.0) section 5.3.
	4.2.3	Definition of switch of treatment removed from the SAP	Analysis of switchers deemed not necessary by Sponsor.
	7.3.1	Section updated	To clarify that analyses will be performed by external provider.
	7.3.2	Definitions of specific microbiological outcomes added.	For clarity.
	7.3.3	Section updated by adding new endpoint. Section updated by removing “and were treated with afabicin for at least 7 days” from the 1st point.	To comply with protocol 7.0 (amendment 4.0) section 9.1.1.4. To comply with protocol.
	7.3.4, 5	New section added	To comply with protocol.
	10	Requirement to flag re-screened patients in listing added. Method for identifying re-screened patients described.	Sponsor request.
	10.2	Explanation for switchers have been removed.	Analysis of switchers deemed not necessary by Sponsor.
	10.3	Definition of baseline clarified.	For clarity.

		For electrocardiogram (ECG) data, assessment performed on Day 1 pre-dose will be considered baseline. Method for deriving visits for pain assessment added.	Sponsor request. Analysis for pain assessment added as per Sponsor request.
	10.4.3, 10.8.1	Clinical response imputation rules updated to: If a patient is a non-responder at EOT or at a later visit, he/she will be considered a non-responder for all subsequent visits. If a patient is a non-responder at any visit before EOT with the reason for non-response on eCRF form "Requirement of subsequent antibiotics with activity against Staphylococcus to treat the initial infection after the start of the study treatment to assign non-response" at certain visit, he/she will be considered a non-responder for all later visits.	To avoid considering a patient a responder due to another treatment.
	10.5	Summary for reasons for screen failure split by cohort for Phase 2 with rationale added. Tables split by before and after mid-cohort review removed. Requirement for listing for all screen failed patients with inclusion/exclusion criteria (not) met, the primary diagnosis and type added. Summary for number of patients in [redacted] population added. Information that patient disposition summaries will include overall (total) column as well added.	Sponsor request. For clarity and consistency with shells.
	10.7.1	Tables split by before and after mid-cohort review removed. Summary in the ITT and PP populations removed.	Sponsor request.
	10.7.2	Summary of medical history in the ITT, mITT and PP populations removed. Summary of disease characteristics in the ITT and PP populations removed.	Sponsor request.
	10.7.3	Empiric treatment definition added.	Sponsor request.

		Summaries of prior and concomitant medications in the ITT, mITT, PK and PP populations removed. Information that summaries will by tabulated by cohort added.	 For clarity and consistency with shells.
	10.7.5	Summaries for baseline microbiological assessments in the PP population removed.	Sponsor request.
	10.7.6	Exposure to treatment moved to Patient Characteristics	Sponsor request.
	10.8	Efficacy analyses in the ITT population removed. Clinical response will be evaluated in the PP population only. Information that summaries will by tabulated by cohort and treatment group (no overall) added.	Sponsor request. For clarity and consistency with shells.
	10.8.1	Sensitivity analyses removed: summary of clinical response will be provided on the overall population for patients randomized (i.e., excluding additional patients due to early withdrawal, see Section 5) and on the overall population excluding patients having experienced an early withdrawal who are eligible for replacement (see Section 5).	Sponsor request.
	10.8.2	Analysis of whole genome sequencing data added.	To account for new data collected.
	10.8.3	Frequency table and figure with the number of clinical signs and symptoms per patient per visit in the mITT population added. Descriptive statistics for pain assessment per visit in the mITT population, Part B only added/ Frequency table in the mITT population for Part B only, with clinically significant reduction as per The Pain Intensity Numerical Rating Scale added. Figure with average pain score per visit in the mITT population, part B only added.	Sponsor request. To account for new data collected.

		Clarification on how imaging results will be analyzed added: "Ultrasound imaging results will be summarized at baseline only. MRI/CT/X-ray imaging results will be summarized altogether per visit. In case there are more than one baseline imaging result obtained on the same date, X-ray will be selected."	
	10.9	Sentence "Adverse events will be tabulated by cohort, treatment group and overall. Remaining safety endpoints and analyses will be tabulated by cohort and treatment group." added.	To clarify which summaries should include total column.
	10.9.1	Sentence added: "AEs having onset time missing and onset date is same as the first study drug administration date will be considered as TEAEs" Clarification that AESIs are defined in protocol and are flagged in the EDC by investigator added. Any serious TEAE and any drug related serious TEAE added to overall AE summary. Separate summaries by SOC and PT added for serious TEAEs and drug related serious TEAEs, TEAEs leading to death. New listing with AEs for patients in the ITT population who withdrew before the first study drug administration added.	To clarify TEAE definition. For clarity. Sponsor request. Sponsor request. Sponsor request.
	10.9.2	Table 10-3 updated to add new criteria [redacted] Summaries will be tabulated by cohort and treatment group, no overall column will be presented.	[redacted] For clarity and consistency with shells.
	10.9.3.1	Summaries will be tabulated by cohort and treatment group, no overall column will be presented.	For clarity and consistency with shells.
	10.9.3.2	Details on ECG timing added. Sentence "In case one or two triplicated	For clarity. To clarify algorithm for mean

		results are missing, mean of remaining will be tabulated" added. Clarification that summaries will be tabulated by cohort as well added.	calculations. To correct omission.
	10.10.1	Sentence "All PK related analyses will be provided by an external vendor under the responsibility of the Debiopharm PK scientist. Only tables and listings with concentrations will be provided. Endpoints are described here only for completeness reasons." added.	To clarify responsibilities regarding performing PK analyses.
	10.10.1.2	Sentence removed: The PK parameters will be listed by patient and summarized by route, by visit, by cohort, overall and by gender in PK population. EOT will be summarized with Day 28, as long as at least 3 oral doses of afabicin were administered, and otherwise excluded from summary statistics.	To avoid confusion regarding responsibilities regarding performing PK analyses.
	12	Section updated to include rationale for not performing analyses as specified in the protocol.	Sponsor request.
	16	Schedule of assessment for Part B updated	To comply with protocol 9.0 (amendment 6.0) schedule of assessment.
4	NA	SAP author and reviewers were updated	To reflect updates in the study team
	9	PP population definition was corrected to "All mITT patients who have completed treatment without protocol deviations which have a **substantial effect on efficacy ~~or safety~~ data.**	PP population is used for efficacy analysis only.
	10.1	Section updated to include "(if specific Cohort was opened)"	For clarity.
	10.1	Sentence "Information on re-screening is not collected in the EDC, external excel spreadsheet with list of re-screened patients approved by the Sponsor will be used in programming." Removed.	Data is available in SDTMs.
	10.3	Section updated to include details on Pain assessment analysis and visit assignment.	To properly analyze data collected.

	10.4.1	Sentence removed “If imputation of missing/incomplete start or stop dates results in a situation “end date < start date”, then start and stop dates will not be imputed for such events”.	To remove contradictory sentence. In case AE/CM start date becomes greater than AE/CM end date after imputation, then AE/CM start date will be replaced with AE/CM end date for analysis purposes rule us to be followed.
	10.7.3	Section updated to specify only empiric treatments will be flagged and duration for empiric treatment will be calculated and provided in the listing instead of prior antibiotics.	To align SAP with mock-TFLs and expected analysis.
	10.7.5	Section updated to specify that the figure with afabicin desphosphono MIC distribution for all baseline pathogens will be produced for Afabicin treatment group only. Section updated to specify that summaries by MecA gene presence will be completed for Part A only, and by *mecA* / *mecC* gene presence for Part B.	Sponsor request. To align with the tests performed in each study part.
	10.8.1, 10.8.3	Section updated to specify that summaries by MecA gene presence will be completed for Part A only, and by *mecA* / *mecC* gene presence for Part B	
	10.8.2	Section updated. Text “between post-baseline isolates and initial isolate (sentinel). PFGE results will be expressed as A, A1, A2, ..., A6, A>6. The interpretation of the PFGE results is as follows: A = indistinguishable; A1, A2, A3 = closely related; A4, A5, A6 = possibly related; A>6 = unrelated. If the PFGE result for testing the identity of pathogens is “indistinguishable” then the pathogens are considered to be identical, otherwise they are considered to be different. PFGE results will be listed.” removed. Text” “Strains will be designated either A or B based on the profile. Strains with the same designation (A or B) will be	Sponsor request.

		considered the same." added. Text updated to "If the two pathogens are from the same ST**, MecA and MecC, and PVL type, they will be considered the same pathogen. In instances where ST is not determined (due to presence of a novel ST), the Allelic variants profile will be used**."	
	10.8.3	Section updated: Frequency table of clinical response at Day 8, Day 28, Day 42, EOT, 4 weeks post-EOT, and 12 weeks post-EOT by pathogen, susceptibility profile to oxacillin, PVL and MecA gene presence **(Part A), the mecA / mecC gene presence (Part B)** in the mITT population	To account for WGS data collected for Part B
	10.10.1.2	Sensitivity analysis added: Patients with an overdose at PK sampling, i.e. at Day 1 and Day 28 (or EOT if the treatment < 28 days) will be marked in the listing with PK concentrations. Overdose is defined as receiving dose 120% greater than planned at specific day. A sensitivity table for the summary statistics for PK concentrations will be created, excluding the overdosed patients. Text added: "Patients with a wrong dose at PK sampling (e.g. 160mg instead of 55mg) may be excluded from the analysis."	Sponsor request.
	13	Example updated to include path for output, and Programmer ID	To correct omission.

APPROVAL SIGNATURES

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*

PROTOCOL NUMBER: *Debio 1450-BJI-205*

SAP *Final version 4, 26-SEP-2025*

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1. LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMR	Antimicrobial resistance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical (class)
AUC_{12h}	Area under the plasma concentration-time curve from time zero to 12 hours post-dose
AUC_{last}	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
AUC_{inf}	Area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC_{tau}	area under the plasma concentration curve over the dosing interval
BID	*Bis in die* (twice a day)
BLQ	Below the limit of quantification
bpm	Beats per minute
°C	Celsius
$C_{av,ss}$	Average concentration at steady state
C_{trough}	Trough (pre-dose and at the end of the dosing interval) plasma concentration
CI	Confidence Interval
CL	Total body clearance
CL/F’	Apparent clearance
CL_{ss}/F’	Apparent clearance at steady state
CM	Concomitant Medications
C_{max}	Maximum observed plasma concentration
$C_{max,ss}$	Maximum observed plasma concentration at steady state
C_{last}	Last observed non-negative concentration
CoNS	Coagulase-negative staphylococci
CRP	C-reactive protein
CT	Computed tomography
CV%	Percent coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DRP	Data review plan
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
EOT	End of treatment
°F	Fahrenheit
fAUC	free-afabicin desphosphono plasma AUC_{24h}

Abbreviation	Description
[redacted]	[redacted]
GLDH	Glutamate dehydrogenase
[redacted]	[redacted]
ICF	Informed consent form
ICPD	Institute for clinical pharmacodynamics, Inc
IDMC	Independent data monitoring committee
ITT	Intent-to-treat
IV	Intravenous
LLQ	Lower limit of quantification
MCSF-R1	Macrophage colony-stimulating factor receptor 1
MecA	Gene conferring methicillin resistance
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
MIC	Minimum inhibitory concentration
MIC_{50}	Minimum concentration required to inhibit ≥50% of the strains within a test population
MIC_{90}	Minimum concentration required to inhibit 90% ≥90% of the strains within a test population
mITT	Microbiological ITT
mmHg	Millimeter of mercury
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRT	Mean residence time
msec	Millisecond
MSSA	Methicillin-susceptible *Staphylococcus aureus*
MW	Molecular weight
n	Number of observations
ng/mL	Nanograms per millilite
nM	nanomolar
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PCS	Potentially clinically significant
PFGE	Pulsed-field gel electrophoresis
PH	PCS high value
PJI	Prosthetic joint infection
PK	Pharmacokinetic
PK/PD	Pharmacokinetics/Pharmacodynamics
PL	PCS low value
PP	Per Protocol
PT	Preferred term
PTF	Peak trough fluctuation
PVL	Panton-Valentine leucocidin
Q1	First quartile

Abbreviation	Description
Q3	Third quartile
QT	Time from electrocardiogram Q wave to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
[redacted]	
SAE	Serious adverse event
SAP	Statistical analysis plan
SCFA	Short chain fatty acids
SD	Standard deviation
SI	International system of units
SNP	Single nucleotide polymorphism
SoC	Standard of care
SOC	System organ class
[redacted]	
ST	Sequence Type
TEAE	Treatment-emergent adverse event
TLF	Tables listings figures
t_{max}	Time corresponding to the occurrence of C_{max}
t_{last}	Time of last non-negative observed concentration
$t_{1/2}$	Terminal elimination half-life
ULN	Upper limit of normal
V_z	Volume of distribution during terminal phase
V_{ss}/F'	Apparent volume of distribution at steady state
V_z/F'	Apparent volume of distribution during terminal phase
WBC	White blood cells
WGS	Whole genome sequencing
$\%AUC_{extrap}$	Percentage of $AUC_{0-\infty}$ that is due to extrapolation beyond t_{last}
λ_z	Terminal elimination rate constant

2. INTRODUCTION

This Statistical Analysis Plan (SAP) covers the statistical analysis and reporting for the protocol Debio 1450-BJI-205 Final version No. 13 amendment 10 dated 11 April 2024, and electronic case report form (eCRF) production version of 19 June 2024.

3. STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

To assess the safety and tolerability of afabicin in the treatment of patients with bone or joint infection (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).

3.2 SECONDARY OBJECTIVES

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

3.3 EXPLORATORY OBJECTIVES

To determine the microbiological outcome. In afabicin-treated patients, to describe the pharmacokinetics (PK) profile and to explore biomarkers linked with response, toxicity, microbiome sparing features, and PK, and to assess the potential for drug-drug interaction (DDI) towards cytochromes P450 (CYP) using endogenous biomarker(s).

4. STUDY DESCRIPTION

4.1 STUDY DESIGN

4.1.1 PART A

Patients were to be recruited in 3 cohorts, with treatment duration lengthened for each subsequent cohort, as outlined below.

[redacted]

Cohort 1

This cohort aimed to recruit patients who require treatment with an antibiotic for 2 to 3 weeks (as judged by the investigator). Initially, 8 patients were to be recruited, randomized at a 3:1 ratio (6 to afabicin: 2 to SoC), and dosed. Additional patients may have been enrolled in case of premature treatment withdrawal, as outlined in the study protocol. After the end of treatment (EOT), all available safety and efficacy data for these 8 evaluable patients (including a minimum of 2-week post-treatment follow-up data) should be reviewed by the Independent Data Monitoring Committee (IDMC) [redacted] The IDMC [redacted] should determine 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 should 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 aimed to recruit patients who require treatment with an antibiotic for 3 to 6 weeks (as judged by the investigator). Initially, 8 patients were to be recruited, randomized at a 3:1 ratio (6 to afabicin: 2 to SoC) and dosed. Additional patients may have been enrolled in case of premature treatment withdrawal as outlined in the study protocol. 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) should be reviewed by the IDMC [redacted]. The IDMC [redacted] should then determine 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 should 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 aimed to recruit patients who require treatment with an antibiotic for 6 to 12 weeks (as judged by the investigator). Initially, 8 patients were to be recruited, randomized at a 3:1 ratio (6 to afabicin: 2 to SoC) and dosed. Additional patients may have been enrolled in case of premature treatment withdrawal, as outlined in the study protocol. 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) should be reviewed by the IDMC [redacted]. The IDMC [redacted] will then determine whether to: (i) continue recruitment into this cohort only to generate further safety data before making a final recommendation on this duration of treatment, (ii) open recruitment into all three cohorts, (iii) continue recruiting into cohorts 1 and/or 2 to generate more safety data in shorter durations of treatment, or (iv) modify or terminate the study.

If cohort 3 is continuing, all cohorts should 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.

4.1.2 PART B

Patients will be recruited in the cohorts B (1B, 2B and 3B) with a stepwise approach. Initiation of cohorts C can only take place if pre-defined futility criteria (see Section 4.3) are met in any of the cohorts B and if recommended by [redacted] IDMC and, when necessary, the concerned health authorities.

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 the protocol.

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. 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, a continuous 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 1C could be initiated if recommended [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 the protocol. 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. 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 could be initiated if recommended by [redacted] 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 the protocol 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. 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 initiated, if recommended by [redacted] IDMC, and if necessary, by concerned health authorities.

4.2 STUDY TREATMENT

4.2.1 AFABICIN

Patients should be treated with open label afabicin intravenous (IV) at a dose of 160 mg twice a day (BID) in Part A and 55 mg BID in Part B for a minimum of 1 day (2 doses) and up to a maximum of 14 days, followed by a switch to oral afabicin at a dose of 240 mg BID in Part A and 80 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 afabicin regimen tested in cohorts C is 80 mg IV BID/120 mg oral BID.

The total treatment durations with afabicin during the different stages of this study are summarized below.

Table 4-1Study treatment duration in Part A

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

[redacted]

Table 4-2 Study treatment duration in Part B

	Cohort 1B	Cohort 2B	Cohort 3B	Cohort 1C, 2C or 3C*	Total during the study
Treatment duration	2 to 3 weeks	3 to 6 weeks	6 to 12 weeks	2-3 weeks, 3-6 weeks or 6-12 weeks	2 to 12 weeks
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], and dose regimen modifications (without jeopardizing safety) may be recommended by the IDMC [redacted].

4.2.2 COMPARATOR: STANDARD OF CARE

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

- Recommendations by the clinical guidelines (e.g. Infectious Disease Society of America),
- Single agent (no multiple drug combinations),
- Coverage for oxacillin-/methicillin-susceptible and oxacillin-/methicillin-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 (per product label).

All the antibiotics recommended by clinical guidelines for the treatment of bone and joint staphylococcal infections (methicillin-susceptible and methicillin-resistant) are reviewed in accordance with the above criteria. 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.

4.2.3 RESCUE TREATMENT

Rescue therapy will be considered under the following conditions:

- For patients who will be discontinued from afabicin due to adverse events (AEs),
- Treatment failure (i.e., non-responders),
- 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 defined in the protocol 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 (defined in the protocol) 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 (defined in the protocol). 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. In this situation, extending the duration of treatment with afabicin may only be carried out under the following conditions:

- 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. The treatment cannot be extended beyond the duration of available data.
- 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. The treatment cannot be extended beyond the duration of available data.

- 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.

For patients who receive afabicin with extension of treatment, EOT visit will occur after end of extended afabicin treatment. For patients who receive afabicin and switch to another SoC as rescue therapy, EOT visit will occur after end of afabicin treatment. For patients who receive SoC with extension of SoC treatment or switch to another SoC, EOT visit will occur at the end of last SoC treatment.

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.

4.3 INDEPENDENT DATA MONITORING COMMITTEE [redacted]

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].

For Part B of the study, 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 based on clinical response rate at EOT (see Table 4-3 Futility criterion based on clinical response at *EOT*). The cohort will be stopped at the earliest if 4 out of the first 9 evaluable patients are non-responders, in this case it will not be possible any more to achieve 6 responses out of the first 9 patients, see table 4-3. This will be a two-stage process: efficacy data will be reviewed in the safety population at every bi-weekly IDMC meeting to trigger the futility rule as soon as possible. Inclusions to microbiological intent-to-treat (mITT) population will be updated each month based on monthly pathogen review meetings outcome (as detailed in Data Review Plan (DRP)) and clinical response rate in mITT population will be evaluated at each time point. The final futility decision will be confirmed based on the mITT population.

Table 4-3 Futility criterion based on clinical response at EOT

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

Details are documented in a separate IDMC [redacted] charter. [redacted] charters are prepared for Part A and Part B.

[redacted]

5. RANDOMIZATION AND BLINDING

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:

The randomization ratio will be changing with the progress of each cohort, as follows:

- Initially, in each cohort, patients will be recruited and randomized at a 3:1 ratio (afabicin:SoC) until a subsequent cohort is open for enrollment (for cohorts 1 and 2) or further enrollment 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).

Part B:

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

As per Section 7.3 of the protocol, additional patients will be enrolled 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. Additional patients will be allocated to the same treatment 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]

- Serious Adverse Events (SAE) considered as possibly related to study treatment, and/or
- Lack of efficacy.

This is an open-label study. No blinding procedure is implemented.

6. SAMPLE SIZE AND POWER CALCULATION

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 [redacted] 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).

- 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]
- Part B is divided in 3 cohorts of 24 evaluable patients (20 in afabicin arm and 4 in the control arm). A 4th 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. [redacted]

[redacted]

7. ANALYSIS ENDPOINTS

7.1 PRIMARY ENDPOINT: SAFETY

The primary endpoint is the nature, incidence, severity, seriousness, and outcome of treatment-emergent adverse event (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 in the Safety population.

7.2 SECONDARY ENDPOINTS: EFFICACY

The secondary efficacy endpoints are the proportion of patients with clinical response (1) 8 days, (2) 28 days (for applicable cohorts), (3) 42 days from randomization (for applicable cohorts or treatment allocation for additional patients), (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 (see Section 10.8.1).

7.3 EXPLORATORY ENDPOINTS

7.3.1 PK/PD – ONLY FOR PATIENTS WHO ARE TREATED WITH AFABICIN

The PK parameters and pharmacokinetics/pharmacodynamics (PK/PD) analyses will include the following parameters:

Day 1 (Intravenous administration)

- AUC_{12h} and, if applicable, C_{max}, t_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$, mean residence time (MRT), CL or CL/F', V_z or V_z/F' for afabicin and/or its active moiety afabicin desphosphono (Debio 1452), as applicable,

Day 28 or EOT (Oral administration):

- AUC_{Tau} and, if applicable, $t_{max,ss}$, $C_{max,ss}$, CL_{ss}/F', V_{ss}/F', C_{trough}, $C_{av,ss}$, peak trough fluctuation (PTF) for afabicin desphosphono,

PK-PD index on Day 1 and at steady-state:

- afabicin desphosphono free-drug plasma AUC_{24h}: MIC [$fAUC_{24h}$:MIC].

All analyses will be performed by an external provider.

7.3.2 MICROBIOLOGICAL OUTCOME

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 of the original site of infection,
- 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 (until EOT visit), in the presence of signs and/or symptoms of infection,
- New Infection: a new pathogen cultured from the original site of infection after therapy (after EOT visit), in the presence of signs and/or symptoms of infection,
- Unknown: outcome assessment is not possible (patient has indeterminate status or missing clinical response evaluation and there is no material available for culture), patient is lost to follow up or had an amputation at the site of the initial infection.

7.3.3 BIOMARKER EXPLORATION

Research will be conducted in patients treated with afabicin in order to identify biomarkers related to response, toxicity, and PK. 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] s 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 if the sponsor deems it necessary based on the toxicities observed. The sponsor also reserves the right in any case to analyze baseline samples of patients with no related toxicities, in order to obtain a baseline value for the study population.

[redacted]

Biomarker exploratory analyses were defined as optionally in the protocol but deemed not necessary by the sponsor. The optional exploratory analyses will not be part of the study analyses defined in this SAP.

7.3.4 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).

A listing with data collected in Electronic Data Capture (EDC) will be provided. All further analyses will be done externally and are not part of this SAP.

7.3.5 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.

This DDI assessment was done in part A (cohort 1) and in part B (cohort 1). The bioanalysis data for this investigation were also generated for Cohort 2B. All the bioanalysis results will be reported in an Appendix to the CSR by DPI and are not part of this SAP. The data analysis (interpretation) will not be performed, as new physiologically based pharmacokinetics data were generated in parallel to the study for these particular assessments and results are available. Consequently, the data analysis is not needed anymore.

7.3.6 IMPROVEMENT OF INFLAMMATION

Exploratory endpoint C-reactive protein (CRP) will be assessed to better understand the patient's overall improvement of inflammation. CRP levels are checked as part of a full panel laboratory assessment.

Inflammation would be considered improved when the baseline CRP level is over the normal range and as indicated by CRP level decrease at EOT visit 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 Bone or Joint Infection as an inflammatory biomarker.

8. PATHOGEN IDENTIFICATION

A pathogen is defined as bacteria implicated as causative in a patient's bone or joint infection. Baseline pathogens and, where possible, post-baseline pathogens will be identified. Additional details regarding the pathogen review process and determination are included in the DRP.

Screening samples for microbiological assessment are defined as all samples that have been collected during the screening period. Screening samples for microbiological assessment can be collected before and/or after the start of an empiric antibiotic treatment given during the screening period. Baseline microbiological assessments are defined as the screening samples for microbiological assessment that have been collected during 10 days before randomization or treatment allocation for additional patients. In case of no screening sample for microbiological assessment is collected during the screening period, the following baseline status for a microbiological assessment will be appraised during the data review meeting prior to the database lock:

1) previous pathogen identification obtained using invasive procedures, performed as a component of routine patient care through the local laboratory before screening period;

these results 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.

2) pathogen identification performed between the randomization or treatment allocation and the first dose of assigned 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.

A pathogen identified from the baseline sample - blood and/or primary site of infection (bone, synovial fluid, or soft tissue biopsy) is considered a baseline pathogen.

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

9. 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 any study drug. This population will be used for the primary analysis and for all further safety related endpoints. If a patient of the SoC arm received at least one time afabicin he/she will be analyzed in the afabicin group for all safety analyses.

mITT population: All randomized patients who received at least one dose of any study drug and have a positive staphylococcal only culture (identified by Gram staining, pathogen identification by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, culture on selective medium, or Polymerase chain reaction). This population will be used for the secondary analysis and for all efficacy related endpoints. The mITT population will be determined based on isolates evaluation on a case by case basis by the sponsor during a data review meeting that will take place prior to database lock, as detailed in the DRP. Bacterial identification and antimicrobial susceptibility determined by the central laboratory will be utilized in the isolate evaluation. The local/regional laboratory results will be used for analysis only if an isolate is not received by the central laboratory (i.e., lost or non-viable). The mITT population will be analyzed according to the Intention-to-treat principle.

Patients who were replaced (see Section 5 and protocol Section 7.3.) after at least one dose of study drug will be part of the Safety population and ITT population but not part of the mITT population. Replaced patients who are excluded from mITT population will be confirmed at the data review meeting.

Per Protocol (PP) population: All mITT patients who have completed treatment without protocol deviations which have substantial effect on efficacy data. This population will be used for secondary analysis. Patient data will be reviewed at the data review meeting and a decision on by-patient basis will be done on how to handle patients in the analysis. Protocol deviations, which have a major effect on the analysis, will be assessed during a data review meeting that will take

place prior to the database lock, as detailed in the DRP. All details will be specified in the DRP and then in the minutes of the review meeting.

PK population: All patients who received at least one dose of afabicin and have a valid PK assessment. A PK assessment will be considered valid if quantifiable and evaluable concentration (afabicin or afabicin desphosphono) is available.

[redacted]

Not-treated ITT Population: all patients in ITT population who didn't receive study dug.

10. ANALYTICAL PLAN AND STATISTICAL METHODS

10.1 GENERAL CONVENTIONS AND STATISTICAL CONSIDERATIONS

All statistical analyses will be performed, and data appendices will be created using the SAS system version 9.4 or higher.

The statistical analysis outlined in this document will apply for both study Part A and Part B and will be performed for each cohort. Part A and Part B cohorts will be presented in different tables. Each table will present afabicin and SoC separately for each cohort and overall for each cohort as well as all patients together (if not specified otherwise) (i.e., tables for Part A will include: Afabicin Cohort 1/ Afabicin Cohort 2/ Afabicin Total/ SoC Cohort 1/ SoC Cohort 2/ SoC Total/ Total, tables for Part B will include (if specific Cohort was opened): Afabicin Cohort 1/ Afabicin Cohort 2/ Afabicin Cohort 3, Afabicin Total/ SoC Cohort 1/ SoC Cohort 2/ SoC Cohort 3/ SoC Total/Total).

Descriptive statistics (number of non-missing values, mean, standard deviation (SD), median, minimum and maximum) will be presented for continuous variables other than time to event variables. For time to event variables, the number and percentage of patients censored and those with events will be summarized. Additionally, the median, 25th and 75th percentile estimates (where calculable based on Kaplan-Meier estimates) will be presented. Frequency distributions (counts and percentages) will be presented for categorical variables. If not specified otherwise, the number of observations with non-missing values will be the denominator for percentage calculation.

Conventions and statistical considerations for PK data are presented in Section 10.10.1.

All data collected will be presented in the data listings. Identification of the study part for each patient will be added. Patients re-screened once will be flagged in the listings.

10.2 TREATMENT GROUPS AND COHORTS

Reporting in the ITT and mITT populations will be according to treatment assignment and according to planned cohort taken from the eCRF.

Reporting in the safety and PP population will be according to the actual treatment group.

Only patients who received afabicin on day 1 will be analyzed in the PK population. Only patients who received afabicin on day 28 will be analyzed for the day 28 PK assessments.

Actual treatment will be defined based on the cohort a patient was assigned to and actual treatment received by a patient as following:

- Only patients who receive the planned treatment can qualify for the PP set. For these patients planned and actual treatment is the same.
- Patients who received at least one dose of afabicin will be analyzed in the afabicin treatment group for the safety population.

All available efficacy and safety data will be analyzed in the tables with analysis of TEAEs being presented separately for treatment (up to EOT) and FU periods (after EOT), and combined for both periods.

Separate tables will be produced for Part A and Part B. Listings will include both, Part A and Part B data.

10.3 DEFINITION OF BASELINE, STUDY VISITS, AND VISIT WINDOWS

Unless specified otherwise, the last non-missing assessment made prior to date and time of the randomization or treatment allocation, including pre-informed consent date if authorized to be collected by the study protocol, will be used to programmatically derive the baseline value for all analyses except baseline pathogen identification. Final decision regarding the baseline pathogen identification will be made based on data review (see Section 10.7.5). If there is no such assessment, last assessment made prior to the first dose of study drug will be used as baseline. Assessments performed on unscheduled visit will be considered when deriving baseline value.

For electrocardiogram (ECG) data, assessment performed on Day 1 pre-dose will be considered baseline.

The data will be analyzed according to the visits recorded in the eCRF, except from ECG data, records with “DAILY ECG” and “DAY X” visit and Pain Assessment data (visits are missing). For ECG and Pain assessments performed prior to the first study drug administration, study day will be calculated as the date of the assessment minus the date of the first dose of study drug. For ECG performed on or after the date of the first dose of study drug, study day will be calculated as the date of the assessment minus the date of the first dose of study drug, plus one. Analysis visit will then be derived as “Day X” where X is study day.

For Pain assessment performed after the date of the first dose of study drug, study day will be calculated as the date of the assessment minus the date of the first dose of study drug, plus one. Analysis visit will then be derived as “Day X” where X is study day, if assessment occurred before EOT visit. If assessment date is same as EOT visit date, analysis visit will be set to “EOT visit”. For assessments occurring after EOT visit, analysis visits will be derived as per table below:

Analysis Visit	Analysis Window Beginning Timepoint (days post EOT)	Analysis Window Target Day (days post EOT)	Analysis Window Ending Timepoint (days post EOT)
1 Week post-EOT Visit	4	7	10
2 Weeks post-EOT Visit	11	14	17
3 Weeks post-EOT Visit	18	21	24
4 Weeks post-EOT Visit	25	28	31
5 Weeks post-EOT Visit	32	35	38
6 Weeks post-EOT Visit	39	42	45
12 Weeks post-EOT Visit	77	84	91

In case of multiple assessments per patient within the specified window, the assessment closest to the target day will be selected. In case of ties, the assessment after the target day will be selected.

On Day 1, vital signs will be checked prior to the first dose administration, at the time of completion of the first dose, and 1 hour after the administration of the first dose was completed. The time points for vital signs will be calculated as described below:

- “Pre-dose”: if assessment date & time < start date & time of the first infusion.
- “At Time of Completion of the First Dose”: if assessment date & time was within 15 minutes before end date & time of the first infusion and 30 minutes (including) after end date & time of first infusion.
- “1 Hour after Completion of the First Dose”: if assessment date & time was within 30-90 minutes after end date & time of the first infusion.

If there is more than one assessment meeting the criteria above, assessment closest to planned timepoint will be analyzed.

On Day 2 and 3, vital signs will be checked within 3 hours of completing the study drug infusion. Only assessments obtained within this timeframe will be included in the table. If there is more than one assessment meeting the criteria above, the assessment closest to the end of the first infusion on the day specified, will be analyzed.

10.4 HANDLING OF MISSING DATA

10.4.1 DATES IMPUTATIONS

The rules below will be used for TEAE and concomitant medication (CM) flag derivation and for TEAEs/CMs assignment to periods (treatment, follow-up) only. Data as collected on the eCRF will be presented in the data listings.

The following rules will be applied for AEs and CMs with incomplete start dates:

- If partial start date is equal to the corresponding part of the treatment start date, then consider the start date equal to the treatment start date.
- If day is missing for start date, and month and year are not the same as month and year for the first treatment date, then impute day 1 of the month.
- If day and month are missing for start date, and the year is not the same as year for the first treatment date, then impute January 1st of the year.

The following rules will be applied for AEs and CMs with incomplete end dates:

- If day is missing for end date and month and year are non-missing, then day will be imputed as last day of the month.
- If day and month are missing for end date and year is non-missing, then day and month will be imputed as December 31st.

The completely missing AEs and CMs start and end dates will not be imputed.

In case AE/CM start date becomes greater than AE/CM end date after imputation, then AE/CM start date will be replaced with AE/CM end date for analysis purposes.

The following rules will be applied for incomplete start dates of symptoms:

- If day is missing, then impute day 1 of the month.
- If day and month are missing, then impute January 1st of the year.

10.4.2 Missing Adverse Events' Attributes Imputation

In summary tables, missing attributes of TEAEs (relatedness and severity) will be imputed. Missing relationship to study drug for such event will be set to "Related". Missing relationship to study drug of events started before first dose will be kept missing in summary tables.

Adverse events with missing severity and outcome will be reviewed at a data review meeting and classified.

Data listings will present data as collected on eCRF.

10.4.3 Missing Clinical Response Imputation and Clinical Response Carry Forward Rules

In case Investigator assessment of clinical response is missing, clinical response will be defined as having indeterminate status.

If a patient is a non-responder at EOT or at a later visit, he/she will be considered a non-responder for all subsequent visits. If a patient is a non-responder at any visit before EOT with the reason for non-response on eCRF form "Requirement of subsequent antibiotics with activity against Staphylococcus to treat the initial infection after the start of the study treatment to assign non-response", he/she will be considered a non-responder for all later visits (in order to avoid a patient being considered a responder at a later visit due to another treatment).

10.5 PATIENT DISPOSITION

The number of patients screened and reasons for screen failure, including exclusion criteria met and inclusion criteria not met, will be summarized in screened population separately for Part A overall and separately for Part B, including Cohort 1, 2 and 3, and total Part B.

The rationale for separate summary of screen failed patients in Part B is that in Protocol V8.0, amendment 5, dated 24 Aug 2022, [redacted]

[redacted]

The number and percentage of patients randomized or allocated to treatment for additional patients and completing the study will be presented overall, by treatment group and cohort, in ITT and Safety population.

Reasons for premature treatment and study discontinuation will also be summarized overall, by treatment group and cohort, in ITT and Safety population.

The disposition of patients will also include information on the number and percentage of patients who:

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

The number of patients included in each of the analysis populations (ITT, mITT, PP, PK, Safety [redacted]) will be summarized with reasons for being excluded, overall, by treatment group and cohort, in ITT and Safety population.

The number of patients in ITT population by country and site will be summarized overall, by treatment group and cohort.

A listing of study completion/premature withdrawal, and study drug completion or premature discontinuation for all patients will be produced. A listing in all screen failed patients with an inclusion/exclusion criteria (not) met, showing the primary diagnosis and type will be produced.

10.6 PROTOCOL DEVIATIONS

The number and percentage of patients with at least one major protocol deviation and the categories of the major protocol deviations will be summarized by cohort, treatment group and overall in the ITT population.

Protocol deviations will be classified as major and minor as specified in the Protocol Deviations Management Plan.

All protocol deviations will be provided in a listing.

10.7 PATIENT CHARACTERISTICS

10.7.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Descriptive statistics for continuous variables (age at screening, height, weight, and body mass index) and frequency counts and percentages for categorical demographic variables (gender, race) will be summarized by cohort, treatment group and overall in the mITT and Safety populations.

Baseline and demographics characteristics will be provided in a listing.

10.7.2 MEDICAL HISTORY AND CURRENT MEDICAL CONDITIONS

The number of patients with a history of:

- alcohol abuse,
- IV drug abuse,
- other drug abuse,
- human immunodeficiency virus infection,
- hepatitis B virus infection,
- hepatitis C virus infection,
- lymphedema,
- recurrent staphylococcal infections,
- any significant prior surgical procedures.

will be tabulated by cohort, treatment group and overall in the Safety population.

Medical history will be tabulated by cohort, treatment group and overall in the Safety population. Medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) classification and summarized by System Organ Class (SOC) and preferred term (PT). Patients having the same medical condition (based on SOC and PT) more than once will be counted only once for a particular SOC and PT.

Disease characteristics will be summarized by treatment group and overall in the mITT and Safety populations, and will include:

- Frequency counts and percentage of patients for:
  - primary diagnosis,
  - origin of infection,
  - type of PJI, septic arthritis or osteomyelitis,
  - primary site or most clinically relevant site of infection,
  - whether infection is in long bone, and if so, anatomic type of infection,
  - type of therapy received prior to screening,
  - clinical signs and symptoms at baseline,
- Descriptive statistics for days since start date of symptoms, calculated as date of informed consent – start date of symptoms.

Medical history, disease characteristics and data on alcohol consumption will be listed.

10.7.3 Prior and Concomitant Medications

All prior and CMs will be coded using latest version of World Health Organization Drug Dictionary.

The number and percentages of patients with at least one of the following prior and/or CMs will be summarized by anatomical therapeutic chemical class (ATC) level 2 and ATC level 4 class, by cohort, treatment group and overall:

- prior antibiotic (empiric treatment),
- prior non-antibiotic medications,
- CMs.

Prior and CMs will be summarized in the Safety population.

Medications with ATC 2 class code equal to J01 (antibacterials for systemic use) will be considered antibiotics.

Patients receiving the same medication more than once will be counted only once for a particular medication class.

A medication is considered prior if the end date of the medication is prior to the first study drug dose date. A medication is considered concomitant if it is administered between the first study drug dose date and EOT visit. Imputation rules specified in Section 10.4 will be applied to partial/missing dates.

Medications having both start and end dates missing will be considered concomitant; in the case of a missing start date and not a missing end date the medication will be considered concomitant, unless the end date is prior to the date of the first dose.

Prior antibiotic is considered empiric treatment if is given during the screening period (i.e. end date is on or after informed consent but before the first study drug date).

All prior and CMs will be provided in a listing, and medications started after EOT visit will be flagged. Empiric treatments will be flagged, and treatment duration in days will be calculated for empiric treatments and provided in the listing.

10.7.4 Concomitant Procedures

All concomitant procedures will be coded using the latest version of MedDRA classification.

A procedure is considered concomitant if performed between the first study drug dose date and EOT visit.

All concomitant procedures will be provided in a listing. Procedures performed after EOT visit will be flagged.

10.7.5 Baseline Microbiological Assessments

Baseline pathogens will be summarized by genus and species, cohort, treatment group and overall in the mITT population. *Staphylococcus aureus* and CoNS will also be summarized by

Panton-Valentine leukocidin (PVL), the methicillin resistance *MecA* gene presence (Part A), the *mecA* / *mecC* gene presence (Part B), and phenotypic susceptibility to oxacillin using the Clinical & Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing breakpoints from 2019, as defined in *Table 10-1*.

Patients with the same pathogen on species level from blood, bone, synovial fluid, or soft tissue biopsy are counted only once for that pathogen. Patients with both methicillin-susceptible and methicillin-resistant pathogen of the same species are counted twice in the overall tabulation for that species.

For baseline pathogens (grouped by species, and also by MRSA, MSSA, and CoNs) the following parameters will be tabulated in the mITT population:

- susceptibility profile (resistant, susceptible, intermediate as defined in *Table 10-1*) to SoC and to the comparator antibiotics tested by the central laboratory,
- MIC_{50} (median), MIC_{90} (90^{th} percentile), mode MIC, and MIC range to SoC, the comparator antibiotics, and afabicin desphosphono (Debio 1452, the active moiety of afabicin) tested by the central laboratory. MIC_{50} and MIC_{90} values will be determined only when at least 10 isolates of a particular species are tested.

For afabicin desphosphono in mITT population in Afabicin treatment group only MIC distribution for all pathogens, *S. aureus* (MRSA, MSSA distinguished), and for CoNS will be presented graphically (bar charts with MIC on x-axis, and isolate count on y-axis).

Table 10-1 Antimicrobial susceptibility interpretative criteria for SoC received and comparator antibiotics tested as of 2019.

Antibiotic	MIC CLSI Criteria (µg/mL)				MIC EUCAST Criteria (µg/mL)			
	Species	S	I	R	Species	S	I	R
Cefazolin	All *Staphylococcus* spp.	(B)	-	(B)	All *Staphylococcus* spp.	(C)	-	(C)
Clindamycin	All *Staphylococcus* spp.	≤ 0.5	1-2	≥ 4	All *Staphylococcus* spp.	≤ 0.25	-	>25
Daptomycin	All *Staphylococcus* spp.	≤ 1	-	-	All *Staphylococcus* spp.	≤ 1	-	>1
Levofloxacin	All *Staphylococcus* spp.	≤ 1	2	≥ 4	All *Staphylococcus* spp.	≤ 1	-	>1
Linezolid	All *Staphylococcus* spp.	≤ 4	-	≥ 8	All Staphylococcus spp.	≤ 4	-	>4
Oxacillin	*S.aureus* *S.lugdunensis*	≤ 2	-	≥ 4	*S.aureus* *S.lugdunensis* *S.saprophyticus*	≤ 2	-	>2
	S.epidermidis S.pseudintermedius S.schleiferi	≤ 0.25	-	≥ 0.5	S.pseudintermedius	NA	NA	NA
	Other[(A)] CoNS	≤ 0.25	-	≥ 0.5	Other CoNS	≤ 0.25	-	>0.25
Rifampin	All *Staphylococcus* spp.	≤ 1	2	≥ 4	All *Staphylococcus* spp.	≤0.06	-	>0.5
Vancomycin	*S.aureus*	≤ 2	4-8	≥	*S.aureus*	≤2	NA	>2

Antibiotic	MIC (µg/mL) CLSI Criteria				MIC (µg/mL) EUCAST Criteria			
	Species	S	I	R	Species	S	I	R
				16				
	CoNS	≤ 4	8-16	≥ 32	CoNS	≤4	NA	>4

S. = *Staphylococcus,* S = susceptible, I = Intermediate, and R = resistant; CoNS = Coagulase-negative staphylococci, MIC = minimum inhibitory concentration, CLSI = Clinical & Laboratory Standards Institute, EUCAST = European Committee on Antimicrobial Susceptibility Testing.
A: CoNS other than: *S.aureus, S.lugdunensis, S.epidermidis, S.pseudintermedius, S.schleiferi*: oxacillin MIC breakpoints may overcall resistance. Isolates for which the oxacillin MICs are: 0.5-2 mg/L have been shown to be MecA positive and MecA negative. Isolates from serious infections with MICs in this range may be tested for MecA or PBP2a.
B: Oxacillin-susceptible *staphylococci* can be considered susceptible to parenteral cephalosporins I, II, III, IV (including cefazolin). Oxacillin-resistant *staphylococci* can be considered resistant to parenteral cephalosporins I, II, III, IV (including cefazolin). However, in this study, susceptibility to both cefazolin and oxacillin will be tested and available for summary reporting.
C: Methicillin resistant strains should be reported resistant to cefazolin as well. Methicillin sensitive strains should be reported sensitive to cefazolin as well. However, in this study, susceptibility to both cefazolin and oxacillin will be tested and available for summary reporting.

Resistance profile (resistant, susceptible, intermediate) provided in the data transfers by the central laboratory, [redacted] will be used in the analyses. It will not be recalculated.

Susceptibility data (including MIC values to all tested antibiotics and resistant profile as defined in *Table 10-1*), PVL and MecA gene presence for all pathogens will be listed.

10.7.6 EXPOSURE TO STUDY TREATMENT

Extent of exposure will be tabulated by cohort and treatment group.

Patients in the afabicin treatment group, including patients who switched afabicin to SoC, will be summarized in tables. The following parameters will be calculated and summarized using descriptive statistics:

- Oral/IV treatment duration (days), calculated as date of last IV/oral dose - date of first IV/oral dose +1
- Overall duration (days), calculated as date of last afabicin dose - date of first afabicin dose +1
- Number of infusions
- Number of tablets taken
- Number of infusion interruptions
- Number of incomplete infusions
- Total IV, oral and overall dose (mg) administered
- IV treatment compliance, calculated as total IV dose administered (mg) *100/expected IV dose (mg)
- Oral treatment compliance calculated as total oral dose administered (mg) *100/expected oral dose (mg)
- Overall treatment compliance calculated as weighted mean of IV and oral compliance: [duration of IV treatment (days)*IV treatment compliance + duration of oral treatment (days)*oral treatment compliance] / overall treatment duration (days).

For patients in the SoC treatment group, overall exposure from the first SoC to the last SoC administered will be summarized. Only total IV, oral dose (mg) administered will be summarized in individual SoCs. Exposure to individual SoC will be presented in data listing. The following parameters will be summarized using descriptive statistics:

- Oral, IV and overall treatment duration, calculated as date of last IV/oral dose - date of first IV/oral dose +1
- Number of infusions
- Number of tablets taken
- Number of incomplete infusions
- IV treatment compliance calculated as weighted mean of IV compliance on individual SoCs, where IV treatment compliance on individual SoC is calculated as total IV dose administered *100/expected IV dose
- Oral treatment compliance calculated as weighted mean of oral compliance on individual SoCs, where oral treatment compliance on individual SoC is calculated as total oral dose administered *100/expected oral dose
- Overall treatment compliance calculated as weighted mean of IV and oral compliances: [duration of individual SoC IV treatment in days*individual SoC IV treatment compliances + duration of each SoC oral treatments*each SoC oral treatment compliances] / overall treatment duration.

Frequency counts and percentage of type of SoC treatments, reasons for infusion interruption (only for patients on afabicin) and reasons for infusion incompletion will also be presented by cohort and treatment group.

The expected dose for afabicin and SoC will be calculated as (IV/oral treatment duration)*(planned IV/oral daily dose). For Cefazolin, planned daily dose entered in the eCRF by the investigator will be used for the compliance calculations. For remaining SoC IV/oral daily dose is provided in *Table 10-2* below.

Table 10-2 Planned daily dose of IV/oral SoC.

	Linezolid	**Clindamycin**	**Vancomycin**	**Cefazolin**
IV	1200 mg (600 mg q12h)	1800 mg (600 mg q8h)	30 mg * weight at baseline (15 mg/kg/q12h)	3 g or 6 g (1-2 g q8h)
oral	1200 mg (600 mg q12h)	1800 mg (600 mg q8h)	-	-

A by-patient listing with the treatment administration data will be presented. This listing will include at least: date and time of study drug administration, details for IV administration, number capsules/tablets, planned dose, actual drug dose and the reason if study drug was not administered. Planned dose for Cefazolin will be taken from eCRF. Planned dose from other SoC will be taken as specified in the protocol.

10.8 EFFICACY ENDPOINTS AND ANALYSIS

Efficacy data will be analyzed in the mITT population unless specified otherwise and will be tabulated by cohort and treatment group.

10.8.1 Analysis of Efficacy Endpoints

The key efficacy evaluation is clinical response at Day 8, Day 28 (for applicable cohorts), Day 42 (for applicable cohorts), EOT, at 4 weeks post-EOT, and 12 weeks post-EOT in the mITT and PP populations. Patients' status will be classified by Investigator 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)
- Radiology: 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 (MRI, CT-Scan, etc.) and additional imaging assessments between screening and 12 weeks post-EOT are at the investigator's discretion.

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).

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.

If a patient is a non-responder at EOT or at a later visit, he/she will be considered a non-responder for all subsequent visits. If a patient is a non-responder at any visit before EOT with the reason for non-response on eCRF form "Requirement of subsequent antibiotics with activity against Staphylococcus to treat the initial infection after the start of the study treatment to assign non-response", he/she will be considered a non-responder for all later visits (in order to avoid a patient being considered a responder at a later visit due to another treatment).

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. In the case that an Investigator assessment of clinical response is missing, the status will also be defined as indeterminate. Patients with missing data contributing to determination of the secondary efficacy endpoint (except for the non-mandatory microbiology and radiology results) will be defined as having indeterminate status.

The number and percentage of patients in each treatment group classified as responder, non-responder, or indeterminate by the Investigator at Day 8, Day 28, Day 42, EOT, at 4 weeks post-

EOT, and 12 weeks post-EOT will be reported in the mITT population. A description by count and percentage, along with a 95% confidence interval (CI) will be calculated for each cohort and treatment group using the Clopper-Pearson method.

Clinical response by visit by baseline pathogen (including S. aureus, MRSA, MSSA, CoNS, PVL+, PVL-, MecA (Part A), mecA / mecC (Part B) – based on the central lab data) and by MIC of afabicin desphosphono will be summarized in the mITT population.

For the analysis of clinical response, where the outcome may be indeterminate, all patients in the population will be included in the denominator. Thus, patients with an indeterminate response are essentially considered as a failure. The reasons for non-response and indeterminate status will also be summarized by treatment group. While the final patient response can be only responder, non-responder or indeterminate, the reasons for non-response are not mutually exclusive, thus, the patient can be counted under multiple criteria for non-response.

The number of patients having imaging results performed on the same visit as per eCRF as the Investigator's assessment of clinical response will be summarized.

The number of patients having microbiology sample collected on the same day or within 3 days before the Investigator's assessment of clinical response will be summarized.

Clinical response assessments and reasons for non-response and indeterminate will be listed.

10.8.2 By-Patient Microbiological Outcome

Microbiological outcome will be evaluated at each on-site visit where the microbiological sample can be collected, based on culture results (if available).

The following microbiological outcomes will be assessed at each visit:

- Documented eradication: absence of baseline pathogen(s) in post-baseline cultures of the original site of infection.
- 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 (until EOT visit), in the presence of signs and/or symptoms of infection.
- New Infection: a new pathogen cultured from the original site of infection after therapy (after EOT visit), in the presence of signs and/or symptoms of infection.
- Unknown: outcome assessment is not possible (patient has indeterminate status or missing clinical response evaluation and there is no material available for culture), patient is lost to follow up or had an amputation at the site of the initial infection.

Pathogen cultured in post-baseline sample will be considered the same as pathogen cultured in baseline sample, if species, MR/MS profile, PVL profile, and PFGE profile is the same (for applicable patients) or whole genome sequencing (WGS) results indicate that the pathogen is the same.

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, pulsed-field gel electrophoresis (PFGE) for Part A patients. PFGE will be performed to determine strain relatedness. Strains will be designated either A or B based on the profile. Strains with the same designation (A or B) will be considered the same. PFGE results will be listed.

Multi locus sequence typing will be performed and isolates will be classed in Sequence Types (ST) i.e. ST5 for Part B patients. If the post-baseline pathogen is from a different ST, pathogens are considered to be different. If the two pathogens are from the same ST, MecA and MecC, and PVL type, they will be considered the same pathogen. In instances where ST is not determined (due to presence of a novel ST), the Allelic variants profile will be used. WGS results will be listed.

For patients' assessment of documented or presumed eradication or persistence, recurrence, new and super infection at a specified visit, the material for culture collected on, 1 day after or up to 3 days before the visit is taken into consideration.

Patient is considered as having a super-infection or new infection, if date of present signs and symptoms of infection recorded on Clinical Signs and Symptoms Form on eCRF is one day before or the same as collection date of the sample on which new pathogen is cultured.

Patient is considered as having recurrence if at least one baseline pathogen is present in post-EOT cultures of the original site of the infection after documented or presumed eradication at EOT visit.

The proportion of patients with each microbiological outcome in each treatment group and cohort will be presented for the mITT population for each study visit. CIs will not be displayed. Summary will be presented only if there is data available for at least 5 patients at a visit; otherwise, data will be presented in the data listings.

By-patient microbiological outcome will be listed.

10.8.3 Additional and Exploratory Efficacy Analyses

Additional efficacy analyses will be conducted including the following:

- Frequency table of the clinical signs and symptoms per visit in the mITT population.
- Frequency table and figure with the number of clinical signs and symptoms per patient per visit in the mITT population.
- Descriptive statistics for pain assessment per visit in the mITT population, Part B only.
- Frequency table in the mITT population for Part B only, with clinically significant reduction as per The Pain Intensity Numerical Rating Scale (PI-NRS), defined as:
  - at least two scale points between two time-points of an assessment, or
  - reduction to at least 3 at EOT.
- Figure with average pain score per visit in the mITT population, part B only.
- Frequency table of the imaging results interpretation by procedure per visit in the mITT population. Ultrasound imaging results will be summarized at baseline only. Magnetic resonance imaging (MRI)/ computed tomography (CT)/X-ray imaging results will be summarized altogether per visit. In case there are more than one baseline imaging result obtained on the same date, X-ray will be selected.
- Descriptive statistics for CRP and white blood cell (WBC) for actual values and percentage change from baseline per visit in the mITT population.

- Frequency tables for improvement of inflammation in the mITT and Safety populations.
- Frequency table of clinical response at Day 8, Day 28, Day 42, EOT, 4 weeks post-EOT, and 12 weeks post-EOT by pathogen, susceptibility profile to oxacillin, PVL and MecA gene presence (Part A), mecA / mecC gene presence (Part B) in the mITT population.
- Time to response (for responders only) and time to progression in the mITT population will be analyzed as described in Section 10.1. Time to response is defined as the duration (in days) from randomization (or assignment to treatment and cohort for additional patients) to first documented clinical response assessment with status responder. Time to progression is defined as the duration (in days) from randomization (or assignment to treatment and cohort for additional patients) to first documented clinical response assessment with status non-responder. Patients without documented clinical response assessment with status non-responder will be censored at last available clinical response assessment date. Patients without clinical response assessment will be censored at randomization date.

10.9 SAFETY ENDPOINTS AND ANALYSIS

All safety outcomes will be analyzed in the Safety population. Patients in the Safety population will be analyzed according to the treatment actually received.

Safety will be evaluated by presenting summaries of AEs, physical examination, vital signs, laboratory evaluations (hematology, chemistry, electrolytes, coagulation and urinalysis), and ECG parameters.

Adverse events will be tabulated by cohort, treatment group and overall. Remaining safety endpoints and analyses will be tabulated by cohort and treatment group.

10.9.1 ADVERSE EVENTS

AEs will be coded using the latest version of MedDRA and will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE). NCI-CTCAE version 4.03 will be used to grade laboratory abnormalities. For QTc-related AEs, NCI-CTCAE version 3.0 will be used.

A TEAE is defined as an AE that occurs or worsens after the first study drug administration. AEs having both onset and end dates missing will be considered as TEAEs. AEs having onset time missing and onset date is same as the first study drug administration date will be considered as TEAEs. AEs having missing onset date and not missing end date AE will be considered as TEAE unless end date is prior to the date of the first dose.

Each summary table with AEs (except TEAEs leading to study drug discontinuation) will be presented for each study period, i.e., treatment (up to EOT visit), follow-up (after EOT visit), separately and overall.

AEs of special interest (AESIs) are defined in Protocol Section 10.1.5. The AEs are flagged as of special interest in the EDC by investigator. An overall summary of AEs will include the number and proportion of patients who experienced at least one AE of the following categories:

- Any TEAE
- Any treatment-emergent SAE

- Any serious TEAE
- Any non-serious TEAE
- Any treatment-emergent Adverse Event of Special Interest (AESI)
- Any drug-related TEAE
- Any drug related serious TEAE
- Any TEAE leading to premature discontinuation of study drug
- Any TEAE leading to premature discontinuation from study
- Any TEAE leading to death

and will be tabulated by cohort, treatment group and overall.

The count and percentage of patients with TEAEs will be presented by SOC and PT for the following categories: all TEAEs, all TEAEs by worst severity, related TEAEs, AESIs, serious TEAEs, serious related TEAEs and non-serious TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to withdrawal from the study, and TEAEs leading to death. For all the summaries, patients with multiple AEs will be counted only once for each SOC and PT and the highest severity.

TEAEs leading to death: this table will be tabulated by Afabicin part (A or B), overall Afabicin total, and SoC.

Drug-related TEAEs will not be tabulated by SoC, as only TEAEs related to afabicin were recorded.

A by-patient AE data listing will be provided including, but not limited to, verbatim term, PT, SOC, NCI-CTCAE grade and/or by severity, and relationship to study drug. AE listings will also be provided for all AEs, SAEs, AEs leading to death, AEs leading to discontinuation from study drug or to withdrawal from the study, AESIs, and AEs with onset before first study drug administration.

AEs for patients in the ITT population who withdrew before the first study drug administration will be presented in a separate listing.

10.9.2 Laboratory Data

Hematology, clinical chemistry, electrolytes, coagulation and urinalysis data processed by the local laboratories will be summarized at each scheduled visit. Laboratory values, changes from baseline and percent changes from baseline in laboratory values will be summarized in SI units using descriptive statistics, by cohort and treatment group. Categorical urinalysis results will be summarized using frequency counts and percentages, by cohort and treatment group.

A summary of shifts based on NCI-CTCAE toxicity grading from baseline to worst post-baseline result (on-treatment, including follow-up) will be given separately for each cohort, treatment group and for each laboratory parameter, if applicable. Toxicity grading related to increased and decreased values will be analyzed separately for applicable laboratory parameters.

[redacted]

[redacted]







Data listings will be produced for all collected laboratory data. By-patient listings of laboratory results will be presented showing at least: laboratory parameters, visit, date and time of measurement, result, information if it is a baseline value, and change from baseline. Patients with values above or below the reference range (at primary endpoint evaluation, EOT and unscheduled visits), regardless of clinical significance, will be identified in the data listings with flags for high and low values. The normal reference ranges will be presented as well.

10.9.3 Vital Signs and Other Safety Parameters

10.9.3.1 VITAL SIGNS

Descriptive statistics of vital signs (temperature [°C], systolic and diastolic blood pressure (mmHg), heart rate (bpm) and respiratory rate (breaths/min) at each time point measured, as well as the change from baseline and percentage change from baseline will be presented by cohort and treatment group.

If needed, the temperature in "°F" will be converted to "°C" as follows:

T (°C) = (T (°F) - 32) / 1.8.

The number and percentage of patients with a post-baseline potentially clinically significant (PCS) vital signs result at any time post-baseline, including unscheduled post-baseline visits, will be summarized, by cohort and by treatment group. Percentages will be calculated based on the number of patients with both baseline and at least one post-baseline vital sign result for each parameter. PCS vital signs will be defined according to the *Table 10-4*.

Table 10-4 Potentially clinically significant Vital Signs.

Test	Criterion	Criterion value
Heart Rate	High	>120 bpm
		Increase from baseline of ≥30 bpm
	Low	<50 bpm
		Decrease from baseline of ≥30 bpm
Systolic Blood Pressure	High	≥180 mmHg
		Increase from baseline of ≥20 mmHg
	Low	<90 mmHg
		Decrease from baseline of ≥20 mmHg
Diastolic Blood Pressure	High	≥105 mmHg
		Increase from baseline of ≥15 mmHg
	Low	≤50 mmHg
		Decrease from baseline of ≥15 mmHg
Temperature	High	>38° C (100.4° F)
	Low	<36° C (95.5°F)

Data listings will be produced for all collected vital signs data. PCS vital sign values will be flagged as PL=PCS low value and PH=PCS high value.

All vital signs data will be presented in a by-patient listing. This listing will include at least: vital signs parameters, visit, date and time of measurement, scheduled time point, measurements/results, a flag for the measurement used as baseline value and the change from baseline values.

10.9.3.2 12-LEAD ECG

Only central readings will be summarized in the tables. For Part A and Part B, Cohort 1 ECG are to be collected on Day 1: pre-dose, 15 min, 5.5 h and 10 h post infusion; and on Day 28 (EOT): pre-dose and 5.5 h after study drug administration. For Part B, Cohort 2 and 3, ECG are to be collected on Day 1: pre-dose and 3.5 h post infusion; Day 28 (EOT): pre-dose and 5.5 h after study drug administration. All ECGs will be recorded in triplicate at intervals of 2 to 3 minutes between tracings. Descriptive statistics for mean ECG results for parameters: ventricular rate, PR interval, RR interval, QRS interval, QT interval, QTcB and QTcF Interval will be summarized at baseline and at each time point measured, and the change from baseline will be presented by cohort and treatment group.

In case one or two triplicated results are missing, the mean of remaining will be tabulated.

Frequency tables for ECG interpretation will be presented at baseline and at each visit by cohort and treatment group. Worst ECG interpretation per triplicate will be analyzed.

The overall post-baseline incidence of abnormal ECG results (averaged values, except from criterion '>500 msec on at least two separate ECGs', which will be calculated based on single

values from the same triplicate), which includes values from unscheduled post-baseline visits, will be summarized by cohort and treatment group for the Safety population, and all abnormal ECG values will be flagged in by-patient listings. Abnormal ECG values are defined according to the following categories (*Table 10-5*).

Table 10-5 Criteria for QTcF prolongation.

Test	Criteria
QTcF Interval	>450 – 470 millisecond (msec)
	>470 – 500 msec or ≥60 msec change from baseline
	>500 msec on at least two separate ECGs
	>30 msec change from baseline

Data listings will be produced for all collected ECG data along with the calculated mean results. PCS vital sign values will be flagged.

10.9.3.3 PHYSICAL EXAMINATION

Listing of physical examination findings will be provided by patient.

10.10 OTHER ENDPOINTS AND ANALYSIS

10.10.1 PHARMACOKINETICS

All PK related analyses will be provided by an external vendor under the responsibility of the Debiopharm PK scientist. Only tables and listings with concentrations will be provided. Endpoints are described here only for completeness reasons.

10.10.1.1 PART A

The concentrations of study drug (afabicin; Debio 1450) and the active moiety (afabicin desphosphono, Debio 1452) will be listed and summarized by route by nominal time point of collection, by cohort, overall and by gender in the PK population.

Summary statistics in the tabulation will include number of observation (n), arithmetic mean, standard deviation (SD), first quartile (Q1), third quartile (Q3), 95% CI of the arithmetic mean, percent coefficient of variation (CV%), median, minimum, maximum, geometric mean, 95% CI of the geometric mean, geometric SD [calculated as: geo SD= exp (SQRT (v))] and geometric CV% [calculated as: geometric coefficient of variation % =SQRT(exp(v)-1)*100%; where v is the squared standard deviation of the log-transformed values].

Concentrations that are below the limit of quantification (BLQ) will be handled as follows: Concentrations will be set to zero, except for the calculation of summary statistics that involve logarithmic transformations. These are the geometric mean, 95% CI of the geometric mean, geometric SD and geometric CV%. In this case concentrations will be set to half of the lower limit of quantification (LLQ). If <2/3 of concentrations that are the basis for the summary calculation are quantifiable then only the minimum (0) and the maximum concentration will be reported and all other descriptive statistics will be reported as “not calculated”.

In addition, a scatterplot will be created, showing each individual change from baseline for QTcF against afabicin desphosphono concentrations for matching time points in the PK Population.

PK parameters and PK/PD indices may be derived from Part A sparse sample data, by population PK analysis, described in a separate analysis plan and then reported separately in a dedicated report for population PK, PK/PD and exposure-response analyses, prepared by the Institute for Clinical Pharmacodynamics, Inc (ICPD).

10.10.1.2 PART B

The concentrations of afabicin and afabicin desphosphono will be listed by patient and summarized by route, by nominal time point of collection, by cohort, overall and by gender in the PK population.

Summary statistics in the tabulation will include: n, arithmetic mean, standard deviation (SD), first quartile (Q1), third quartile (Q3), 95% CI of the arithmetic mean, percent coefficient of variation (CV%), median, minimum, maximum, geometric mean, 95% CI of the geometric mean, geometric SD [calculated as: geo SD= exp (SQRT (v))] and geometric CV% [calculated as: geometric coefficient of variation % =SQRT(exp(v)-1)*100%; where v is the squared standard deviation of the log-transformed values].

Concentrations that are below the limit of quantification (BLQ) will be handled as follows: Concentrations will be set to zero, except for the calculation of summary statistics that involve logarithmic transformations. These are the geometric mean, 95% CI of the geometric mean, geometric SD and geometric CV%. In this case concentrations will be set to half of the lower limit of quantification (LLQ). If <2/3 of concentrations that are the basis for the summary calculation are quantifiable then only the minimum (0) and the maximum concentration will be reported and all other descriptive statistics will be reported as “not calculated”. For logarithmic transformed summaries (including geometric mean calculation), plasma levels below LLQ will be set to ½ LLQ.

In addition, a scatterplot will be created, showing each individual change from baseline for QTcF against afabicin desphosphono concentrations for matching time points by cohort and gender in the PK population.

Patients with an overdose at PK sampling, i.e. at Day 1 and Day 28 (or EOT if the treatment < 28 days) will be marked in the listing with PK concentrations. Overdose is defined as receiving dose 120% greater than planned at specific day. A sensitivity table for the summary statistics for PK concentrations will be created, excluding the overdosed patients.

Pharmacokinetic Parameter Calculation Methods

During the course of the study Part B, derivation of PK, PK/PD parameters and summary statistics will be the responsibility of Clinical Pharmacology and Drug Metabolism, Translational Medicine, Debiopharm and will be performed as described hereafter. Final PK, PK/PD and exposure-responses analysis will be performed by ICPD, as described in a separate analysis plan. The final

PK parameters will be derived by non-compartmental analysis or by population PK data analysis using a nonlinear mixed-effects modelling approach. The results will be reported separately.

Plasma concentration-time data (generated in afabicin treated patients only) for afabicin and afabicin desphosphono on Day 1, and for afabicin desphosphono on EOT/Day 28, will be used to calculate the PK parameters listed in Table 10-6.

Table 10-6 Plasma Pharmacokinetic Parameter

C_{max} [a]	maximum observed plasma concentration
$C_{max,ss}$	maximum observed plasma concentration at steady state
C_{last}	Last observed non-negative concentration
t_{max} [a]	time corresponding to the occurrence of C_{max}
t_{last}	Time of last non-negative observed concentration
AUC_{12h}	area under the plasma concentration-time curve from time zero to 12 hours post-dose
AUC_{last}	area under the plasma concentration-time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the plasma concentration-time curve from time zero extrapolated to infinity
$\%AUC_{extrap}$	percentage of AUC_{inf} that is due to extrapolation beyond t_{last}
$t_{1/2}$	terminal elimination half-life
λ_z	terminal elimination rate constant
CL/F'	apparent* clearance
V_z/F'	apparent* volume of distribution during terminal phase
MRT	mean residence time
AUC_{Tau}	area under the plasma concentration curve over the dosing interval
CL	total body clearance
V_z	volume of distribution during terminal phase
C_{trough}	trough (pre-dose and at the end of the dosing interval) plasma concentration
$C_{av,ss}$	average concentration at steady state
CL_{ss}/F'	apparent* clearance at steady state
V_{ss}/F'	apparent* volume of distribution at steady state
PTF	peak trough fluctuation
fAUC	free-afabicin desphosphono plasma AUC_{24h} calculated as $[2 \times AUC_{12h}]/50$ and $[2 \times AUC_{Tau}]/50$, for Day 1 and steady-state, respectively
*F defined as overall bioavailability times fraction converted into active drug in case of afabicin desphosphono for oral administration and as fraction converted into active drug in case of IV administration)	

PK parameters will be calculated by non-compartmental analysis methods using Phoenix® WinNonlin® (Version 8.3 or later [Certara, St. Louis, MO, USA]) following these guidelines:

- The PK population will be used for all PK analysis.
- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- There will be no imputation of missing data.
- All below the limit of quantification (BLQ) values pre-dose and in the absorption phase prior to the first quantifiable concentration will be substituted by zeroes. Thereafter BLQ values will be set missing except that BLQ values between evaluable concentrations will be set to half of the LLQ before the calculation of the PK variables.
- For afabicin desphosphono the administered dose to be used in the non-compartmental analysis will be calculated using the molecular weight (MW) of afabicin and afabicin desphosphono (485.4 and 375.4 g/mol for afabicin and afabicin desphosphono, respectively) as follows:
    - Dose afabicin desphosphono = (Dose afabicin × MW afabicin desphosphono) /

MW afabicin

PK parameters will be estimated according to the following guidelines:

- C_{max} and $C_{max,ss}$ will be obtained directly from the concentration-time data.
- t_{max} is the nominal time at which C_{max} or $C_{max,ss}$ is observed.
- λ_z will be estimated at terminal phase by linear regression after log-transformation of the concentrations:
    - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.
    - A minimum number of three data points in the terminal phase will be used in calculating λ_z with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope) and including C_{last}, t_{last}.
    - The time range over which linear regression is performed ($\lambda_p=(\lambda_{up}-\lambda_{low})/t_{1/2}$) should be >2 for the $t_{1/2}$ estimate to be considered reliable. Any $t_{1/2}$ values estimated over <2 x the $t_{1/2}$ will be flagged and listed only and not included in the summary statistics. This applies to all parameters derived using λ_z for that patient (e.g. AUC_{inf}, CL/F', V_z/F' and MRT).
    - The adjusted correlation coefficient (R^2 adjusted) in general should be greater than 0.90. Any value less than 0.90 may be used at the PK Scientist's best knowledge and judgment.
    - Any R^2 adjusted values less than 0.80 will be flagged and listed only and not included in the summary statistics and subsequent derived parameters (e.g. $t_{1/2}$, AUC_{inf}, CL/F', V_z/F' and MRT) will also be listed only.
- $t_{1/2}$ will be calculated as $\ln 2/\lambda_z$.
- AUC is calculated as follows:
    - The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations (linear up/log down).
    - $AUC_{last}=\int_0^t \mathbf{C(t)dt}$.
    - $AUC_{inf}=\int_0^t \mathbf{C(t)dt}+\int_t^\infty \mathbf{C(t)dt}$ = $AUC_{0\text{-}t}+C_t/\lambda_z$.
    - C_{last} is last observed quantifiable concentration.
- $\%AUC_{extrapol}$ will be calculated as $(1-[AUC_{last}/AUC_{inf}])\times 100$.
    - If the $\%AUC_{extrapol}$ is greater than 20% this will be flagged in the listings and discussed in the report
- CL and CL/F' will be calculated as $Dose/AUC_{inf}$
- CL_{ss}/F' will be calculated as $Dose/AUC_{tau}$
- V_z/F' will be calculated as CL/F'/λ_z
- V_{ss}/F' will be calculated as CL_{ss}/F'/λ_z
- MRT is calculated as $AUMC_{inf}/AUC_{inf}$
    - Where $AUMC_{inf}=\int_0^t t\cdot C(t)dt+\int_t^\infty t\cdot C(t)dt$ = $AUMC_{last}+t\cdot Ct/\lambda z+Ct/\lambda_z^2$.
- $C_{av,ss}$ will be calculated as AUC_{tau}/tau
- C_{trough} at steady state will be obtained directly from the concentration-time data as the pre-dose or last sample at the end of the dosing interval
- PTF will be calculated as $(C_{max,ss}-C_{trough})/C_{av,ss}$
    - where C_{trough} is the last sample in the dosing interval

The statistical analyses will also be performed using Phoenix® WinNonlin® Software Version 8.3 or later.

Graphical Presentation of Results

Individual profile plots of PK concentrations will be based on the PK population.

- Individual afabicin (Day 1), afabicin desphosphono (Day 1) and afabicin desphosphono (EOT/Day 28) plasma PK profile for each patient, using observed concentration (nanomolar (nM)) vs. actual time with concentrations on the original and semi- logarithmic (base 10) scale in each two-panel display.
- Spaghetti plot (all patients on the same graph) of individual afabicin (Day 1) plasma concentration (ng/mL) vs. actual time, with concentrations on the original and semi-logarithmic (base 10) scale in each two-panel display. Different symbols will be used for each cohort, and for different gender if applicable.
- Spaghetti plot (all patients on the same graph) of individual afabicin desphosphono (Day 1) plasma concentration (ng/mL) vs. actual time, with concentrations on the original and semi- logarithmic (base 10) scale in each two-panel display. Different symbols will be used for each cohort, and for different gender if applicable.
- Spaghetti plot (all patients on the same graph) of individual afabicin desphosphono (Day 28) plasma concentration (ng/mL) vs. actual time, with concentrations on the original and semi- logarithmic (base 10) scale in each two-panel display. Different symbols will be used for each cohort, and for different gender if applicable.
- Mean concentration (+/- SD) afabicin (Day 1), afabicin desphosphono (Day 1) and afabicin desphosphono (EOT/Day 28) plasma PK profile, using observed mean or geomean concentration (nM) vs. nominal time, on the original and semi- logarithmic (base 10) scale, respectively, in each two-panel display.
- Mean concentration (+/- SD) afabicin (Day 1) plasma PK profile, using observed mean or geomean concentration (ng/mL) vs. nominal time, on the original and semi- logarithmic (base 10) scale, respectively, in each two-panel display.
- Mean concentration (+/- SD) afabicin desphosphono (Day 1) plasma PK profile, using observed mean or geomean concentration (ng/mL) vs. nominal time, on the original and semi- logarithmic (base 10) scale, respectively, in each two-panel display.
- Mean concentration (+/- SD) afabicin desphosphono (EOT/Day 28) plasma PK profile, using observed mean or geomean concentration (ng/mL) vs. nominal time, on the original and semi- logarithmic (base 10) scale, respectively, in each two-panel display.
- Graphic displays of PK parameters overall vs cohort and/or gender may be presented on both linear and log10/linear scale as geometric means ± geometric standard deviations and as individual values. Different symbols will be used for each cohort or gender.

Additional displays may be added if necessary to the assessment of the exploratory PK endpoints.

For concentration profiles presented in figures:

1. In mean linear concentration-time profiles, all BLQ values are replaced with zero and the concentration mean (SD) will be equal to values reported in tables
2. In mean semi-log profiles plot the geometric mean as reported in summary tables.
3. Plot only those individual profiles that have at least one quantifiable concentration.
    a) In individual linear plots all BLQ are plotted at zero
    b) In individual semi-log plots, a BLQ concentration between 2 quantifiable

concentrations will plot at half of the LLQ and all other BLQ will be missing.

Patients with a wrong dose at PK sampling (e.g. 160mg instead of 55mg) may be excluded from the analysis.

Reporting

The PK, PK/PD results and summary statistics generated during the course of study Part B will be reported in a separate report.

11. INTERIM ANALYSIS

Part A

No interim analysis was planned in the study during Part A. [redacted] For that purpose, data on microbiological outcome and clinical response were to be analyzed and summarized, supportive listings, including microbiological outcome, clinical response, PFGE results, protocol deviations, clinical sign and symptoms, imaging results, CRP and WBC counts will be produced, as listed below as per mock Tables Listings Figures (TLFs) final version 1.0 from 05 December 2019:

- Table 14.2.1.2 Clinical Response - PP Population
- Table 14.2.5.2 Microbiological Outcome - PP Population
- Listing 16.2.2 Protocol Deviations - ITT Population
- Listing 16.2.6.1 Clinical Response - ITT Population
- Listing 16.2.6.2 Clinical Signs and Symptoms - ITT Population
- Listing 16.2.6.6 PFGE Results - ITT Population
- Listing 16.2.6.7 Imaging Results - ITT Population
- Listing 16.2.6.8 By-Patient Microbiological Outcome - mITT Population
- Listing 16.2.8.1 Laboratory data – Hematology - Safety Population (limited to White Blood Cells Counts)
- Listing 16.2.8.2 Laboratory data - Clinical Chemistry - Safety Population (limited to C-reactive Protein Results).

Final outputs for the ad-hoc interim analysis for Part A were produced on 12 March 2020.

Part B

No interim analysis is specified in the study protocol. However, during the study, the sponsor will decide - based on the IDMC [redacted] recommendation – whether to proceed or terminate the study

12. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

Section 4.1.2: The protocol contains a typo in the description of the conditions under which Cohort 3C will be started. The word 'initiated' is omitted in the protocol Section 6.1.2 due to being overlooked and added for more clarity in the SAP:

> *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 initiated, if recommended by* [redacted] *IDMC, and if necessary, by concerned health authorities.*

Section 4.3: The protocol Section 6.5 contains a typo in the expression "*The cohort will be stopped if 5 out of the first 9 evaluable patients are non-responders*" which should be should read as "'The cohort will be stopped if 5 out of the first 9 evaluable patients are responders" which corresponds to the numbers presented in table in the same section of the protocol. It is clarified in the SAP that the cohort will be stopped at the earliest if 4 out of the first 9 evaluable patients are non-responders

Section 6:

> Recruitment to Cohort 1B was initiated in January 2021 in the U.S. and Ukraine. However, clinical operations in Ukraine were halted since February 2022 due to the ongoing conflict with Russia. All enrolled patients but one, were enrolled in Ukraine. Discussions with U.S. investigators revealed that contribution from U.S. sites is unlikely to increase until initiation of Cohort 2B. Twenty-two patients were enrolled into cohort 1B. Eighteen patients were treated with afabicin and 4 with SOC. The safety and efficacy data from Cohort 1B was reviewed by [redacted] IDMC prior to submission to the health authority [redacted]. Although the actual number of randomized patients is slightly lower than the planned total of 24, the Sponsor considered that available results were sufficient to show that treatment of up to 3 weeks is well tolerated and efficacious. [redacted] agreed with the Sponsor's assessment and with the immediate initiation Cohort 2B. The Sponsor promptly shared this information with IDMC (written communication on 31 August 2022).

Section 7.3.3:

Biomarker exploratory analyses were defined as optionally in the protocol but deemed not necessary by the sponsor.

Section 7.3.5:

DDI assessment was done in part A (cohort 1) and in part B (cohort 1). The bioanalysis data for this investigation were also generated for Cohort 2B. All the bioanalysis results will be reported in an Appendix to the CSR by DPI and are not part of this SAP. The data analysis (interpretation) will not be performed, as new physiologically based pharmacokinetics data were generated in parallel to the study for these assessments and results are available. Consequently, the data analysis is not needed anymore.

Section 9:

Clarification: The mITT population does not include replaced patients. Protocol Section 7.3 states that patients will be replaced and the new patients will substitute for the withdrawn patients.

Therefore, a replaced patient cannot be in the mITT – he/she is substituted. The Section 7.3 also states that lack of efficacy (among other reasons) cannot be a reason for withdrawal. Therefore, there is no risk to introduce a positive bias in favor of afabicin. Replaced patients were not meant to be part of the mITT population.

Each major protocol deviation will not lead to exclusion of a patient from PP population. Protocol deviations which have a major effect on the analysis will be assessed during a data review meeting that will take place prior to the database lock, as detailed in the DRP.

Section 10.3: The baseline definition was modified to account for assessments made after randomization or treatment allocation for additional patients but before first dose of study drug, if there is no assessment made prior the randomization or treatment allocation for additional patients).

The baseline definition for ECG was modified, assessment performed on Day 1 pre-dose will be considered baseline.

Section 10.7.4: Concomitant procedures will only be listed, and not summarized per cohort and study drug.

13. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each output the protocol number and deliverable type will be presented. In the top right the company name and page number will be presented. In the next 3 lines, centre-adjusted the *table/listing number*, title and population information will be displayed. Footnotes will be placed under the main body at the bottom of the page. There should be one blank line between table content and the footnotes. The SAS program name and its location and creation date will appear bottom left. The source listing number or analysis data set name will appear on the bottom right corner of each output. The database cut-off date will appear just below the source listing.

Example:

```
Debio 1450-BJI-205                                          Debiopharm International SA
Final Analysis                                                              Page 1 of n

                                        Table 14.x.x
                                          Title 2
                                         Population
                                     Title 4 (optional)
XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Program: \xxx\xxx\Debio 1450-BJI-205_Table_14XXX.sas; Programmer ID: AB
Output: \\xxx\xxx\Debio 1450-BJI-205_Table_14XXX.rtf                    Source: Listing XXX/ADXX
Created DDMMMYYYY at HH:MM                              Database Cut-off date: DDMMMYYYY
```

Courier New 8-point font will be used for all tables and listings. Landscape layout will be used. Any date information in the listing will use the date9. format, for example, 25OCT2018.

Tables, figures and listings will be produced in:

- “rtf” format, each output in separate file,
- “rtf” format, all tables, figures and all listings in one file each,
- “pdf” format, all tables and all listings in one file each.

Percentages for categorical data summaries will be displayed with 1 decimal point (e.g. 51.4), except for 100% which will be presented with no decimals (i.e., 100).

Use of decimal places in descriptive statistics:

- Min, Max: same as the actual data,
- Mean, Geometric mean, Median, Q1, Q3, 95% CI: actual data + 1 decimal,
- Standard deviation (SD), geometric SD, CV% and geometric CV%: actual data + 2 decimals.

A maximum of 3 significant digits will be displayed.

All raw data will be presented to the original number of decimal places in the listings.

In case a table break across multiple pages, the heading rows should be repeated.

In case there are no data to present in a table, listing or figure, the file will still be created, containing only a short message to explain: e.g. the listing of SAEs will only show a message like ‘No SAEs in the study’ if there were no SAEs in the study.

For listings, if the answer to a question is “other”, “other” should be displayed and then what the other represents should be specified in parentheses in the cell.

14. LIST OF TABLES, LISTINGS AND FIGURES

Shells for unique tables, listings and figures are provided in a separate Mock-Up TLFs document.

15. REFERENCES

None.

16. APPENDIX I. SCHEDULE OF ASSESSMENTS

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]									

				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
	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
EFFICACY	Concomitant medications	X	X	X	X	X	X	X	X	X
EFFICACY	Clinical signs and symptoms of infection[g]	X	X		X		X		X	X
EFFICACY	Imaging *(at Investigator's discretion)*	X			X		X		X	X
EFFICACY	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; ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, ULN = Upper Limit of Normal

a: [redacted] 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 Protocol, Section 6.4.1).

c: For patients with septic arthritis, EOT is expected between D 22 and D 29 (i.e., 3-4 weeks of treatment); if EOT occurs prior to D 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 D 43 and D 85 (i.e., after 6-12 weeks of study treatment). The EOT visit should be scheduled within 24 hrs (±4hrs) of the last dose.
d: Blood samples drawn every 3 to 4 days during study treatment 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 min) and 5.5 hr (± 0.5 hr) 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 [redacted] while on study treatment..
At Day 28 visit (or at EOT [redacted] se and just before PK sampling at 5.5 hr (± 0.5 hr) 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 afabicin esphosphono 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 min), 3.5 hr (± 0.5 hr) and 5.5 hr (± 0.5 hr) 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 is shorter than 28 days): at pre-morning dose; then at 5.5 hr (± 0.5 hr) 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. For a subset of patients, intense PK sampling may be performed according to the time points listed in Protocol, Section 9.2.7.1. An additional blood sample may be collected during the study period in case of safety events see Protocol, 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.

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
Notes		*Screening (≤ 7 days)*	*Start of treatment*	*D3 or D4*		*Weekly*	*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]	*1-wks 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*
Visit windows				*Interval between visits: >2 d & ≤6d*	±1 d	*Weekly* ±1 d	+1d	±2d	±2d	±2d	±2 d	±2d	±2d	±7 d
BASELINE	ICF reviewed and signed	X												
BASELINE	Demographics, disease characteristics, medical history, prior medications	X												
BASELINE	Inclusion/exclusion criteria	X												
BASELINE	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*											
Treatment	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
SAFETY	Laboratory assessment (full panel)	X	X		X		X				X			X
SAFETY	Laboratory assessment (safety panel)[c]			X		X		X	X	X		X	X	
SAFETY	[redacted]													
SAFETY	12-ECG *(in triplicate[d])*	X	X		X at D28		X[d]							
SAFETY	Physical examination	X	X		X		X				X			X
SAFETY	Vital signs[f]	X	X		X		X				X			X
	Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X

				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
Notes		*Screening (≤ 7 days)*	*Start of treatment*	*D3 or D4*		*Weekly*	*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]	*1-wks 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*
Visit windows				*Interval between visits: >2 d & ≤6d*	±1 d	*Weekly* ±1 d	+1d	±2d	±2d	±2d	±2 d	±2d	±2d	±7 d
	Assessment of Pain	Daily during the treatment period						*X*	*X*	X	X	X	X	X
EFFICACY	Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
EFFICACY	Clinical signs and symptoms of infection[g]	X	X		X		X				X			X
EFFICACY	Imaging[j]	X												X
EFFICACY	Microbiological assessment [g]	X	*Whenever clinically indicated [g]*											
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 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; 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), 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.

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) 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 i).