MENARINI RICERCHE

DRESS

DELAFLOXACIN INTRAVENOUS AND ORAL MONOTHERAPY IN SURGICAL SITE INFECTIONS - DRESS Study

Statistical Analysis Plan

Version 1.0

Date: 02 SEP 2019

Study code	DELA-01
EudraCT-Number	2018-001082-17
Investigational Medicinal Product	Delafloxacin 300 mg powder for solution for IV infusion and 450 mg Oral Tablet
Development phase of study	III b
Sponsor	MENARINI RICERCHE S.p.A. Via Sette Santi, 1 50131 Florence, Italy
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LIST OF ABBREVIATIONS

ABSSSI	Acute Bacterial Skin And Skin Structure Infection/s
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area Under the plasma concentration time Curve
BMI	Body Mass Index
CA	Competent Authority
CDC	Centers for Disease Control and Prevention
CE	Clinically Evaluable
CI	Confidence Interval
cIAI	Complicated Intra-Abdominal Infection
CrCl	Creatinine Clearance
CLSI	Clinical and Laboratory Standards Institute
CNS	Central Nervous System
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C-reactive Protein
CS	Clinically Significant
CTM	Clinical Trial Medication
DNA	Deoxyribonucleic Acid
DRM	Data Review Meeting
DSUR	Drug Safety Update Report
EC	Ethics Committee
ECDC	European Centre for Disease Prevention and Control
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
EEA	European Economic Area
eGFR	Estimated Glomerular Filtration Rate
EEA	European Economic Area
EMA	European Medicines Agency
EOT	End Of Treatment
eTMF	Electronic Trial Master File
EU	European Union
FDA	Food and Drug Administration
FQ-NS	Fluoroquinolone Non Susceptible
FU	Follow Up

GCP	Good Clinical Practice
HR	Heart Rate
ICF	Informed Consent Form
ICSR	Individual Case Safety Report
ICH	International Conference of Harmonization
ID	Identification
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRLOS	(Hospital) Infection-Related Length of Stay
ITT	Intent-to-Treat
IV	Intravenous(ly)
IWRS	Interactive Web Response System
LFU	Late Follow Up
LL	Lower Limit
LOS	(Hospital) Length of Stay
ME	Microbiologically Evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MIC_{90}	The lowest MIC that inhibits 90% of the strains within a single species
MITT	Microbiologically Intent-to Treat
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NSAE	Non-Serious Adverse Event
OS	Oral(ly)
PMNs	Polymorphonuclear leukocytes
Pro-CT	Procalcitonin
PT	Preferred Term
PTE	Post-treatment Evaluation
QA	Quality Assurance
QoL	Quality of Life
QRDR	Quinolone Resistance Determining Region
RR	Respiratory Rate
RTC	Research Toxicology Centre
SAE	Serious Adverse Event
SDSM	Study Drug Safety Manager
SF-36v2	Short Form-36 version 2
SIRS	Systemic Inflammatory Response Syndrome

SIV	Site Initiation Visit
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SSI	Surgical Site Infection/s
TEAE	Treatment-Emergent Adverse Event
TDM	Therapeutic Drug Monitoring
TOC	Test Of Cure
UK	United Kingdom
US	United States of America
WBC	White Blood Cell

1 INTRODUCTION

The purpose of this document is to provide further details about the statistical analysis methods specified in study protocol for the Phase III-b study of IV / oral delafloxacin fixed-dose monotherapy in a microbiologically enriched population with surgical site infections.
The study is sponsored by Menarini Ricerche S.p.A. A brief description of the study objectives and study design are given in sections 2 and 3 respectively. Subsequent sections include the definition of analysis populations, efficacy and safety endpoints including details about statistical methods and hypotheses.

Delafloxacin was approved for treatment of adult patients with ABSSSI by the United States (US) Food and Drug Administration FDA on June 19, 2017. US Commercial distribution started in early 2018.

[redacted]

In this study, patients will receive delafloxacin 300mg IV or 450mg OS Q12h or the selected Reference Treatment which represent the best available therapy (BAT) for either cardiothoracic /related leg or abdominal SSI.

[redacted]

The Reference Treatments are already on the market for the treatment of ABSSSI since many years and their benefits are documented in published literature. In this study, they will be administered according to the relative Summary of Product Characteristics (SmPC).

Considering that this study aims to enroll a representative rate of difficult-to-treat population affected by a mixed bacterial flora and multiple comorbidities, posing them at an increased risk of adverse events and drug-drug interactions when treated with the standard of care, at least a comparable therapeutic benefit is expected for subjects who will be randomized to the delafloxacin arm versus the Reference Treatment arm. To note that the Investigator can choose the most adequate treatment between two pre-selected BAT for each type of infection; in addition the antimicrobial cover of the Reference Treatment can be also optimized by the addition of another antibiotic in case of suspected MRSA or Gram negative bacteria for abdominal or cardiothoracic SSI, respectively (the only exclusion is any quinolone). No additional therapy is requested for delafloxacin because of its wide antimicrobial cover.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To assess the comparability of delafloxacin and BAT in terms of Clinical Success in patients with superficial or deep incisional SSI following a cardiothoracic / related leg or abdominal surgical procedure.

2.2 SECONDARY OBJECTIVE

To assess the comparability of delafloxacin and BAT in patients with cardiothoracic / related leg or abdominal SSI, in terms of:

- Effectiveness, microbiological response [redacted]
- safety and tolerability

[redacted]

2.3 [redacted]

[redacted]

3 INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This is a randomized, observer-blinded, active-controlled, parallel-group, multicenter, phase IIIb study for the treatment of incisional, superficial or deep, cardiothoracic / related leg or abdominal SSI (i.e. an expected microbiologically enriched population with SSI), comparing IV/oral monotherapy delafloxacin with selected Reference treatments which represent the BAT for either cardiothoracic/ related leg or abdominal SSI. The study is intended to be conducted in approximately 70 sites in Europe. Eligible patients will be randomly assigned in a 1:1 ratio to receive Test or Reference treatment and stratified by site of infection (at least approximately 180 patients either for the cardiothoracic / related leg or abdominal SSI) and superficial / deep infections.

The Reference treatment arm includes two options for each SSI. The selection of one of the two allowed options for each SSI is upon Investigator's judgment based on the patient characteristics and the local epidemiological pattern and will be done prior to the Interactive Web Response System (IWRS) assignment of Test or Reference treatment.

A schematic design of study treatments and visits is provided in Figure 1 and Figure 2.

Approximately 750 male and female patients aged ≥ 18 years with diagnosis of SSI will be enrolled. Assuming that approximately 20% of screened patients will not fulfill the eligibility criteria, it is anticipated that about 750 patients will be screened to obtain 600 randomized patients. The overall clinical phase is expected to start in Q3 2019.
The enrolment of patients will be competitive; however, eligibility of patients with one out of the two types of SSI (cardiothoracic / related leg or abdominal surgical procedure) will end when overcoming the 70% of the overall study population. Additionally, approximately 20% - 30% of total sample size of patients is expected to be recruited altogether in Italy, Spain and/or UK.

Study participation of individual patients is based on the treatment duration (range: minimum 5 to maximum 14 days, as per Investigator's judgment) and will last at most 45 days.
The study will encompass up to 8 site visits (depending upon the individual duration of study treatment) and ends with the Late Follow Up (LFU) Visit which represents the End of Study Visit.
Patients will be hospitalized from Screening and will remain hospitalized as per Investigator's judgment. Patients can be discharged while are on treatment: a) if the patient is still on treatment with IV formulation, outpatient parenteral antimicrobial therapy at site could be implemented wherever allowed by local standard practice (patients will travel to site to receive drug administration as per treatment schedule); b) if the patient is switched to oral treatment, outpatients will return to the site for the study visits.

The clinical benefit of treatment is intended to be evaluated in terms of "Success" (cure or improved) according to the standard medical practice when making the decision of antibiotic termination and hospital discharge. The clinical response of 'Success" (cure or improved) is therefore the primary efficacy endpoint to be assessed at TOC Visit in accordance with the EU specific requirements1 for ABSSSI.
Testing of non-inferiority of delafloxacin vs BAT is also in compliance with current international guidelines[6] for the development of antibiotics. In particular, non-inferiority is considered appropriate for ABSSSI in light of the high medical need of new antibiotics addressing Multi Drug Resistance pathogens.

Clinical and microbiological standard parameters will be assessed to test comparability of delafloxacin versus Reference treatment(s) in terms of efficacy and safety. Additional assessments will include: Quality of Life (QoL) by Short Form-36 (SF-36v2) Health Survey, eligibility of patients to switch to oral formulation and/or to hospital discharge (IRLOS), and actual hospital discharge (LOS).
No interim analysis is planned.

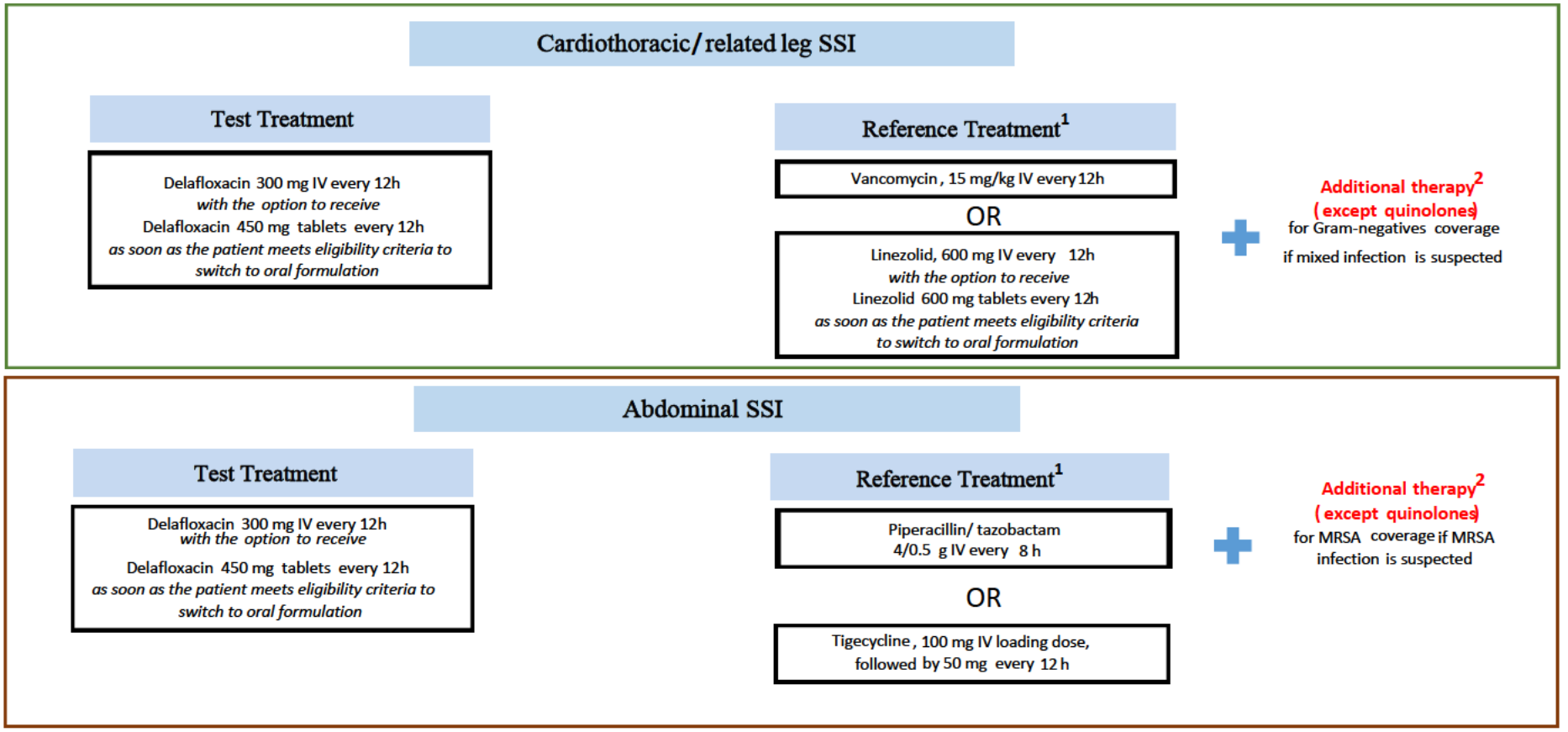
An observer-blinded, randomized design was selected in order to increase the objectivity in the clinical assessments and to minimize the intentional or unintentional Investigator's bias with respect to the assigned treatment. For this reason at each study site an unblinded Principal Investigator (referred to as

"Investigator") and a blinded observer will be designated. The responsibilities of each role are described below:

Investigator: The Principal Investigator or his/her delegates and site staff are unblinded and manage all study procedures except the assessment of patient's eligibility to switch from IV to oral formulation and eligibility to hospital discharge relevant to IRLOS. The Investigator and designee are responsible for ensuring that patient will receive study treatment as per IWRS assignment (i.e. Test or Reference). Prior to Randomization, based on the patient characteristics and the local epidemiological pattern, the Investigator records which treatment (among the allowed pre-selected BAT) he/she would select in case the IWRS actually allocates the patient to the Reference treatment.
Study staff will provide the blinded observer with data relevant to define the eligibility of the patients to IV/PO switch and hospital discharge for IRLOS assessment.

Blinded observer: This role will be assigned by PI to a physician who will be responsible for the assessment of parameters relevant for defining the patient as eligible to IV/PO switch of therapy and dischargeable from the hospital (IRLOS assessment).
In his role, the blinded observer will never have to be informed about the actual patient allocation to Test or Reference treatment arm and about the additional therapy, if any.
To ensure the blinding, the observer will not be permitted to see in any way the study medications being dispensed to the patient, as well as actual prescription logs and study medications will never have to be discussed in presence of the blinded observer. Whenever possible, the same blinded observer should complete all the assessments for the patient, every day approximately at the same time, and within 12:00.

Figure 1: Schematic Study Treatment(s) and Visit schedule



[1]As per Investigator's choice, to be documented prior to Randomization.
[2] As per Investigator's choice, prior to Randomization, additional therapy (selected by the Investigator as per local SoC) might be added to the Reference treatment in order to expand the coverage. Additional therapy has to be prolonged/discontinued based on microbiological results.

Figure 2: Schematic Study Outline

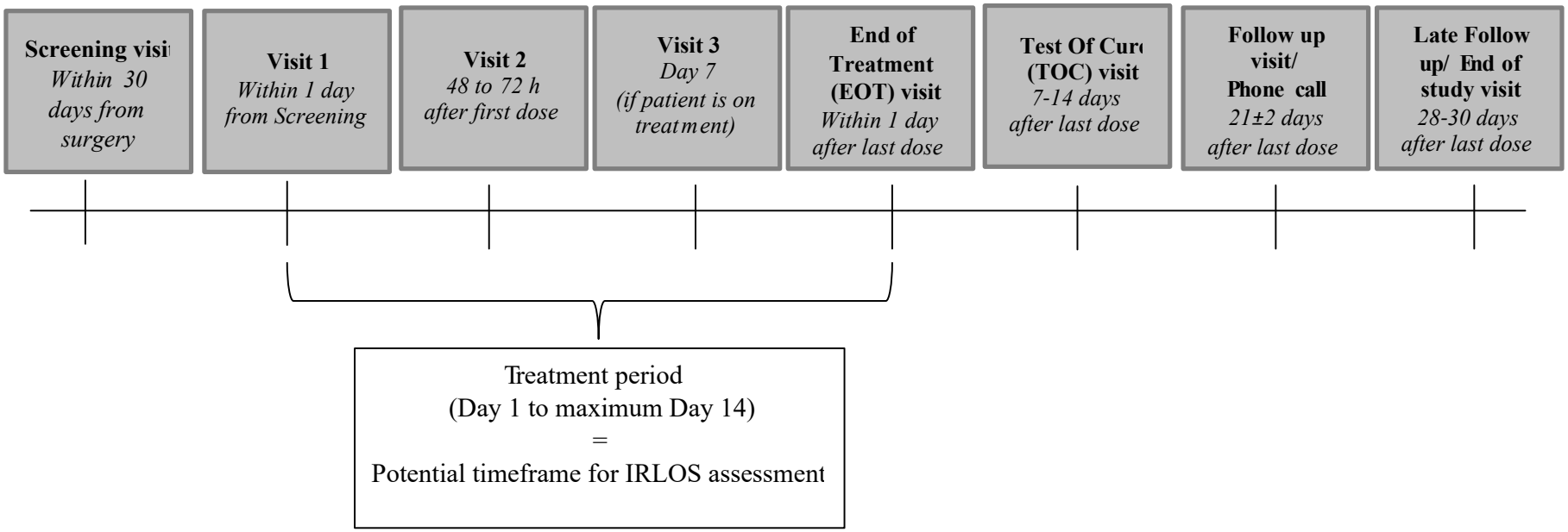


Table 1: Study flow-chart

	Treatment period[a]							
	Screening (within 30 days from surgery)	**Visit 1** (Day 1; within 1 day from Screening)	**Visit 2** (Day 3 - 4; 48 to 72h after first dose)	**Visit 3** (Day 7, if patient is on treatment)	**EOT Visit** (within 1 day after last dose)	**TOC Visit** (7-14 days after last dose)	**FU Visit or ☎** (21 ± 2 days after last dose)	**LFU/End of Study Visit** (28-30 days after last dose)
Informed consent	X[b]							
Incl / Excl criteria	X	X[c]						
Hospitalization[d]	X →							
Demographic data / Medical history	X							
Randomization		X						
IMP dispensing[e]		X →						
Prior and/or Concomitant medications	X →							
Physical examination[f]	X				X			
Pregnancy test[g]	X				X			
Vital signs[h]	X	X[c]	X	X	X	X		
12-lead ECG	X				X	X		
TDM for Vancomycin[i], if appropriate				X				
Haematology[j]	X		X	X	X	X		
Biochemistry[k]	X		X	X	X	X		
Coagulation test	X		X	X	X			
Virology (and HbA1c for diabetics only)	X							
[redacted]	X		X	X	X			
Urinalysis	X		X	X	X	X		
Infection site assessment	X	X[c]	X	X	X	X		X
Eligibility to discharge assessment (IRLOS)[l]		Day 2 →						
Eligibility to switch to oral formulation assessment[m]		Day 2 →						
Recording of SSI wound care management[n]	X	X[c]	X	X	X	X		X
Microbiological culture of infection site	X	X[c,o]	X[o]	X[o]	X	X		
Blood culture	X	X[c,p]	X[p]	X[p]	X[p]	X[p]		
Study drug administration[q]		X →						
Clinical Events/AE recording[r]	X	X						
AEs recordings		X →						
SF-36v2 Health Survey QoL[t]		X		X	X	X		X

	Treatment period[a]							
	Screening (within 30 days from surgery)	**Visit 1** (Day 1; within 1 day from Screening)	**Visit 2** (Day 3 - 4; 48 to 72h after first dose)	**Visit 3** (Day 7, if patient is on treatment)	**EOT Visit** (within 1 day after last dose)	**TOC Visit** (7-14 days after last dose)	**FU Visit or ☎** (21 ± 2 days after last dose)	**LFU/End of Study Visit** (28-30 days after last dose)
Clinical Response					X	X		X
End of Treatment Notification in IWRS					X			

a. Treatment period includes both IV and OS (if applicable) treatment duration.

b. Informed Consent can be administered prior to Screening.

c. If Visit 1 falls on the same day of Screening, this procedure has not to be repeated.

d. If not yet hospitalized, patients will be hospitalized upon successful completion of the Screening; duration of hospitalization (LOS) is per Investigator's judgment.

e. IMP is dispensed by unblinded staff, as per IWRS, at randomization, for kit re-supply (note: each kit covers 5 treatment days) and for switch to oral formulation. Upon hospital discharge, patients with oral delafloxacin or linezolid shall receive IMP together with a paper diary for daily recording of tablet intake.

f. Height and weight will be collected only at Screening Visit.

g. At Screening both urine dipstick and serum (or plasma) pregnancy test. At EOT Visit only serum (or plasma) pregnancy test.

h. Starting from Day 2 up to EOT, Systolic BP, HR, and Body Temperature to be performed daily until patient is considered eligible to switch to oral formulation / to be discharged by the blinded observer.

i. Therapeutic drug monitoring for vancomycin to be performed after 3 doses of vancomycin (steady state), at Visit 3, and when clinically indicated.

j. Starting from Day 2 up to EOT, WBC count to be performed daily until blinded observer considered the patient eligible for IV to PO switch and eligible for hospital discharge.

k. CrCl will be calculated at Screening and when needed for dose adjustment. After EOT Visit, chloride, bicarbonate, magnesium, blood urea nitrogen or urea, creatine phosphokinase, total protein, alkaline phosphatase, and uric acid will be no longer assessed, unless previous significant results to be monitored.

l. Eligibility assessed by the blinded observer (in the morning, within 12:00), based on Systolic BP, HR, T, WBC count and wound status.

m. Eligibility assessed by the blinded observer (in the morning, within 12:00), based on Systolic BP, HR, T, WBC count and ability to tolerate PO diet/no GI absorption problems.

n. Including wound dressing changes, at the visit or whenever occurred since the previous study visit.

o. If clinically indicated. In case of treatment withdrawal for any reason, the infection site specimen for microbiological culture should be collected before initiation of any alternative antibacterial therapy.

p. Blood culture to be repeated if the previous culture is positive and when clinically indicated.

q. Drug administration is under unblinded site staff responsibilities, and never disclosed to the blinded observer.

r. Clinical events (not associated with drug intake) /AE associated with any drug taken prior to IMP administration since the ICF signature.

s. Recording and follow-up of AEs after first IMP administration to the LFU /End of Study Visit.

t. Questionnaire should be completed prior to any other study visit procedure.

3.2 EFFICACY AND SAFETY ASSESSMENT

3.2.1 Efficacy Assessment

3.2.1.1 Infection Site Assessment

Signs and symptoms of SSI will be assessed at each visit by the Investigator who will record the following:

- Anatomical site of infection and classification of superficial or deep SSI (at Screening only)
- Presence/absence of:
  - drainage / discharge
  - fluctuance
  - heat / localized warmth;
  - swelling / induration;
  - pain / tenderness;
  - erythema/extension of redness (and maximum extension from the wound edge)
  - lymphangitis
  - lymphadenopathy (with number and anatomical site of lymph nodes)

Additionally only at screening visit the following information will be also collected:

- Longest head-to-toe length of erythema/redness
- Longest perpendicular width of erythema/redness
- Longest head-to-toe length of the wound
- Longest perpendicular width of the wound
- Area of the erythema/redness (directly derived as the difference between the area of erythema/redness and the area of wound)
- Presence/absence of abscess

3.2.1.2 Clinical response

Clinical response will be based on the Investigator's assessment of the patient's signs and symptoms of infection at the EOT, TOC, and Late Follow-up Visits and classified as Cure, Improved, Failure or Indeterminate defined as follows:

- **Cure:** The complete resolution of all baseline signs and symptoms of SSI
- **Improved:** two or more signs and/or symptoms (but not all) were considered resolved thus the patient has improved to an extent that no additional antibiotic treatment is necessary.
  NOTE: Clinical **Success** is defined as Cure or Improved.

- **Failure:** Response will be classified as failure if
  - any administration of antibacterial therapy for SSI is required because of lack of efficacy after at least 2 days (i.e. 4 or 6 doses, based on daily posology scheme) of study treatment (delafloxacin or Reference treatment with or without additional therapy) as defined prior to and confirmed at Randomization by the Investigator, OR
  - the patient would have been in need to continue study treatment for more than 14 days OR
  - the need for unplanned major surgical intervention on SSI after Randomization OR
  - antibiotic therapy is required to treat *P. aeruginosa* (ONLY for tigecycline treated patients)

  NOTE: If clinical response is considered as Failure at a visit, then it will be considered Failure at any subsequent visit.

- **Missing**: A missing response will be considered a Failure for the analyses on the ITT population and the patient will be excluded from the CE population.
- **Indeterminate:** A response cannot be assigned because an assessment was not completed at the respective visits or because the patient received potentially effective non-study antibacterial drug therapy for treatment of a condition other than SSI. An indeterminate response will be considered a Failure for the analyses on the ITT population and the patient will be excluded from the CE population.

3.2.1.3 Microbiological Assessment

3.2.1.3.1 SSI specimen

SSI specimen must be obtained from all patients at Screening to identify the causative pathogen, and repeated at EOT and TOC Visits and whenever it is clinically indicated. In addition, SSI specimen should be obtained before initiation of any alternative antibacterial therapy.
The specimen may be obtained by biopsy, needle aspiration, surgical sterile techniques including aspiration of purulent material from an abscess. Swabs will not be accepted as a mean for specimen collection; however, the use of a sterile swab deep inside the cavity of a post-incision and drainage wound to absorb drainage is allowed.
The method used to obtain the specimen and the specific anatomical site (e.g. chest, abdomen, leg) will be documented in the patient's source records and in the eCRF.

SSI specimen(s) (up to 3 specimens/visit) shall provide adequate aliquots for all microbiological analyses, i.e. bacterial culture, bacterial morphology and polymorphonuclear leucocites (PMNs) assessment.
Specimen(s) will be collected and shipped from the study site to the Local/Regional laboratory for Gram stain and culture using adequate materials, timing, and shipping conditions which ensure specimen integrity and viability.

Specific instructions for collection, handling and shipping of specimens will be provided in the Laboratory manual.

Gram stain: Four Gram stain slides of the specimen will be prepared by the Local/Regional laboratories for PMNs (n= 2 slides) and bacterial morphology assessments (n=2). One slide/each assessment will be stained and read at Local/Regional laboratory; the Local/Regional laboratory will then send all 4 slides (stained and unstained) to Central laboratory to confirm results.
An additional Gram stain slide may be retained by the Local/Regional microbiology laboratory until the conclusion of the study, if required by local regulations.

Culture: Bacterial culture and antimicrobial susceptibility testing will be performed at Local/Regional laboratory, as applicable, following local practice.
All isolates, including the ones considered contaminants, will be forwarded to the Centralized laboratory for confirmation of identity and antimicrobial susceptibility testing and any further phenotypic or molecular characterization (please refer to laboratory manual for details).
Local/Regional laboratory will send the primary samples (under ambient condition) and two back-up samples (frozen) of the isolate(s) to the Centralized laboratory. Samples will be stored until one year after the end of the clinical trial.

In vitro susceptibility: Susceptibility of target pathogens to delafloxacin and Reference treatments will be determined at the Central laboratory according to CLSI and EUCAST guidelines for broth and agar dilution. Susceptibility to additional antibiotics may also be evaluated. The results will be also released according to the EUCAST official clinical breakpoints for delafloxacin, when available.

3.2.1.3.2 Blood Culture

A minimum of two sets of blood cultures will be collected from different anatomical sites from all patients at Screening, with each set including both an aerobic and an anaerobic bottle. In case of positive results in at least one bottle, an alert will be sent to the Investigator and other two sets of bottle will be collected immediately following the same procedure defined for Screening.
Isolates will be forwarded to the Centralized microbiology laboratory for confirmation of identity, antimicrobial susceptibility testing, and any further molecular or phenotypic characterization. For each organism isolated and identified at Local/Regional laboratory, the primary samples (under ambient condition) and two back-up samples (frozen) will be sent to the Centralized laboratory.
Additional blood samples will be collected for culture at subsequent visits if the previous culture is positive and whenever it is clinically indicated following the same procedure defined for Screening.
Samples will be stored until one year after the end of the clinical trial. Specific handling and shipping instructions that will maintain viability of all organisms will be provided in the laboratory manual.

3.2.1.4 Microbiological Response

Microbiological response will be generated at the EOT and TOC assessments at both pathogen and patient levels on the basis of the results of the infection site specimen and blood culture at baseline and follow-up and susceptibility testing performed at the microbiological Centralized laboratory.
Data regarding all baseline and post baseline organisms isolated at the Centralized laboratory from the infection site and blood will be evaluated by blinded external expert, who will review and identify which organisms are causative pathogens of SSI, and will assign the correspondent microbiological response for each causative pathogen among the definitions listed below:

- **Documented eradicated**: The baseline pathogen is absent in the specimen collected at the relevant timepoint.
- **Documented persisted**: The baseline pathogen is present in the specimen collected at the relevant timepoint.
- **Not evaluable**: it is not feasible to assess the microbiological response (e.g. there is no material available for specimen)
- **New pathogen**: a pathogen known to cause SSI different from the baseline causative pathogen is detected in the specimen.

When it is not feasible to assess the microbiological response, Sponsor will assign one of the following options based on the Investigator's assessment of clinical response:

- **Presumed eradicated**: The patient has a "not evaluable" microbiological response and a clinical response of "success" at the relevant timepoint.
- **Presumed persisted**: The patient has a "not evaluable" microbiological response and a clinical response of "failure" at the relevant timepoint.
- **Indeterminate**: The patient has a "not evaluable" microbiological response and a clinical response of "indeterminate" at the relevant timepoint.

In addition, emergent infections will be separately classified as per the definitions below when a microbiological sample taken post-baseline through the TOC is positive for "new" pathogen(s).
Emergent Infections:

- **Superinfection**: A new pathogen known to cause SSI is cultured from the original site of infection during treatment with a clinical response of "failure".
- **New infection**: A new pathogen known to cause SSI is cultured from the original site of infection after end of treatment with a clinical response of "failure".

3.2.1.5 Switch from IV to PO treatment and Hospital discharge

Starting from Day 2 up to maximum the End Of Treatment, the blinded observer will review DAILY if laboratory and clinical parameters meet all the criteria listed below for considering the patient:

- eligible to switch from IV to the oral formulation (relevant for the assessment of theoretical vs actual duration of IV treatment): all criteria 1 to 5 must be satisfied
- eligible to be discharged (relevant for the assessment of the hospital Infection-Related Length Of Stay-IRLOS vs actual hospital Length Of Stay-LOS): all criteria 1 to 4 and criterion 6 must be satisfied

1)	Systolic blood pressure normal/not clinically significant abnormal
2)	No infection related tachycardia
3)	Afebrile status; body temperature <38°C for at least 24 hours*
4)	WBC count normalized/not clinically significant abnormal
5)	Patient able to tolerate PO diet/to take PO treatment and no GI absorption problem
6)	Wound status idoneous for home care management

*maximum T° recorded from the last 24h

Whenever possible, the same blinded observer should review the lab/clinical parameters and complete the assessments for the patient, every day approximately at the same time, and within 12:00, with WBC results made available on time for the assessment.

Upon the observed blinded assessment is completed, the Investigator has the duty to record:

- date and time of the actual switch to oral formulation (i.e. first intake of the oral formulation)
- date and time of the actual discharge (i.e. when the letter of hospital discharge is issued)
  NOTE: at the time of actual discharge, if the patient is on treatment with
  a) IV formulation and outpatient parenteral antimicrobial therapy at site could be implemented as allowed by local standard practice, he/she will travel to site to receive drug administration as per treatment schedule;
  b) oral formulation (i.e. delafloxacin or linezolid), he/she will be provided with the IMP box (covering maximum 5 days of treatment) and a paper diary to record daily the tablets intake.

In case eligibility will not translate into actual IV to PO switch and/or actual hospital discharge, the Investigator has the duty to record:

- reasons which don't allow the actual switch to oral formulation
- reasons which don't allow the actual hospital discharge of the patient (e.g., need for IV treatment, comorbidities, social issue).
  NOTE: reason shall not be recorded if the actual hospital discharge occurs within 12 hours from eligibility to be discharged.

In the event that Investigator discharges the patient prior he /she met the IRLOS criteria, the Investigator has the duty to fully justify the reason.

3.2.1.6 [redacted]

[redacted]

3.2.1.7 [redacted]

[redacted]

3.2.2 Safety Assessments

3.2.2.1 Demographic data and Medical History

Demographic data and medical history are recorded at Screening. Demographic data include age, sex, race and ethnicity. Medical history includes clinically significant medical illnesses or underlying / accompanying diseases existing 2 years prior to or on entry to the trial as well as the type of surgical intervention the patient underwent and as a result of which the infection has been diagnosed. Data related to the SSI (see §3.2.1.1) should be recorded on the Infection Site Assessment pages of the eCRF.

3.2.2.2 Physical Examinations and Vital signs

A complete physical examination will be performed at Screening and at the EOT Visit. Measurement of height (in whole centimeters) and weight (in kilograms to one decimal place) will be performed at Screening only.

Vital signs, i.e. systolic and diastolic-BP (mmHg), HR (beats / minute, assessed by ECG if needed), RR (breaths / minute), and body T by tympanic digital thermometer (°C) will be measured at Screening, at Visit 1 (prior to any study treatment intake), and at each following visit till TOC. Vital signs (except RR) will be also recorded daily for blinded observer review until patient is considered eligible to switch to oral formulation and to hospital discharge, and up to maximum End Of Treatment. The highest body

temperature recorded for the specific visit or on 24-hour basis will be reported in the eCRF. Any use of antipyretic or analgesic should be recorded.

3.2.2.3 Clinical Laboratory Evaluation

Safety laboratory testing will be performed by a local laboratory at the timepoints specified in the Study Flow Chart (§0). Tests to be performed are as follows:

Haematology: A haematology panel test will be taken at Screening, Visit 2, Visit 3 (if performed), EOT and TOC Visits to include complete blood count with haematocrit, haemoglobin, platelet count, red blood cell count, mean corpuscular volume, and WBC count with differential (neutrophil, bands, lymphocyte, monocyte, eosinophil and basophil counts, absolute and %). At Screening glycated haemoglobin will be measured only in patients with medical history of diabetes. WBC count will be repeated daily until in the normal range or abnormal but not clinically significant for blinded observer review until patient is considered eligible to switch to oral formulation and to hospital discharge, and up to maximum EOT.

Biochemistry: A complete serum chemistry panel will be taken at Screening, Visit 2, Visit 3 (if performed), EOT and TOC Visits to include sodium, potassium, chloride, bicarbonate (or alternatively total CO_2 concentration obtained through venous blood gas test), magnesium, calcium, phosphorus, blood urea nitrogen or urea, creatinine, creatine phosphokinase, albumin, glucose, total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, uric acid and total and direct bilirubin. After EOT Visit, chloride, bicarbonate, magnesium, blood urea nitrogen or urea, creatine phosphokinase, total protein, alkaline phosphatase, and uric acid will be no longer assessed, unless previous significant results to be monitored.
CrCl will be calculated at Screening and at any time is clinically indicated for treatment dose modification by the Cockcroft-Gault formula.

Virology: Hepatitis B virus surface antigen and Hepatitis C virus antibody will be tested only at Screening and will not be exclusionary.

Coagulation tests: Prothrombin time/activity, international normalized ratio (INR) will be measured at Screening, Visit 2, Visit 3 (if performed) and EOT Visit.

Urinalysis: Urine analysis, i.e. specific gravity, pH, leucocytes, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, blood (erythrocytes / haemoglobin) will be performed at Screening, Visit 2, Visit 3 (if performed), EOT and TOC Visits as per standard practice at the site. Alternatively, a Roche-Combur dipstick will be provided to the site and same parameters analyzed. An overall clinical judgment will be recorded in eCRF.

3.2.2.4 Pregnancy test

At Screening, the pregnancy test will be performed in women of childbearing potential by commercial dipstick to obtain result in timely manner. A serum or plasma pregnancy test will be performed at Screening (to confirm the dipstick result), and at EOT Visit.

3.2.2.5 12-Lead ECG

Standard 12-lead ECG will be performed at Screening, at EOT and TOC Visits as summarized in the study flowchart (§0), and whenever clinically indicated.
12-lead ECG will be recorded after the patient has been in a supine position and at rest for at least 3 minutes. 12-lead ECGs will be performed, using standard equipment available at the study sites.
All ECG print-outs should be identified with patient number, as well as with the date and time of recording. The ECG tracings should be collected and retained with the source documents for study monitoring.

4 STATISTICAL METHODS

4.1 DATA QUALITY ASSURANCE

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Menarini Ricerche procedures.

4.2 GENERAL PRESENTATION CONSIDERATIONS

'Baseline' is defined as the last available non-missing pre-treatment assessment (including unscheduled measurements if available and appropriate), unless otherwise specified.
'End of Study' is defined as having completed the EOS visit.
'Duration of Treatment' will be calculated relative to the date and time of randomization:

Duration of Treatment (h) = Last Treatment Date/Time - Randomization Date/Time.

The same formula is also applied for the calculation of IV and Oral treatment.

The Screening Visit will be performed within 30 days after the surgical intervention. Patients may be inpatients or outpatients at the time of Screening. Outpatients successfully completing the Screening will be hospitalized.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean,

median, lower quartile and upper quartiles (if required) will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place and will be calculated using n as the denominator unless otherwise specified.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

All report outputs will be produced using SAS® version 9.3 or a later version in a secure and validated environment.

4.3 ANALYSIS POPULATIONS

The following analysis population will be considered:

ITT population: all randomized and treated subjects analyzed according to the randomized treatment arm (Test or Reference).

MITT population: all subjects in the ITT population who have at baseline bacterial pathogen(s) identified, that is known to cause cardiothoracic / related leg and/or abdominal SSI.

CE population: Six CE analysis set based on type and/or timing of the assessment are defined. All subjects in the ITT population who meet the following criteria will be include in the relative CE:

- All CE population:
  - Diagnosis of cardiothoracic or abdominal SSI
  - Received the correct treatment based on the Randomization assignment
  - Received 80% of the expected doses of study drug in the treatment period
- CE at EOT (CEEOT) for clinical response:
  - Did not receive any concomitant, systemic antibacterial therapy except for lack of efficacy prior to EOT
  - Had no protocol deviations prior EOT that would affect clinical response assessment at EOT
- CE at TOC (CETOC) for clinical response:

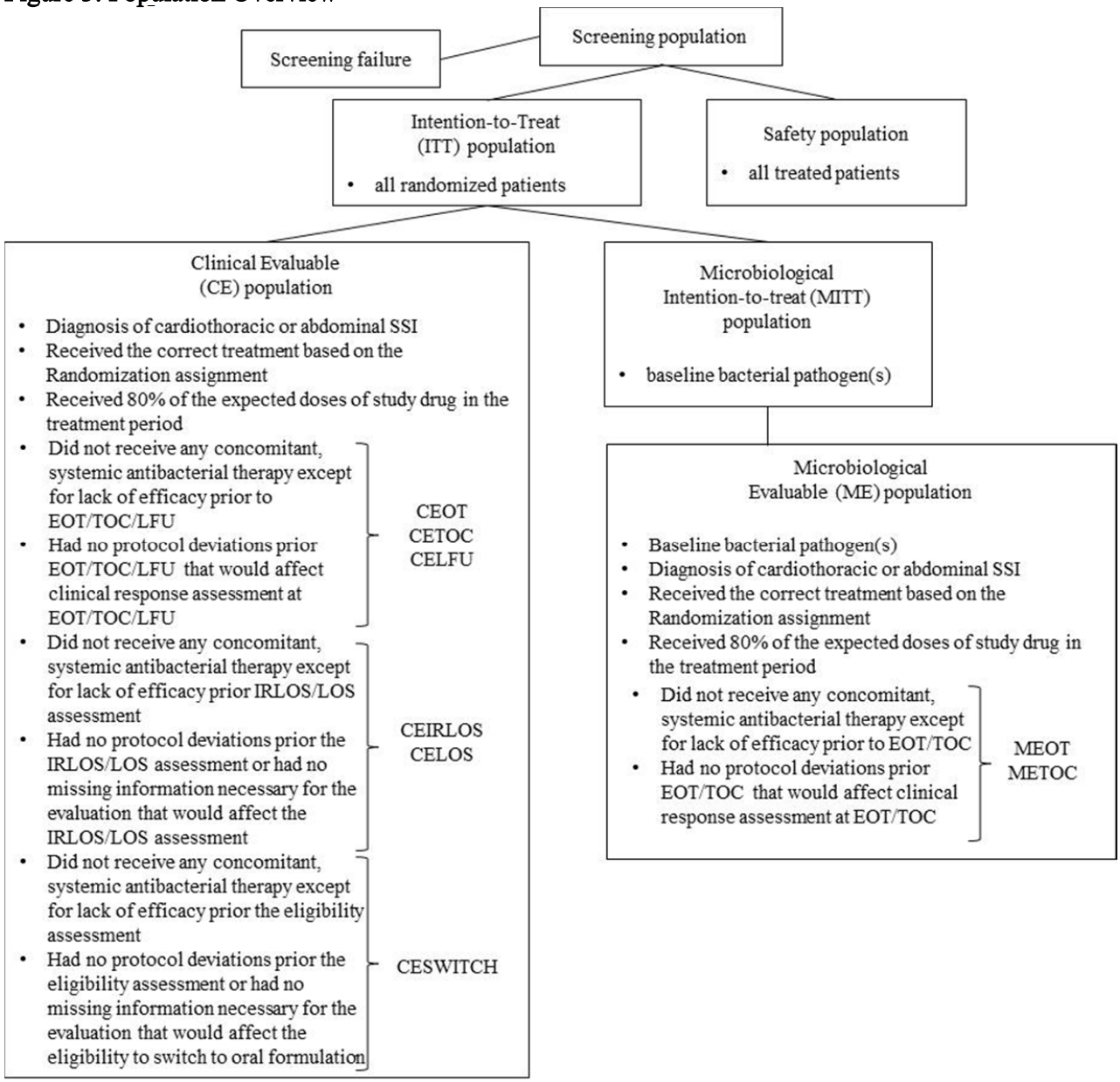
  - Did not receive any concomitant, systemic antibacterial therapy except for lack of efficacy prior to TOC
  - Had no protocol deviations prior EOT that would affect clinical response assessment at TOC
- CE at LFU (CELFU) for clinical response:
  - Did not receive any concomitant, systemic antibacterial therapy except for lack of efficacy prior to LFU
  - Had no protocol deviations prior EOT that would affect clinical response assessment at LFU
- CE for eligibility to switch to oral formulation (CESWITCH):
  - Did not receive any concomitant, systemic antibacterial therapy except for lack of efficacy prior the eligibility assessment
  - Had no protocol deviations prior the eligibility assessment or had no missing information necessary for the evaluation that would affect the eligibility to switch to oral formulation.
- CE for IRLOS (CEIRLOS):
  - Did not receive any concomitant, systemic antibacterial therapy except for lack of efficacy prior IRLOS assessment
  - Had no protocol deviations prior the IRLOS assessment or had no missing information necessary for the evaluation that would affect the IRLOS assessment.
- CE for LOS (CELOS):
  - Did not receive any concomitant, systemic antibacterial therapy except for lack of efficacy prior LOS assessment
  - Had no protocol deviations prior the LOS assessment or had no missing information necessary for the evaluation that would affect the LOS assessment.

ME population: all subjects in the MITT population who also meet the criteria for the CE population. ME populations will be defined at EOT and TOC.

Safety population: all subjects who have received at least one dose of study medication.

A schematic overview of study population is presented in Figure 3 below:

Figure 3: Population Overview



4.4 STUDY PATIENTS

4.4.1 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion.

Participation in the study is strictly voluntary and patients have the right to withdraw from the study at any time without explanation. This will not affect their rights for future medical care. Patients may also be withdrawn at the Investigator's discretion or at specific Sponsor's request at any time.

Treatment or Study Withdrawal: In the event that the patient withdraws from the treatment or from the study for whatever reason, the Investigator must be informed immediately and the date, reasons, and circumstances for premature discontinuation will be recorded in the corresponding section of the eCRF. Patients have to prematurely discontinue the treatment/study if:

- in the opinion of the Investigator, it is not in the best interest of the patient to continue treatment or study;
- there is a change in compliance with an inclusion or exclusion criterion that is clinically relevant or affects patient safety;
- protocol violation (e.g. prohibited medication, poor compliance with study procedures / treatment, need for a major surgical procedure);
- patient's request.

Any patient, who prematurely terminates the treatment/study after having received the study treatment will be encouraged to complete the assessments scheduled at the EOT Visit at the time of withdrawal and a final LFU Visit, if applicable.

Consent Withdrawal: Patients who withdraw consent will always be asked about the reason(s) and the presence of any AEs: no additional data should be collected since the time of withdrawal. Data already collected will be used and analyzed for the purpose of the study. In regard to biological samples already collected, the patient will be asked if samples already obtained but not yet analyzed shall be destroyed or analyzed.

Lack of Efficacy / Treatment Related AE: In the event patient interrupts prematurely the study treatment for lack of efficacy (including the need for non-study antimicrobial agents such as antifungals) or due to a treatment related AE which request treatment discontinuation, the patient will undergo EOT Visit at the time of withdrawal and, then, any other study visit as per protocol till LFU Visit.
At the time of and after treatment discontinuation the following shall be collected, whenever applicable (maximum up to LFU Visit):

- Reason for discontinuation
- Description of AE
- Second line antibiotic therapy
  NOTE: the specimens for microbiological cultures should be collected before initiation of any alternative antibacterial therapy.
- Hospital ward unit(s) where patient will be moved after treatment discontinuation and duration of stay in the ward unit.
- Concomitant medications including those relative to AE treatment

- Any specialist visit, laboratory or radiologic examination performed on top of procedures schedule
- Date of discharge

The number and percentage of patients screened, randomized, treated, terminating early and completing the study will be summarized by treatment arm and overall (Analysis population: All patients screened).

A by-patient listing of eligibility details, randomization details, visit dates and withdrawal/study completion details will be provided.

4.4.2 Protocol Deviations

Major or minor protocol deviations are defined as those deviations from the protocol likely to have an impact on the efficacy or safety of study treatments. The impact of major protocol deviations on the efficacy results will be investigated by assessing the robustness of the study results.
Before any analyses of the data, a data review meeting (DRM) will take place to identify protocol deviations. [redacted]
Cases of major protocol violations will be discussed, and on a case-by-case basis it will be determined whether or not to exclude the patients from the different CE populations. The final decisions on which patients to include or exclude from the CE populations will be finalized prior to database lock.

Major protocol deviations and any action to be taken regarding the exclusion of patients or affected data from specific analyses will be described in a separate document.

The following protocol deviation summaries will be produced:

- The number and percentage of patients with a major protocol deviation by treatment arm and overall and by type of deviation (Analysis population: ITT)
- The number and percentage of patients with a major protocol deviation that brings to the exclusion from the different CE populations by treatment arm and overall and by type of deviation (Analysis population: ITT)
- The number and percentage of patients with a minor protocol deviation by treatment arm and overall and by type of deviation (Analysis population: ITT)
- A by-patient listing of all major protocol deviations.
- A by-patient listing of all minor protocol deviations.

4.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The demographic and baseline characteristic variables identified below will be summarized by treatment arm and overall for the ITT, PP and/or Safety population:

- Demographic data (ITT population):
  - Age
  - Sex
  - Race
  - Ethnicity
  - Country
  - Childbearing potential
- Baseline characteristics (Safety population):
  - Physical examination
  - VS (HR, BP, RR, Temperature, Height, Weight, BMI,)
  - Laboratory safety tests (hematology, biochemistry, virology, coagulation test, urinalysis)
  - Pregnancy test
  - Area of the erythema/redness
  - Presence/absence of abscess

By-patient listings of all demographic data and baseline characteristics as stated above will be provided.

Medical history will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0, summarized by treatment arm and overall and listed.

Prior and concomitant medications as specified in the eCRF will be tabulated separately by treatment arm and overall. The proportion of patients receiving prior medications (medications ended within 4 weeks of the screening date) will be summarized by preferred medication name. A patient will be counted at most once for each prior preferred medication, even if the patient took the same medication on multiple occasions. Concomitant medications (medications started on/after the screening date) and Prior and Concomitant medications (medications started prior to the screening date but ended after this date or still ongoing) will be summarized similarly. Prior and concomitant medications will be classified according to the World Health Organization (WHO) Drug Dictionary version B3 201809 and presented by ATC code level 3.

Medication start and stop dates/times will be compared to the date of screening date to allow medications to be classified as either prior only, both prior and concomitant, or concomitant only. Prior and concomitant and concomitant only medication will be summarized in the same table.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of screening date. Medications will be assumed to be concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started within 4 weeks prior to the screening date. If there is clear evidence of that, the medication will be assumed to be both prior and concomitant, unless there is clear evidence to suggest that the medication stopped prior to

the screening date. If there is clear evidence to suggest that the medication stopped prior to the screening date, the medication will be assumed to be prior only.

4.6 ESTIMANDS

The "ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials" (ICH E9 Addendum) indicates the need to appropriately defined the target of estimation and the scientific question addressed with the trial or, in other words, the treatment effect of interest.
For this purpose ad-hoc estimands will be created.
A description of an estimand includes four attributes:

1. The population, that is, the patients targeted by the scientific question.
2. The variable (or endpoint), to be obtained for each patient, that is required to address the scientific question.
3. The specification of how to account for intercurrent events to reflect the scientific question of interest.
4. The population-level summary for the variable which provides, as required, a basis for a comparison between treatment conditions.

4.6.1 Target Population

The population targeted by the scientific question is defined via the inclusion and exclusion criteria and it includes patients with superficial or deep incisional SSI following a cardiothoracic / related leg or abdominal surgical procedure treated with Delafloxacin or the selected BAT. Since the non-inferiority nature of the study two population are evaluated, ITT population and CE_{TOC} population. They are defined in section §4.3 .

4.6.2 Variable

The primary endpoint to be obtained for each patient to address the scientific question is the clinical success response at TOC.

4.6.3 Intercurrent events

Premature interruption of the study treatment is the primary potential intercurrent event that could occur. The most common reasons are expected to be lack of efficacy (including the need for non-study antimicrobial agents such as antifungals) or treatment related AE which requests treatment discontinuation. In this situation patients will be asked to undergo EOT Visit at the time of withdrawal and, then, any other study visit as per protocol till LFU Visit.

4.6.4 Population-level summary

The population-level summary for the primary variables is the proportion of clinical success response at TOC. The basis for the comparison will be made using both the CE_{TOC} and the ITT populations. The clinical success response is defined and analyzed as described in section §4.6.5 .

4.6.5 Estimand definitions

Clinical success response is defined as cure or improve response within 7-14 days. Otherwise a patient will be considered as a failure. In the failure definition also missing outcome are included.
As per primary variable definition in case of any administration of antibacterial therapy for SSI is required because of lack of efficacy the patient will be considered as failure. In case, instead, treatment is discontinued due to treatment related AE response won't be imputed as failure by definition.
In this context the following estimands will be considered:

- Composite Estimand
- Hypothetical Estimand
- Treatment Policy Estimand

4.6.5.1 Composite Estimand

- Population: subjects in the CE_{TOC} and ITT populations with superficial or deep incisional SSI following a cardiothoracic / related leg or abdominal surgical procedure treated with Delafloxacin or the selected BAT.
- Variable: clinical success response at TOC
- Intercurrent events: the following intercurrent events approach will be used:
  - If a subject discontinued the treatment due to lack of efficacy the response outcome will be imputed as failure as per variable definition.
  - If a subject discontinued the treatment due to treatment related AE the response outcome will be imputed as failure.
- Population-level summary: the proportion of clinical success response at TOC.

4.6.5.2 Hypothetical Estimand

- Population: subjects in the CE_{TOC} and ITT populations with superficial or deep incisional SSI following a cardiothoracic / related leg or abdominal surgical procedure treated with Delafloxacin or the selected BAT.
- Variable: clinical success response at TOC
- Intercurrent events: the following intercurrent events approach will be used:
  - If a subject discontinued the treatment due to lack of efficacy the response outcome will be imputed as failure as per variable definition.
  - If a subject discontinued the treatment due to treatment related AE the collected response outcome will be assumed **as missing**.

- Population-level summary: the proportion of clinical success response at TOC.

Please note that since the population-level summary is the proportion of clinical success response at TOC the Hypothetical Estimand will coincide with the Composite Estimand.

4.6.5.3 Treatment Policy Estimand

- Population: subjects in the CE_{TOC} and ITT populations with superficial or deep incisional SSI following a cardiothoracic / related leg or abdominal surgical procedure treated with Delafloxacin or the selected BAT.
- Variable: clinical success response at TOC
- Intercurrent events: the occurrence of an intercurrent event is irrelevant. Clinical response collected after the treatment discontinuation due to lack of efficacy and /or treatment related AE will be used regardless the occurrence of intercurrent events and without any imputation even if a 2^{nd} line therapy is taken.
- Population-level summary: the proportion of clinical success response at TOC.

4.7 EFFICACY EVALUATION

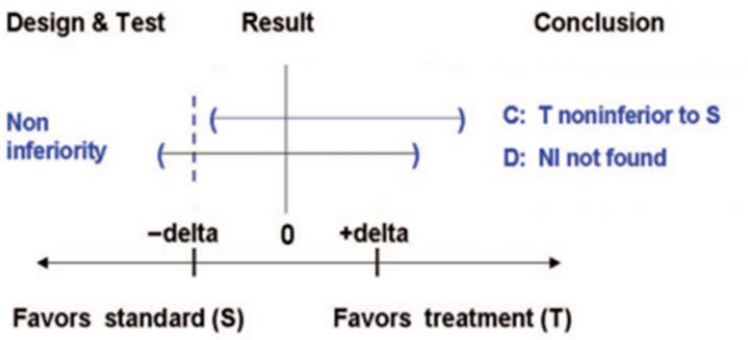
4.7.1 Analysis and Data Conventions

4.7.1.1 Study Hypotheses

All the statistical comparisons will be a test for non-inferiority of delafloxacin versus the Reference treatment arm with the possibility of switching to the superiority based upon the primary endpoint. No multiplicity adjustment will be used for testing superiority if non-inferiority has been demonstrated following the principles reported in the CPMP/EWP/482/99 EMA guideline: "Points to consider on switching between superiority and non-inferiority".

A non-inferiority test aims to demonstrate that results obtained from the test drug are not appreciably worse than the ones of standard drug. A non-inferiority margin ( ) has to be specified in order to characterize the largest difference that you consider to be dismissible (Figure 3).

Figure 3: Hypotheses of Non-inferiority tests.



The non-inferiority margin is set as =10% (unless otherwise specified).
The null (H_0) and alternative (H_a) hypotheses to be tested in order to establish the non-inferiority of delafloxacin are:

H_0: $P_d - P_r \leq -0.10$
H_a: $P_d - P_r > -0.10$

where P_d and P_r are the probabilities of responder for delafloxacin and the reference treatment arm, respectively.

If the lower limit (LL) of the two-sided 95% CI is greater than -0.10, it will be concluded that delafloxacin is non-inferior to the reference treatment arm for treating patients with cardiothoracic or abdominal SSI.

The null (H_0) and alternative (H_a) hypotheses to be tested in order to establish the superiority of delafloxacin are:

H0: $P_d - P_r \leq 0$
H_a: $P_d - P_r > 0$

4.7.1.2 Estimand approach

In general analysis will be based on the Composite Estimand, coincident to the Hypothetical one. For the primary endpoint sensitivity analyses will be performed using the Treatment Policy Estimand.

4.7.1.3 Multi-center Studies

The term ‘Center’ will be used to define each investigator site. As center is not a stratification variable for the randomization, it is not included in the main model for the primary analysis. The center effect, as random, will be investigated and reported, if significant, in the final report as sensitivity and exploratory analysis.

Additionally within each center more than one Blinded Observer will be involved for the assessment of parameters relevant for defining the patient as eligible to IV/PO switch of therapy and dischargeable from the hospital (IRLOS assessment). For these endpoints also the Blinded Observer effect will be investigated as random effect.

4.7.1.4 Adjustments for Covariates

For the primary efficacy analysis and for the secondary efficacy analyses when specified, site and depth of infection will be used as covariate additionally to the treatment arm (Test or Reference) since they will be used as stratification factors during the IWRS procedure and the analysis should reflect the restriction on the randomisation implied by the stratification as stated in the European guideline EMA/ CHMP/295050/2013: "Guideline on adjustment for baseline covariates in clinical trials". The interaction between the additional covariates and the treatment will be also examined and kept in the model in case of significant effect.

Site of infection will be classed as being one of the following:

- Cardiothoracic / related leg SSI.
- Abdominal SSI.

depth of infection will be classed as being one of the following:

- Superficial infection.
- Deep infection.

Since site of infection and depth of infection could be potentially highly associate, a Chi-Square correlation test between the two variables will be performed.
In case an high correlation is detected (i.e. greater/lower than ±0.8) only the most significant variable between the two will be included in the model.

Additionally as sensitivity analysis a model without additional covariates will be implemented in order to compare the adjusted and the unadjusted estimates.

4.7.2 Handling of Dropouts or Missing Data

A missing clinical response will be imputed as defined in §3.2.1.2. and following the Estimand definition described in §4.6 .
No missing responses are expected for the microbiological response.

4.7.3 Multiplicity

There is one primary endpoint comparison for non-inferiority (as detailed in Section §4.6.1.1) for this study. For the switch from non-inferiority to superiority no multiplicity adjustment is needed, since, as stated in CPMP/EWP/482/99, the superiority interpretation of results corresponds to a simple closed test procedure.

4.7.4 Examination of Subgroups

The uniformity of the treatment effects for the primary efficacy variable will be examined (if applicable) for the following subgroups:

- elderly patients (≥ 65 years)
- patients with diabetes
- patients with body mass index (BMI) ≥ 30kg/m^2
- patients with baseline bacteremia
- patients with polymicrobial infection
- patients with MRSA
- patients with severe renal impairment (CrCl between 15, inclusive, and <30 mL/min)
- patients with ≥ 2 signs and symptoms at baseline
- patients with baseline COPD
- patients with baseline SIRS, i.e with at least two of the following:
  - fever >38°C or < 36°C
  - heart rate >90 beats per minute
  - respiratory rate >20 breaths per minute or PaCO2 <32 mm Hg
  - abnormal white blood cell count (>12,000/mm3 or <4,000/ mm3 or >10% bands)
- patients with SSI more difficult to treat (i.e. area of the erythema/redness ≥ 75 cm^2 and/or presence of abscess)

The subgroup analysis on clinical success at TOC has been described under §4.6.6.1.

4.7.5 Primary Efficacy Analysis

The clinical success response at TOC is defined as cure or improved response within 7 - 14 days after last dose.
The rate of the efficacy variable is the sample responder rate defined in the following equation:

$$= \frac{}{+}$$

All the statistical comparisons will be a test for non-inferiority of delafloxacin versus the reference treatment arm as described in section §4.6.1.1. The relative study hypotheses are described as well under §4.6.1.1.

If the LL of the two-sided 95% CI is greater than -0.10, it will be concluded that delafloxacin is non-inferior to the Reference treatment arm for treating patients with cardiothoracic or abdominal SSI.
If the LL of the two-sided 95% CI is greater than 0, then delafloxacin will be declared superior to the Reference treatment arm for treating patients with cardiothoracic or abdominal SSI.
Confidence intervals will be calculated using Miettinen and Nurminen method.
The homogeneity of the treatment effects will be analyzed for non-inferiority in the ITT and the relative CE populations, while for superiority only on the ITT population.
The primary analysis will be adjusted by site and depth of infection additionally to the treatment arm as stated in section §4.6.1.3.

The following SAS program will be implemented:

```
proc freq data=dataset;
tables site*depth *trt*var / RISKDIFF(CL=MN COLUMN=2 common);
run;
```

Where:
var = dependent variable of interest.
trt = randomized treatment.
site = site of infection.
depth= depth of infection

4.7.6 Secondary Efficacy Variables

4.7.6.1 Clinical Success

The clinical success response at EOT and LFU will be analyzed in the ITT and CE populations analogously to the primary efficacy variable as described in §4.6.5.
The same SAS program used for the primary endpoint are also applied.

[redacted]

4.7.6.2 [redacted]

[redacted]

[redacted]

[redacted]

4.7.6.4 Microbiological response

Microbiological efficacy responses at EOT and TOC, as defined in §3.2.1.4, will be statistically analyzed for the MITT and ME analysis set by patient and pathogen analogously to the primary efficacy variable.

Statistical testing will be performed only if applicable, otherwise only frequencies and the relative percentages will be reported.

4.7.6.5 Eligibility to switch to oral formulation

Eligibility to switch to oral formulation is defined as the cumulative percentage of patient eligible to switch along the study treatment duration, beginning at study treatment initiation (Day 1) and ending when the criteria reported §3.2.1.5 are met.
Percentages are statistically analyzed analogously to the primary efficacy variable, in the ITT and CE populations.

Additionally, time to eligibility to switch will be also analysed.
The time to eligibility to switch is defined as the time elapsed between study treatment initiation (Day 1) and the time when the criteria reported §3.2.1.5 are met.
The formula for the calculation is:

$$\text{Time to eligibility to switch} = t_{CM} - t_{TI}$$

where t_{CM} is the time (hours and minutes) of when the criteria reported §3.2.1.5 are met,
t_{TI} is the time (hours and minutes) of the study treatment initiation.

In the case the criteria reported §3.2.1.5 are not met, time to eligibility to switch will be calculated as the time that occurred between t_{TI} and the end of treatment and the relative patient will be considered as censored.

Time to eligibility to switch will be compared using a log-rank test. The 25th, 50th and 75th percentiles of the Kaplan-Meier estimate with associated 95% CI's will be produced and presented with the log-rank p-value. In addition, a Kaplan-Meier plot of will be presented.
The following SAS code will be applied for this analysis:

```
proc lifetest data=dataset;
time dur*censor(1);
strata trt;
run;
```

Where:
trt = randomized treatments
dur = time to variable of interest
censor = censoring variable (assuming a value of 1 indicates a censored observation)

The underlying assumptions for the above analysis will be examined by reviewing the data and checking the assumption of proportional hazards by analyzing the interaction term 'treatment*log(duration)', where the logarithmic transformation is implemented to maintain the linearity. If the interaction term is not significant the hazards can be considered as proportional.
In addition the estimated hazard functions plot by using the Epanechnikov kernel-smoothed estimates will be produced as a graphical check.
Should these examinations indicate that an assumption has been violated then an alternative method of analysis (e.g. Wilcoxon Test) may be applied.

The following SAS Syntax will be implemented:

```
proc phreg data=dataset;
class trt;
model dur*censor(1)=trt trt_time;
trt_time = trt*log(dur);
run;
ods select HazardPlot;
proc lifetest data=dataset plots=H;
time dur * censor (1);
strata trt;
run;
```

As explained in §3.1 the responsible for the assessment of parameters relevant for defining the patients as eligible to IV/PO switch of therapy are different physicians (blinded observers) assigned by the PI. To keep under control the variability due to this random effect a sensitivity analysis by using a frailty model is implemented.
The following SAS code will be applied for this analysis:

```
proc phreg data=dataset;
class trt blider_observer;
model dur*censor(1)=trt;
random blider_observer;
run;
```

4.7.6.6 Hospital IRLOS (Infection Related Length of Stay)

Hospital IRLOS is defined as the cumulative percentage of patient eligible to discharge along the study treatment duration, beginning at study treatment initiation (Day 1) and ending when the criteria reported in §3.2.1.5 are met.
Percentages are statistically analyzed analogously to the primary efficacy variable, in the ITT and CE populations.

Additionally, time to Hospital IRLOS will be also defined and analyzed by using the same approach adopted for time to eligibility to switch as described in §4.7.6.5.

4.7.6.7 Hospital LOS (Length of Stay)

LOS is defined as the cumulative percentage of patients who are discharged along the overall study duration, beginning at the Investigator diagnosis of the infection (Screening) and ending on the date of actual hospital discharge. Percentages are statistically analyzed analogously to the primary efficacy variable, in the ITT and CE populations.

Additionally, time to actual discharge will be also defined and analyzed by using the same approach adopted for time to eligibility to switch as described in §4.7.6.5. with the exception of the frailty model that is not applicable.

4.7.6.8 [redacted]

[redacted]

[redacted]

[redacted]

```
proc univariate data          normal
class
HISTOGRAM
qqplot
var
run
quit
```

[redacted]

[redacted]

```
proc glm data
class
model
means                          hovtest
run
```

[redacted]

[redacted]

[redacted]

[redacted]

4.7.6.9 [redacted]

[redacted]

[redacted]

[redacted] *mb,* [redacted] *E.* [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

```
proc corr data
var
with
run
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4.8 SAFETY EVALUATION

All safety summaries and analyses will be based upon the safety population as defined in Section 4.3. No formal statistical testing will be performed and only descriptive statistics provided unless otherwise noted. The number of non-missing values and the mean with the respective SD (for continuous

variables) or the percentage (for ordinal/categorical variables) will be reported. Missing safety data will not be imputed.

4.8.1 Adverse Events

AEs will be coded using MedDRA Version 22.0.

AEs will be summarized by primary System Organ Class (SOC), Preferred Term (PT) and treatment. An overview of AEs will be provided, with the number and percentage of patients reporting an event, presented for the following categories:

- Any AEs
- Any serious AEs
- Any AEs leading to study discontinuation.
- Any AEs leading to death

Additionally, the following summaries of AEs will be presented by SOC and PT:

- The number of AEs and the number and percentage of patients with AEs by treatment and overall.

TEAE will be defined as those adverse events that occur for the first time or worsen in terms of intensity (severity)/ seriousness after the drug intake.

Where dates are missing or partially missing, adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to the study treatment administration.

TEAE will be summarized by primary System Organ Class (SOC), Preferred Term (PT) and treatment. An overview of TEAEs will be provided, with the number and percentage of patients reporting an event, presented for the following categories:

- Any TEAE
- Any serious TEAE
- Any mild/moderate/severe TEAE
- Any causally related TEAE (Adverse drug reaction [ADR])
- Any TEAE leading to study discontinuation.
- Any TEAE leading to death

Additionally, the following summaries of TEAE will be presented by SOC and PT:

- The number and percentage of patients with TEAE by treatment and overall.
- The number and percentage of patients with TEAE by intensity (mild, moderate and severe).
- The number and percentage of patients with TEAE by causality (related/not related).

Any TEAE is defined as related (ADR) if the causality category falls into one of the following: certainly related, probably related, possibly related and unassessable/unclassifiable. Otherwise TEAE will be considered as not related.

ADRs will be summarized by primary System Organ Class (SOC), Preferred Term (PT) and treatment. An overview of ADRs will be provided, with the number and percentage of patients reporting an event, presented for the following categories:

- Any ADR
- Any serious ADR
- Any mild/moderate/severe ADR
- Any ADR leading to study discontinuation.
- Any ADR leading to death

Additionally, the following summaries of ADR will be presented by SOC and PT:

- The number and percentage of patients with ADR by treatment and overall.
- The number and percentage of patients with ADR by intensity (mild, moderate and severe).

For each patient and each event, the worst intensity recorded will be attributed and used in the by-intensity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If intensity or causality is missing, the worst case will be assumed.

A by-patient listing of all AEs (including non-TEAE) will be provided together with a listing of TEAE.

The same tables will be provided also for the Adverse Events of Special Interest (AESI).
Any recorded AE that could potentially be related to class-effect AESIs will be identified by medical review and use of Standardized MedDRA queries (SMQ) where possible.

4.8.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

The number and percentage of deaths (if any) during the study by treatment arm (if numbers allow) will be reported.
Serious AEs (SAEs) will be summarized by primary System Organ Class (SOC), Preferred Term (PT) and treatment. An overview of SAEs will be provided, with the number and percentage of patients reporting an event, presented for the following categories:

- Any SAE
- Any mild/moderate/severe SAE
- Any SAE leading to study discontinuation.
- Any SAE leading to death

4.8.3 Clinical Laboratory Evaluation

Safety laboratory testing will be performed by a local laboratory at the timepoints specified in the Study Flow Chart (Table 1).

Patient's continuous haematology, biochemistry and coagulation laboratory values will be compared to normal ranges provided by the laboratory and flagged as "Low" or "High" in case they are below or above the ranges, respectively. Out-of-range laboratory values will also be flagged for abnormality by the Investigator (abnormal-not clinically significant [NCS] or abnormal-clinically significant [CS]).
The observed values of haematology, biochemistry and coagulation test results will be summarized for each timepoint by treatment arm and overall, using descriptive statistics. Also the investigator judgment for each parameter will be summarized for each timepoint by treatment arm and overall based on the following categories: Normal, Abnormal NCS and Abnormal CS.

Virology and Pregnancy test results will be reported as categorical values: "Positive", "Negative" or "Not Done".
Also 12-Lead ECG results will be reported as categorical values: "Normal" or "Abnormal". Abnormal results will then be flagged by the Investigator as abnormal-not clinically significant [NCS] or abnormal-clinically significant [CS]).
Categorical results of Virology, Pregnancy test and 12-Lead ECG will be summarized for each timepoint by treatment arm and overall.

Urinalysis test could be performed using local laboratory or, alternatively, Roche-Combur dipstick. Due to the possibility to use different method no parameter results will be provided in eCRF, the Investigator should only confirm whether there are abnormal-clinically significant tests and, if any, record them as Adverse Events or Medical History.
For Urinalysis no tables will be prepared, urinalysis abnormal-clinically significant test(s) will be visible in by-patient listing of Adverse Events or Medical History.

A by-patient listing of all laboratory data (as expected from Urinalysis) will be also presented.

Unscheduled examinations can be performed for safety reasons according to the Investigator's judgement and will be displayed only in listings.

4.8.4 Vital Signs, Physical Findings and Other Observations Related to Safety

At study visits vital signs will include SBP, DBP, HR, RR and T, while for the daily assessments only SBP, HR and T are required.
For each vital sign parameter the result will be compared to normal range provided by the Sponsor and, if out-of-range, flagged for abnormality by the Investigator (abnormal-not clinically significant [NCS] or abnormal-clinically significant [CS]).
Continuous results will be summarized for each timepoint by treatment arm and overall, using descriptive statistics.

Also the investigator judgment for each parameter will be summarized for each timepoint by treatment arm and overall based on the following categories: Normal, Abnormal NCS and Abnormal CS.

No Physical Examination results will be provided in eCRF, the Investigator should only confirm whether there are abnormal-clinically significant tests and, if any, record them as Adverse Events or Medical History.
Therefore no table will be prepared for Physical Examination, any abnormal-clinically significant test will be visible in by-patient listing of Adverse Events or Medical History.

Measurement of height (cm) and weight (kg) will be performed at Screening only. The values will be summarized in the table of baseline characteristics by treatment arm and overall, using descriptive statistics.

By-patient listings of all vital sign parameters will be presented.

Unscheduled values will only be presented in listings.

4.9 [redacted]

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4.10 DETERMINATION OF SAMPLE SIZE

A sample size of 600 randomized patients (300 per treatment arm: delafloxacin or Reference treatment) will provide about 80% power in the ITT population and higher than 95% in the CE population to demonstrate the non-inferiority of delafloxacin versus the reference treatment arm in terms of clinical response (Clinical Success) rate with a non-inferiority margin of 10%, an alpha equal to 0.025 (1-side test). Clinical Success rate at TOC of 78.0% and 78.1% in the ITT and of 98.3% and 99.4% in the CE population are assumed respectively for delafloxacin and the Reference treatment arm.

Assuming about 20% of Screening failures, approximately 750 patients are anticipated to be screened to reach a total of 600 randomized patients.

4.11 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

Not Applicable. SAP finalized prior to the first patient in since the unblinded condition.

5 GENERAL DEFINITIONS

5.1 DATA VALIDATION

Medidata Classic Rave 2019.1.0 will be used, as Electronic Data Capture system for data entry, by site personnel and for data cleaning and data locking by the Menarini Data Management team.

5.2 COMPUTER SYSTEMS AND SOFTWARE TO BE USED IN THE ANALYSIS

SAS v.9.3 (or upper) by SAS Institute Inc., Cary, NC, USA.

Database and SDTM and ADAM datasets will be created by using SAS Clinical Data Integration Studio version 4.9.
All tables and listings will be produced using PROC REPORT or procedure specific output displays using output delivery system (ODS) within SAS version 9.3 (or upper) and using SAS Office analytics.

5.3 CODING SYSTEMS USED

5.3.1 Clinical Terms

Concomitant diseases, medical procedures, and AEs will be coded with MedDRA 22.0

5.3.2 Drugs

Drugs will be coded with WHODrugGlobalB3 201903

5.4 REPORT TYPE, LANGUAGE AND FORMAT

The statistical output will be in Microsoft Word 2010 format and in English language.

- Dates will be presented as DDMMMYY.
- Numeric values will be decimal-point aligned.
- Counts and percentages: <group 1> XXX (XX.X%)
- Descriptive statistics:

N	XXX
Mean	XXX.X
SD	XXX.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- Character values will be left aligned.

6 TABLES FIGURES AND LISTINGS

6.1 STATISTICAL ANALYSIS REPORT (TFL)

The TFL (Tables, Listings and Figures) will follow the list of tables, plots, and listings of section 6.3 and 6.4, which are intended to provide the overall idea of the general output and ordering of the TFL and will not necessarily be reproduced in the final TFL document.

6.2 TABLES, HEADINGS, AND FOOTNOTES

All tables stratified by treatment and gender will also contain the treatment overall column. The tables repeated for analysis population will be produced only once if the analysis populations are identical. All tables are provided for ITT population unless specified otherwise.

Line 1: Study code: DELA-01

Line 3: *Table/Listing/Figure n: Table name (Study population)*

Line 4: *Table/Listing/Figure n.n: Table name*

Line 5: *Table/Listing/Figure n.n.n: Table name* [if applicable]

Line 6: *Table/Listing/Figure n.n.n.n: Table name* [if applicable]

Line 7: *Table/Listing/Figure n.n.n.n.n: Table name* [if applicable]

Footnote: *Relevant notes (if any)*

6.3 LIST OF TABLES AND FIGURES

Tables:

1 Patient disposition

Note: all tables by treatment/overall for ITT population (where applicable)

- 1.1 Overall patient disposition
- 1.2 Presence of patients at study visits
- 1.3 Protocol violations by category

2 Baseline and general characteristics

Note: all tables by treatment/overall for ITT population (otherwise specified)

- 2.1 Demographics and pregnancy test
- 2.2 Medical history by MedDRA SOC and PT
- 2.3 Physical examination
- 2.4 Vital Signs
- 2.5 Safety Laboratory Test
- 2.6 Prior and concomitant medication by ATC-Code

3 Safety analysis

Note: all analyses will be done on safety population by treatment/overall, unless otherwise stated

3.1 AEs
3.2 TEAEs
3.3 ADRs
3.4 Serious
3.5 Vital signs
3.6 Safety Laboratory Test
3.7 Pregnancy test at End of Study

4 Efficacy analysis

Note: all tables by treatment/overall for ITT and PP population.

4.1 Primary analysis
4.2 Secondary analysis

Figures:

Graph 1: Success Responders
Graph 2: Cure Responders
Graph X: Kaplan-Meier for XXX

6.4 PATIENT DATA LISTING

Key variables (KV) are the variables present in each patient data listing: Subject number, age, gender, planned treatment, study population (Yes/No for Safety, ITT and PP).
Screening Failures will be excluded from the listing.
The following list is intended to provide the overall idea of the general output.

L.1 Patient disposition

L.2 Demography

L.3 Baseline characteristics

L.4 Medical History

L.5 Previous and Concomitant Medication

L.6 Drug Exposure

L.7 All Adverse Events

L.8 Laboratory results

L.9 Pregnancy Test Data

L.10 Vital Signs Data

L.11 Physical Examination Data

L.12 Clinical Response

L.13 Microbiological Response

L.14 Time to event Variables

7 REFERENCES

1. DELA-01 Study protocol, Final Version 1.0, April 05, 2019 , Menarini Ricerche, S.p.A
2. International Conference on Harmonisation ICH Topic E9: Statistical principles for clinical trials. 1998.
3. International Conference on Harmonisation ICH Topic E10: Choice of control group and related issues in clinical trials. 2001
4. Points to consider on switching between superiority and non-inferiority. 2000
5. Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. EMA/CHMP/351889/2013. October, 2013.
6. Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. CPMP/EWP/558/95 rev 2. December, 2011.
7. SAS Institute, SAS/STAT® 9.2 User's Guide The POWER Procedure
8. [redacted]
10. https://support.sas.com