MENARINI RICERCHE

DRESS

CLINICAL TRIAL PROTOCOL
VERSION 1.0, 5 APRIL 2019

A randomized, observer-blinded, active-controlled, Phase IIIb study to compare IV / Oral delafloxacin fixed-dose monotherapy with best available treatments in a microbiologically enriched population with surgical site infections

Study Code	DELA-01
Study Nick Name/Acronym	DRESS- DELAFLOXACIN INTRAVENOUS AND ORAL MONOTHERAPY IN SURGICAL SITE INFECTIONS
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	IIIb
Sponsor	MENARINI RICERCHE S.p.A. Via Sette Santi, 1 50131 Florence, Italy
Co-ordinating Investigator	[redacted]
CRO	[redacted]

1 SIGNATURES

The signatories bave read thè clinical trial protocol titled A randomized, observer-bUndedf active-conirolledf Phase IIIb study to compare IV / Orai delafloxacin ffxed dose monotherapy with best available treatments in a mic obiologically enrichedpopulation witli surgical site infections** - Version 1,0, OS Aprii 2019 - carefiiliy and agree to adhere to its provisions. Changes to thè protocol bave to he stateri by thè Sponsor in amendments to thè clinical trial protocol, which, if they are substantial, bave to be authorized by thè Competent Authorities and Ethics Committees before translating them into action.

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PRINCIPAL INVESTIGATOR'S STATEMENT

a) Clinical Statement

My signature below documents my agreement with the contents of this clinical trial protocol titled *"A randomized, observer-blinded, active-controlled, Phase IIIb study to compare IV / Oral delafloxacin fixed-dose monotherapy with best available treatments in a microbiologically enriched population with surgical site infections" – Version 1.0, 05 April 2019* - with regard to the execution of the study and the required documentation / data collection. I agree to comply with this clinical trial protocol in its entirety and with the ICH guidelines for Good Clinical Practice (GCP).

b) Anti-Corruption Statement

I agree to - I will and I will cause any of my collaborators to - perform any activity in accordance with the principles any international anti-corruption legislations, such as OECD Convention on Combating Bribery of Foreign Public Officials in International Business Transactions, UK Bribery Act and US Foreign Corrupt Practices Act, including Italian Legislative Decree 231/2001. In particular, along the performance of the study, I will not - and I will cause any of my collaborators not to - directly or indirectly offer, pay, give, or promise to pay or give or receive any payment or gift of any money or thing of value to or from any government officer to influence any acts or decisions or to induce such officer to use its influence to effect or influence the decision of the relevant government body or any other decision maker. I accept to promptly inform the Sponsor in writing in case of violations of or deviations from any of the above prescriptions in the conduct of the study and I acknowledge and accept Sponsor's rights to conduct audits in order to verify compliance with the above during or in connection with the performance of the study. I agree and accept that a violation of any of the above prescriptions may result in the termination of the research activities of the site I work in and / or the entire study.

Principal Investigator	Signature	Date
.....	.....	.....
(printed name)		

2 PROTOCOL SYNOPSIS

A **randomized, observer-blinded, active-controlled, Phase IIIb study to compare IV / Oral delafloxacinfixed-dosemonotherapywith best available treatments in a microbiologically enriched population with surgical site infections**	
Sponsor Code:	DELA-01
Nick Name/Acronym:	**DRESS- D**ELAFLOXACIN INT**R**AVENOUS AND ORAL MONOTH**E**RAPY IN **S**URGICAL **S**ITE INFECTIONS
Phase	IIIb
Indication	Acute Bacterial Skin and Skin Structure Infection (ABSSSI) The study target population includes patients with superficial or deep incisional Surgical Site Infections (SSI) following cardiothoracic / related leg or abdominal surgical interventions.
No. of sites & countries	Approx. 70 sites in Europe.

Investigational Medicinal Product/Treatment Regimen and Duration

Test treatment: IV / Oral Delafloxacin

- Freeze-dried powder for solution for IV infusion; one vial contains 433 mg delafloxacin meglumine which corresponds to 300 mg delafloxacin free acid.
- Tablet; one tablet contains 649 mg of delafloxacin meglumine which corresponds to 450 mg delafloxacin free-acid

Test treatment will be administered every twelve hours, with the IV infusion lasting 60 minutes.

Reference treatment(s): Pre-selected Best Available Therapy (BAT) for cardiothoracic / related leg or abdominal SSI and described in §2.1. Additional therapy to BAT might be added to optimize the antimicrobial coverage as per Investigator's judgment.

For the Reference treatment(s)/additional therapy, the posology scheme should reflect the instructions reported in the relevant SmPC.

Duration of Test or Reference treatment(s) is minimum 5 days up to 14 days based on Investigator's judgment.

Please refer to §8.5 and §8.6 for further details on Test and Reference treatment(s) and to §8.4.3 for study treatment restrictions.

Study Design

Randomized, observer-blinded, active-controlled, parallel-group, multicenter, phase IIIb study in 600 patients with superficial or deep incisional SSI following a cardiothoracic / related leg or abdominal surgical procedure, i.e. an expected microbiologically enriched population with SSI.
Observer blinded design means that the Principal Investigator (PI) or his/her delegates are unblinded whereas a blinded observer is designated to conduct pre-specified assessments without access to the assigned treatment to patients. Details on their respective responsibilities are reported in §8.2.

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 or 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 local epidemiological pattern and will be recorded prior to the Interactive Web Response System (IWRS) assignment of Test or Reference treatment. In addition, in case Gram-negatives or MRSA bacteria are suspected in the cardiothoracic or abdominal SSI, respectively, additional therapy according to the site Standard of Care (SoC) -with the only exclusion of quinolones- can be assigned prior to Randomization by the Investigator (see Schematic study design §2.1). The additional therapy will be discontinued as soon as possible if those organisms will be not identified in baseline cultures as per Local/Regional microbiological results.

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.

Secondary Objectives

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]

Study duration

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 as follows:

- ➢ Screening Visit, for study eligibility assessment (within 30 days from surgery)
- ➢ Randomization and treatment administration (Visit 1; Day 1, within 1 day from Screening)
- ➢ Assessment period that includes:
  - Visit 2 (Day 3 – 4, between 48 to 72h after first dose)
  - Visit 3 (Day 7) (if applicable)
  - End of Treatment (EOT) Visit (within 1 day after last dose)
  - Test of Cure (TOC) Visit (7 - 14 days after last dose)
  - Follow-up (FU) Visit (or phone call) (21 ± 2 days after last dose)
  - Late Follow-up (LFU) / End of Study Visit (28 - 30 days after last dose)

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.

Inclusion Criteria

Eligible patients shall meet all the following criteria at Screening:

1. Male or female patients aged more than 18 years.
2. Patients with a history of cardiothoracic / related leg or abdominal surgery, occurred within 30 days and no implant is left in place, and a diagnosis of SSI according to the CDC definition1, namely:

   Superficial Incisional Surgical Site Infection, involving only skin and subcutaneous tissue of the incision, and at least one of the following local findings:
   - purulent drainage from the superficial incision;
   - organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision;
   - superficial incision is deliberately explored by surgeon AND the patient has at least one of the following signs or symptoms of infection:
     - o pain or tenderness,
     - o localized swelling,
     - o redness or heat;
   - diagnosis of superficial incisional SSI made by the Investigator.

   Or

   Deep Incisional Surgical Site Infection, involving deep soft tissues (e.g. fascia and muscle layers) at the incision site and at least one of the following findings:
   - purulent drainage from the deep incision but not from the organ / space component of the surgical site;
   - a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms of infection:
     - o fever (> 38 °C),
     - o localized pain or tenderness;
   - an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination;
   - diagnosis of deep incisional SSI made by the Investigator.

3. The severity of infection requires an IV treatment and patient hospitalization according to the Investigator's judgment.
4. [redacted]

[redacted]

5. [redacted]
6. [redacted]
7. [redacted]

Exclusion Criteria

Patients who meet any of the following criteria at Screening are not eligible to the study:

1. Previous IV antimicrobial therapy exceeding 24 hour duration administered during 72 hours prior to the first dose of study treatment.
2. Any infection expected to require systemic antimicrobial agents other than study treatment(s) (§ 2.1).
3. Medical history of significant hypersensitivity or allergic reaction or contraindication to the pharmacological classes of study treatment(s) or excipients of their formulation according to the Investigator's judgment.
4. Medical history of known or suspected central nervous system (CNS) disorders (e.g., severe cerebral arteriosclerosis, epilepsy).
5. Medical history of myasthenia gravis.
6. Medical history of C. difficile diarrhea.
7. [redacted]
8. Organ-space infection.
9. Complicated Intra-Abdominal Infection (cIAI).
10. Any chronic or underlying skin condition at the site of infection that may complicate the assessment of clinical response (e.g., atopic dermatitis or eczema) or any skin condition that, in the opinion of the Investigator, would interfere with the SSI healing.
11. [redacted]
12. Patients with known underlying diseases leading to deep immunosuppressive status (e.g., HIV/Acquired Immune Deficiency Syndrome-AIDS, malignancies and recent chemotherapy) that, in the opinion of the Investigator, would compromise the clinical response.
13. [redacted]
14. Patients with end-stage renal disease on hemodialysis or peritoneal dialysis or creatinine clearance (CrCl) < 15 mL/min using the Cockcroft-Gault formula.
15. [redacted].
16. [redacted].
17. [redacted].
18. [redacted].

19. [redacted].
20. [redacted].

Study Visits, and Efficacy and Safety assessments

The study encompasses up to 8 site visits (depending upon the individual duration of study treatment) and ending with the Late Follow Up Visit that represents the End of Study Visit.

Each patient will undergo the study procedures described below and summarized in the study flowchart (§2.2). Along the study period, any planned and unplanned procedure (e.g. specialist visit, laboratory or radiologic examinations) will be documented and recorded in eCRF.

Pre-screening

Pre-screening of potential patients in person or by reviewing medical history / medication to determine their initial eligibility for a study is a common strategy in the recruitment process and can be done before informed consent is obtained.
The Investigator will be trained to encourage patients, at time of hospital discharge after surgical intervention, in coming back to the site in case they should experience any signs or symptoms of SSI.
Before performing any study procedures, all potential eligible patients will sign an Informed Consent Form (ICF) after receiving any clarification by the Investigator. The Investigator will sign the ICF as well.

Screening Visit

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.

The following procedures shall be performed after the patient provides informed consent:

- Check of Inclusion / Exclusion Criteria (§8.4.1 and §8.4.2)
- Collection of demographic data and medical history (§8.7.12.1)
- Physical examination (§8.7.12.2)
- Recording of prior medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, if any (§8.6.5.3)
- Gram stain and microbiological culture of infection site specimen (§8.7.11.3)
- Blood culture (§8.7.11.3)
- Vital signs (§8.7.12.2)
- 12-lead electrocardiogram (ECG) (§8.7.12.5)
- Blood sampling for safety laboratory tests (haematology, biochemistry, coagulation, virology) (§8.7.12.3)
- [redacted] (§8.7.11.7)
- Urinalysis (§8.7.12.3)
- Serum (or plasma) and urine pregnancy test, if applicable (§8.7.12.3)

- Recording of any Clinical Event, not associated to any drug intake (§8.8.1.2) and/or any Adverse Event associated to any drug intake (§8.8.1.1) that occurs for the first time or worsens after the signature of the ICF and prior to Investigational Medicinal Product (IMP) administration, if any.

Randomization and Treatment Administration - Visit 1 (Day 1)

Visit 1 has to be scheduled within 1 day from Screening, with the following procedures to be performed prior to first administration of study treatment:

- Instructions and completion of the Short Form-36 (SF-36v2) Health Survey questionnaire (§8.7.11.6), to be performed as first procedure
- Re-check of Inclusion and Exclusion criteria (§8.4.1 and §8.4.2)
- Recording of prior and concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)
- Gram stain and microbiological culture of infection site specimen (§8.7.11.3), if clinically indicated
- Blood culture, if the previous culture was positive or if clinically indicated (§8.7.11.3)
- Vital signs (§8.7.12.2)
- Recording of any Clinical Event, not associated to any drug intake (§8.8.1.2) and/or recording of any Adverse Event associated to any drug intake (§8.8.1.1) that occurs for the first time or worsens after the signature of the ICF and prior to IMP administration, if any
- Investigator's choice of Reference treatment plus any additional therapy, if needed (§2.1)
- Assignment of the randomized treatment as per IWRS (§8.6.2)
- Administration of study medication.

NOTE-1: If Visit 1 falls on the same day of Screening, all the procedures done at Screening should not be repeated.

NOTE-2: In case of vancomycin assignment, vancomycin trough levels shall be monitored after 3 doses (steady state), at Visit 3 and whenever clinically indicated, for dose or duration of infusion adjustment[2]. See §8.6.4 for further details.

Day 2 Onwards Daily Assessments

Starting from Day 2 up to maximum the End Of Treatment, laboratory and clinical parameters/assessment reported below will be evaluated **DAILY** by the blinded observer who will be responsible to define:

- Eligibility of the patient to switch from IV to the oral formulation (§0).

- Eligibility of the patient to be discharge relevant for assessment of the Hospital Infection-Related Length of Stay-IRLOS 0).

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.
The following procedures shall be daily performed until the eligibility criteria are considered as met (§0) by the blinded observer:

- Vital signs: BP, HR and Body Temperature (maximum T° recorded from the last 24h)
- Blood sampling for haematology (WBC count only)
- Assessment of patient ability to tolerate PO diet and no gastrointestinal absorption problem
- Wound status idoneous for home care management

NOTE-1: At Visit 2 and Visit 3, vital signs and WBC count are also contemplated and shall be performed only once.

NOTE-2: date and time of the actual switch to oral formulation (i.e. first intake of the oral formulation), will be recorded by the Investigator. Assignment of delafloxacin or linezolid oral kit will be performed through IWRS by unblinded site staff.

NOTE-3: date and time of the actual hospital discharge (i.e. the time when the letter of discharge is issued) will be recorded by the Investigator upon occurrence along the study up to End of Study Visit.

NOTE-4: 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.

Visit 2 (Day 3-4)
The following procedures shall be performed between 48h and 72 h after first dose administration.
Outpatients (i.e. patients already discharged from the hospital) shall return to the site for the study visit.

- Recording of AEs occurred since previous visit, if any (§8.8.2)
- Recording of concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)
- Gram stain and microbiological culture of infection site specimen, if clinically indicated (§8.7.11.3)
- Blood culture if the previous culture was positive or if clinically indicated (§8.7.11.3)
- Vital signs (§8.7.12.2)
- Blood sampling for safety laboratory test (haematology, biochemistry, coagulation, (§8.7.12.3)
- [redacted] (§8.7.11.7)

- Urinalysis (§8.7.12.3).

In case of early treatment withdrawal, patients should undergo the EOT Visit, and should be followed as described in §8.4.4.

NOTE: The infection site specimen for microbiological culture should be collected before initiation of any alternative antibacterial therapy.

Visit 3 (Day 7)

The following procedures shall be performed at Day 7 if the patient is still on treatment.
Outpatients (i.e. patients already discharged from the hospital) shall return to the site for the study visit.

- Patient's completion of the SF-36v2 Health Survey (§8.7.11.6) to be performed as first procedure
- Recording of AEs occurred, since previous visit, if any (§8.8.2)
- Recording of concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)
- Gram stain and microbiological culture of infection site specimen, if clinically indicated (§8.7.11.3)
- Blood culture if the previous culture was positive or if clinically indicated (§8.7.11.3)
- Vital signs (§8.7.12.2)
- Blood sampling for safety laboratory test (haematology, biochemistry, coagulation) (§8.7.12.3)
- [redacted]
- Urinalysis (§8.7.12.3)
- Therapeutic Drug Monitoring for vancomycin (§8.6.4)

In case of early treatment withdrawal, patients should undergo the EOT Visit, and should be followed as described in §8.4.4.
NOTE: The infection site specimen for microbiological culture should be collected before initiation of any alternative antibacterial therapy.

End Of Treatment - EOT Visit

The following procedures shall be performed at EOT Visit (within 1 day after last dose administration).
Outpatients (i.e. patients already discharged from the hospital) shall return to the site for the study visit as per Investigator's prescription.

- Patient's completion of the SF-36v2 Health Survey (§8.7.11.6) to be performed as first procedure
- Contact IWRS to report treatment completion status (§8.6.2)
- Recording of AEs occurred, since previous visit, if any (§8.8.2)

- Recording of concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)
- Gram stain and microbiological culture of infection site specimen (§8.7.11.3)
- Blood culture if the previous culture was positive or if clinically indicated (§8.7.11.3)
- Physical examination (§8.7.12.2)
- Vital signs (§8.7.12.2)
- 12-lead ECG (§8.7.12.5)
- Blood sampling for safety laboratory test (haematology, biochemistry, coagulation, (§8.7.12.3)
- Blood sampling for infection biomarkers (CRP, ProCT) (§8.7.11.7)
- Urinalysis (§8.7.12.3)
- Serum (or plasma) pregnancy test, if applicable (§8.7.12.3)
- Assessment of clinical response (§8.7.11.2).

In case the EOT Visit is performed for early treatment withdrawal, patients should be followed as described in §8.4.4.

Test Of Cure - TOC Visit

The following procedures shall be performed at TOC Visit (7 - 14 days after last dose).
Outpatients (i.e. patients already discharged from the hospital) shall return to the site for the study visit.

- Patient's completion of the SF-36v2 Health Survey (§8.7.11.6) to be performed as first procedure
- Recording of AEs occurred, since previous visit, if any (§8.8.2)
- Recording of concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)
- Gram stain and microbiological culture of infection site specimen (§8.7.11.3)
- Blood culture if the previous culture was positive or if clinically indicated (§8.7.11.3)
- Vital signs (§8.7.12.2)
- 12-lead ECG (§8.7.12.5)
- Blood sampling for safety laboratory tests (haematology and biochemistry) (§8.7.12.3)
- Urinalysis (§8.7.12.3)
- Assessment of clinical response (§8.7.11.2).

Follow Up -FU Visit (or phone call)

Recording of AEs and concomitant medications will be performed 21 days (± 2 days) after the last dose. Outpatients (i.e. patients already discharged from the hospital) will receive a follow-up telephone call to collect this information or will be invited to the site.

Late Follow Up -LFU / End of Study Visit

The following procedures shall be performed at LFU Visit (28 - 30 days after last dose).

Outpatients (i.e. patients already discharged from the hospital) shall return to the site for the study visit. LFU Visit represents the End of Study Visit.

- Patient's completion of the SF-36v2 Health Survey (§8.7.11.6) to be performed as first procedure
- Recording of AEs occurred, since previous visit, if any (§8.8.2)
- Recording of concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)
- Assessment of clinical response (§8.7.11.2).

Efficacy Study Endpoints

Primary Endpoint:

Clinical Success defined as the clinical response of "Cure" or "Improved" at TOC (7 - 14 days after last dose) in the Intent-to-Treat (ITT) and the Clinical Evaluable (CE) populations.

Secondary Endpoints:

- [redacted]
- [redacted]
- [redacted]
- Eligibility to switch to oral formulation in the ITT and CE populations according to the blinded observer's assessment as per criteria in §0
- Hospital IRLOS (Infection Related Length of Stay) in the ITT and CE populations, beginning with first dose of study treatment and ending when the patient is considered eligible to discharge up to maximum end of treatment according to the blinded observer's assessment as per criteria in §0
- Hospital LOS (Length of Stay) in the ITT and CE populations, beginning with the diagnosis of the SSI (Screening) and ending with actual discharge
- Microbiological response at EOT and at TOC Visits in the Microbiologically Intent-to-Treat (MITT) and in the Microbiologically Evaluable (ME) populations
- [redacted]
- [redacted]

[redacted]

Safety Endpoints

- Incidence, intensity (severity), seriousness and treatment-causality of Treatment-Emergent

AEs (TEAEs, i.e. AEs that occurred after the first study drug intake).

- Frequency of clinically significant changes in vital signs, 12-lead ECG and laboratory parameters (haematology, biochemistry, coagulation and urinalysis), post-dose versus baseline.

NOTE: The latest assessments performed before first study treatment administration will represent the baseline.

[redacted]

Criteria for Evaluation:

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 LFU 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 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.

Microbiological response

Microbiological response will be generated at EOT and TOC assessments at both pathogen and patient levels on the basis of the results of the infection site specimen(s) and blood cultures at baseline and follow-up and susceptibility testing, performed at the microbiological Centralized

laboratory.

Data relative to baseline and post baseline organisms isolated at the Centralized laboratory from the infection site and blood will be evaluated by a 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".

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.

Analysis populations

Intention-to-treat (ITT): All randomized and treated subjects analyzed according to the randomized treatment arm (Test or Reference).

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

Clinically Evaluable (CE): All subjects in the ITT population who meet the following criteria:

- Diagnosis of cardiothoracic/related leg 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
- Did not receive any concomitant, systemic antibacterial therapy except for lack of efficacy
- Had no protocol deviations that would affect assessment of efficacy at the reference visit.

CE populations will be defined at EOT, TOC and LFU timepoints and for eligibility to switch to oral formulation, IRLOS, and LOS.

Microbiologically Evaluable (ME): 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: All subjects who have received at least one dose of study medication.

Statistical Analysis

Primary Efficacy Analysis

The primary efficacy variable (Clinical Success defined as cure or improved at TOC in the ITT and CE populations) will be used to assess the non-inferiority of delafloxacin versus the Reference treatment arm. The treatment difference (delafloxacin minus Reference treatment arm) will be presented with the relative 2-sided 95% confidence interval (CI) on the difference in response rate.
If the lower limit is greater than -0.10, it will be concluded that delafloxacin is non-inferior to the Reference treatment arm for treating patients with cardiothoracic / related leg and abdominal SSI.
In case the non-inferiority will be confirmed, the superiority of delafloxacin versus the Reference treatment arm will be tested by using a Chi²-Test test.
Non-inferiority will be tested on the CE and ITT populations, while superiority only on the ITT population.

Secondary Efficacy Analysis

All the secondary efficacy endpoints will be descriptively analyzed and tested, when applicable, for non-inferiority with the possibility to switch for superiority analogously to the primary efficacy variable through an *ad hoc* inferential analysis, as reported below:

- Binary outcomes will be analyzed analogously to the primary efficacy variable.
- Continuous variables will be tested by using an ANOVA model with treatment arm as main factor. [redacted].
- Time to event variables will be assessed using a Log-rank test.

[redacted]

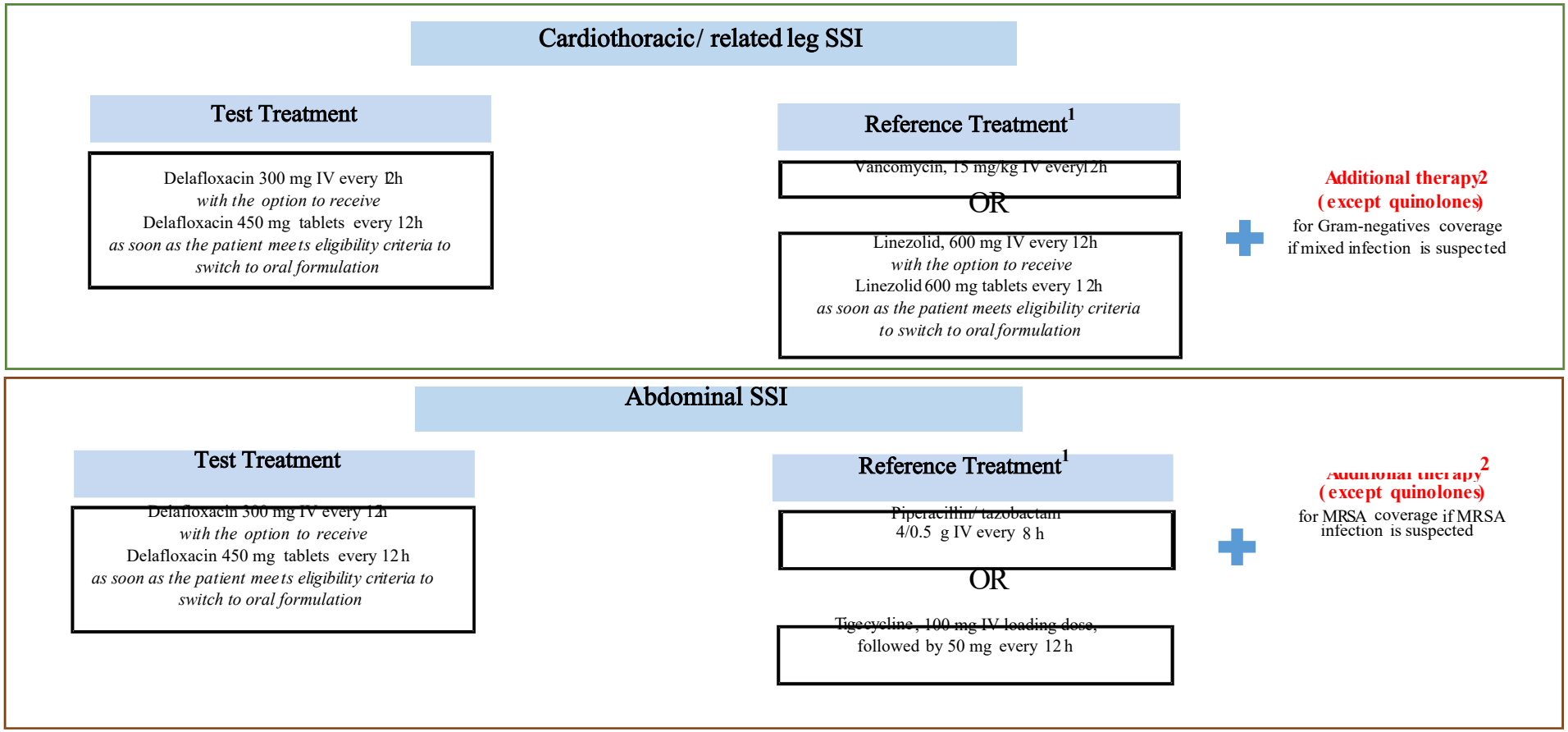
Safety Analysis

AEs will be coded using the MedDRA dictionary and summarized by treatment arm/individual treatment. The incidence of each TEAE and the number of patients with at least one TEAE will be summarized by System Organ Class (SOC) and Preferred Term (PT). Clinically significant abnormal findings in vital signs, 12-lead ECG and laboratory parameters (haematology, biochemistry, coagulation and urinalysis) will be summarized by treatment arm/individual treatment as per TEAEs. Safety variables will be analyzed only by descriptive statistics and will be run on the Safety population.

[redacted]

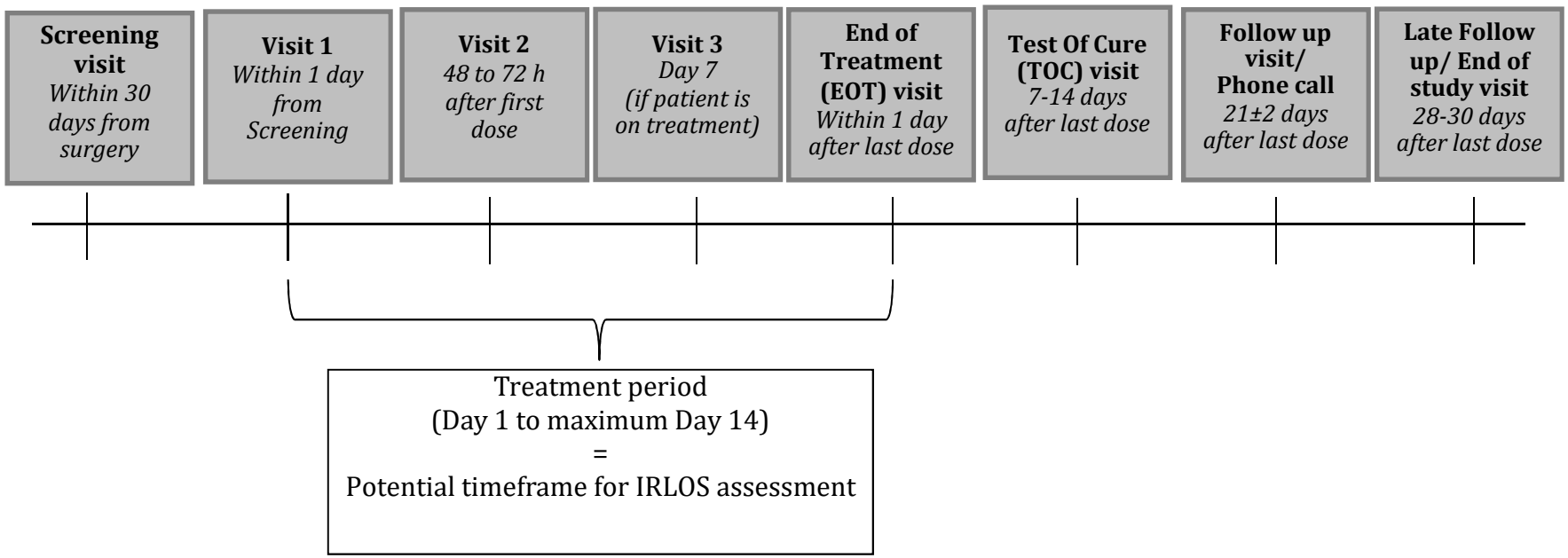
2.1 Schematic Study Treatment(s) and Visit Schedule

Study Treatment(s)



[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.

Visit Schedule



2.2 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[s]	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)
SF-36v2 Health Survey QoL[t]		X		X	X	X		X
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 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

Co-ordinating Investigator	[redacted]

Sponsor	**Menarini Ricerche S.p.A.** **Clinical Sciences Department** **Via Sette Santi, 1** **50131 Florence, Italy**
Corporate Director of Clinical Sciences / Sponsor's Representative	[redacted]
Expert Head of Anti-infectives	[redacted]
Study Physician / Study Medical Expert	[redacted]
Study Manager	[redacted]
Clinical Research Associate	[redacted]
Biostatistician	[redacted]
Data Manager	[redacted]

Sponsor's Pharmaceutical Manufacturer of the IMP	**A. Menarini Research & Business Service GmbH Department of Pharmaceutical Development** Glienicker Weg 125 D-12489 Berlin, Germany
Head of the Department of Pharmaceutical Development	[redacted]
Packaging, Labelling, and Distribution of the IMP	[redacted]
Sponsor's Pharmacovigilance Unit	[redacted]
Study Drug Safety Manager	[redacted]
CRO	[redacted] *More information are provided in the separate Operational Contact List*
Centralized Laboratory	[redacted] *More information are provided in the separate Operational Contact List*
IWRS	[redacted] *More information are provided in the separate Operational Contact List*

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4.1 Glossary

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
SAP	Statistical Analysis Plan
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

5 ETHICAL AND LEGAL ASPECTS

5.1 General aspects

This study will be carried out in compliance with the study protocol, the recommendations on biomedical research on human subjects of the *Declaration of Helsinki*[3], International Conference of Harmonization – Good Clinical Practice (ICH - GCP) Guidelines, EU regulations in force (EU Regulation No 536/2014 of 16 April 2014), and national requirements of the participating Country(ies).

The Sponsor has contracted the Contract Research Organization (CRO, for details refer to the Study Operational Contact List) to perform some of the Sponsor's trial related duties and functions like site selection and monitoring. The Sponsor will perform medical monitoring, safety management, data management, statistical analysis and medical writing. The ultimate responsibility for the quality and the integrity of the study resides with the Sponsor. The study will be conducted in agreement with Sponsor's or CRO's Standard Operating Procedures' (SOP) requirements as agreed.

All clinical work conducted under this protocol is subject to GCP rules. This includes audits/inspections by the Sponsor and/or its delegate (e.g., CRO), and/or by national/international Health Authority representatives at any time. All Investigators must agree to the audits / inspection of the study site, facilities, and of study-related records by the Health Authority representatives and / or by the Sponsor, and / or its delegates, which must be performed in accordance with national laws concerning personal data protection.

5.2 Independent ethics committee and legal requirements

Before starting the study in a study site, study protocol and relevant documentation must be submitted to and approved by the Independent Ethics Committee(s) (IEC) and the Competent Authority(ies) (CAs) of the participating country(ies).

In addition, all local national legal requirements for the conduct of a clinical study have to be followed prior to the start of the study. The CA(s) and IEC(s) of the participating country(ies) will be informed about any changes in the study protocol, the end of the study, or the premature study termination as appropriate and within the requested time period.

5.3 Patient information and declaration of consent

Before any study-related procedures may be performed, informed consent must be obtained from the patient by means of a signed declaration.

The Informed Consent Form (ICF) must be approved in the corresponding local language and in accordance with local laws and regulations by the IEC prior to being submitted to the patient.

In the patient information leaflet, patients will be given information and fully comprehensive explanation in easily understandable terms of the study procedures, regarding the benefits, restrictions, discomforts, and risks in taking part in the study, the properties of the Investigational Medicinal Product (IMP), the method of assignment to treatments, and any medically accepted and readily available treatment other than the IMP.

Patients will also be informed about the measures taken to ensure their confidentiality according to the pertinent legislation.
After being duly informed and interviewed by the Investigator, the patient freely has to date (including time) and sign in duplicate the ICF before being enrolled into the study and before undergoing any study procedure. The Investigator must store one original of the signed ICF in the Investigator's File, and the patient will be provided with the other one. The process of obtaining the ICF has to be documented in the source documents.
If a protocol amendment would affect the terms of the ICF, it will be revised to reflect the protocol change and submitted to IEC for approval. The Investigator will ensure that this new consent form is signed by all patients subsequently entered in the study and those currently in the study, before the changes take effect on their participation in the trial. Patients who will not sign the new consent form needs to be terminated from the study participation.

5.4 Patient insurance

The Sponsor Menarini Ricerche S.p.A. has stipulated an insurance policy for patients participating in the study, in accordance with local regulatory requirements.
Details on the insurance company, the insurance number and conditions will be made available to patients in the ICF and / or provided as a separate document, in accordance with national requirements.
A copy of the insurance certificate will be provided to each Investigator and will be filed in the Investigator's File at the sites and in the electronic Trial Master File (eTMF) of the study.

5.5 Documentation of study-related data and record retention

It is the responsibility of the Investigator to document all study-related data for each patient in a case report form (CRF). For this study, an electronic CRF (eCRF) will be used. The Investigator has to guarantee the accuracy of the documented data and has to comment any missing or spurious data.
In addition to the eCRF the Investigator will maintain adequate records that fully document the participation of the patient in the clinical study including the study assessments (patient source data documentation). Details on the source data documentation are provided in §10.3.
As required by ICH - GCP guidelines, the Investigator will keep essential documents until at least two years after the last approval of a marketing application in an ICH region; until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the IMP or 25 years from the end of the clinical trial, whichever occurs last (EU-Directive 2001/20 of April 4, 2001, as amended). These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.
Subjects' records have to be archived according to national law requirements.

No study documents should be destroyed without prior written agreement between Sponsor and Investigator. Should the Investigator wish moving the study record to another location, he / she must notify the Sponsor in writing.
Details on the archiving of electronic documents / data are provided in §12.1.

5.6 Confidentiality

By signing the study protocol, the Principal Investigator affirms that any information provided by the Sponsor will be maintained in confidence, and that such information will be divulged to IECs or CAs only under an appropriate understanding of confidentiality with such a committee or institution.
In order to maintain the patient's confidentiality, all data collected by the Investigator will be recorded pseudonymously in the eCRF. Patient's data will be identified by a unique patient number. The Investigator agrees that within national regulatory restrictions and ethical considerations, representatives of the Sponsor, any regulatory agency, and IEC may consult study source documents in order to verify data in the eCRF. Patient medical records pertinent to the study will be reviewed by the study monitor to assure adequate source documentation, accuracy, and completeness of eCRFs. The review will be conducted in accordance with relevant SOPs and with strict adherence to professional standards of confidentiality, GCP, and the relevant data protection legislation.

5.7 Protocol / protocol modifications

The protocol must be read thoroughly by everybody whom the information therein concerns and the instructions must be exactly followed.

Changes in the study protocol will require a protocol amendment. Such amendments will be agreed upon and approved in writing by all signatories of the protocol. If amendments are substantial, i.e. they are likely to have an impact on the safety of the patients or to change the interpretation of the scientific documents in support of the conduct of the study, or if they are otherwise significant, the IECs and the CAs in the participating countries have to approve these amendments before implementation.

Changes which have no significant impact on medical or scientific validity of the study will be agreed upon and approved in writing by all signatories of the protocol and the IECs and the CAs will be notified of this protocol amendment.

Any substantial amendments of the protocol will be integrated in an updated study protocol. The Principal Investigator must ensure full compliance with the updated study protocol.

5.8 Study commencement

The study can commence in an individual study site only after all prerequisites are fulfilled according to ICH/GCP guidelines, any local regulatory requirements, and the Sponsor / CRO's SOPs.

5.9 Patient's safety

If any event(s) related to the conduct of the study or the development of the IMP affects the safety of the study participants, the Sponsor and the Investigator will take appropriate urgent

safety measures to protect the patients against any immediate hazard. The CAs and IECs will be informed forthwith about these new events and the measures taken.

5.10 Data property / publication policy

All data generated in the study (e.g. eCRFs, patient questionnaires, the structured data files in the clinical database system, the results of the statistical evaluation, microbiological data and evaluation, and medical interpretation as well as the final clinical study report) are the property of Menarini Ricerche S.p.A.
It is intended that study design and main results will be published on www.clinicaltrials.gov and on other applicable websites (e.g., https://eudract.ema.europa.eu/results-web). In addition, the results of the study may be published as scientific literature. Results may also be used in submissions to CAs. The conditions mentioned below are intended only to protect confidential commercial information (patents, etc.), and not to restrict publication.

All information concerning delafloxacin (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information) supplied to the Investigator by Menarini Ricerche S.p.A. and not previously published is considered confidential by Menarini Ricerche S.p.A. and will remain the sole property of Menarini Ricerche S.p.A. The Investigator agrees not to use it for other purposes without written consent from Menarini Ricerche S.p.A.

Menarini Ricerche S.p.A. will use the information obtained in this clinical study in connection with the development of delafloxacin and therefore may be disclose it to other Investigators or concerned CAs in the European Union (EU) or abroad. In order to allow for the use of information derived from this clinical study, the Investigator and laboratories involved in the study have an obligation to provide Menarini Ricerche S.p.A. with complete test results and all data recorded during this study.

Prior to submitting the results of this study for publication or presentation, the Investigator will allow Menarini Ricerche S.p.A. at least 60 days to review and comment upon the publication manuscript. Menarini Ricerche S.p.A. will provide any manuscript of the results of this study to the authors at least 30 days before submission for a complete review. In accordance with generally recognised principles of scientific collaboration, co-authorship with any Menarini Ricerche S.p.A. personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.
It is agreed, that the results of the study will not be submitted for presentation, abstract, poster exhibition, or publication by the Investigator until Menarini Ricerche S.p.A. has reviewed / commented and agreed to any publication.

5.11 Data Protection

5.11.1 General Principles on Personal Data Compliance

All clinical trial information shall be recorded, processed, handled, and stored in such a way that it can be accurately reported, interpreted and verified; at the same time, the

confidentiality of records and of the personal data of the patients shall remain protected in accordance with the applicable law on personal data protection such as the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014.
This section defines the appropriate technical and organizational measures that shall be implemented to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss as well as to assure the fulfillment of patients' privacy rights.

5.11.2 Acknowledgment

Sites, the Principal Investigator, the Centralized Laboratory, the Regional laboratory, the CRO, the IWRS provider as well as their appointed staff and service providers acknowledge that:

(a) the performance of the study will imply processing of sensitive personal data;
(b) personal data processing is regulated by the applicable European (i.e. the EU General Data Protection Regulation 679/2016 and the EU Regulation on clinical trials on medicinal products for human use 536/2014) and local laws (i.e. the laws of the country where the study is conducted) as well as by the Sponsor's national legislation. In particular, it is hereby acknowledged that being the Sponsor a company incorporated under Italian law, it has to mandatorily comply with Italian legal provisions on data protection: therefore the Site, the Principal Investigator, the Centralized Laboratory, the Regional laboratory, the CRO shall cooperate with the Sponsor to allow the fulfillment of such obligations;
(c) strict compliance with the applicable data protection laws and this section of the protocol is deemed by the Sponsor as an essential condition of collaboration with the Sites, the Principal Investigator, the Centralized Laboratory, the Regional laboratory, the CRO.

5.11.3 Data Controllers and Data Processors

The Sponsor, the Site, the Principal Investigator and the CRO acknowledge that according to the applicable privacy laws, Sponsor and Sites will act as independent data controllers while CRO and the Principal Investigator will act as data processors respectively of the Sponsor and of Site. Before the beginning of the study, the Site will instruct in writing Principal Investigator as its data processor. However, if specific local laws or regulations mandate a different definition of the privacy roles, the Sponsor, the Sites, the Principal Investigator and the CRO will implement the relevant legal instruments (e.g. if pursuant to the local laws the Site is a data processor of the Sponsor, a Data Processing Agreement will be finalized; if pursuant to the local laws Sponsor and Site are join controllers, a Joint Controllership Agreement will be finalized).

5.11.4 Duties of the Parties involved in the performance of the study

Collection and use of patients' personal data (i.e. subjects' data), including their biological samples, will be carried out in full respect of the provisions of the information notices submitted to patients, as well as the privacy rights, the fundamental freedoms and the dignity of data subjects. All the parties involved in this study undertake to adopt adequate measures to warrant that data will always be processed securely and in compliance with privacy laws.
Sites, the Principal Investigator, the Sponsor, the CRO, the IWRS provider, Regional laboratory and the Centralized Laboratory - as well as their appointed staff and service providers, each in its respective remit and within the limits of their specific role in the study, shall implement the following safety measures (physical, logical, organizational, technical, electronic, I.T. etc) to ensure adequate protection of the personal data of the patients involved in the study. In particular:
(i) DATA SAFETY. Sites and/or the Principal Investigator shall adopt all the necessary measures to prevent or minimize the risks of theft, fire, flooding, partial or total loss, accidental disclosure or illegal/unauthorized access to patient's data or Sponsor's proprietary confidential information; to this extent, before the beginning of the study, Sites and/or the Principal Investigator shall ensure that the actual measures they have implemented are fit-for-purpose and law-compliant, and in particular:

- in order to minimise the risk of unauthorized access and theft, the hardware on which patients' personal data are stored shall be placed in a restricted-access area, accessible only to those individuals who need to retrieve the patients' personal data included in the database for professional purposes; the same safeguards shall be put in place for non-electronic databases;
- any electronic database containing the patients' personal data shall be password-protected by means of a strong password. Systems shall be set so that passwords must be updated at least every three months and feature at least 8 characters, with upper-case and lower-case recognition, containing at least three "special" characters, such as upper case letters [A-Z], lower case letters [a-z], numbers [0-9], symbols [!, #, $, etc.] or other special characters [Á, ë, ö etc.]. Passwords shall not include elements which may easily be associated with the assignee or information regarding him/her, such as name and year of birth (e.g. "johnbrown80") or easily predictable strings of characters (e.g. "qwerty", "12345", "admin", "user", etc.);
- adequate cryptographic protection measures shall be put in place for data "at rest" and "in transit" (these include, for example, file system or database cryptography, or any other equivalent IT measure which renders data unintelligible to those who are not authorised to access them);
- high level security measures shall be implemented also on the files or databases which contain the "key" to match the patients' personal data (i.e. name, surname, etc.) with their respective "Patient IDs" (as defined at point (iv) below);
- Backup processes and other measures that ensure rapid restoration of business critical systems shall be implemented;
- Updated Antivirus and firewall programs shall be installed on the IT devices.

Sites shall, regularly test and update the measures listed above.
Sites shall, upon request from the Sponsor and/or the CRO, provide detailed written information about the measures listed above.
The CRO shall ensure that the selected sites for the study have implemented the above listed measures.
(ii) TRANSMISSION OF DATA. All the parties that transfer data through internet and/or to the centralized database(s) used to process study's data or to generate statistical analyses shall implement secure protocols based on cryptographic standards which make data unintelligible to unauthorized individuals.
(iii) SECURITY OF THE CENTRALIZED DATA BASE. The centralized database held by the Sponsor shall have the following safeguards in place:

- appropriate authentication methods, which differentiate between different users according to their respective roles so as to ensure that access to a specific set of subjects' data is permitted exclusively to those for whom access to such data is essential in the context of their work for the study;
- appropriate measures to ensure that the authentication credentials are periodically updated (i.e. password change);

(iv) PSEUDONYMIZATION. All personal data that may allow identification of the patients involved in the study shall be adequately dissociated from the other data pertaining to the study ("pseudo-anonymisation" process). The Principal Investigator shall adequately dissociate the identification data of patients from the data pertaining to the study by linking results to an alphanumerical code ["Patient ID"], whose format shall not make it possible to identify the patient directly or indirectly, so as to ensure that only anonymous data are transmitted to the Sponsor, the Regional laboratory, the Centralized Laboratory, the IWRS provider and / or the CRO. Site/Principal Investigator shall securely store a separate list (e.g: identification log) with the identification code, together with all signed informed consents, in accordance with the security measures as defined above.
As outlined below, samples shall only be stored for as long as strictly necessary for the study's performance: in particular, at Centralized laboratory blood samples for laboratory tests will be stored no longer than 12 months from sampling while both blood and SSI samples for microbiological analysis will be stored until one year after the end of the clinical trial. Blood and SSI samples analyzed at Local/Regional laboratory for safety and microbiological analyses respectively will be destroyed in accordance with the Local/Regional laboratory procedures after analyses are completed. Biological samples and any other examination (e.g. X-ray, ECG) shall bear Patient ID, and in no case will they bear other information that may lead to the direct or indirect identification of the patient, especially when, in accordance with this protocol, samples shall be forwarded and shared outside the clinical Site (e.g. in case of centralized reading or local laboratory analysis).
(v) TRAINING. The parties shall ensure that any personnel involved in the study have received proper training on data protection issues.
All actions related to the implementation of the aforementioned measures shall be provided by the Sponsor, the Site and/or the CRO to the competent authorities (including data protection authorities) and Ethics Committees if and when requested. If such authorities or the

Sponsor consider the implementation of the afore mentioned measures insufficient to guarantee an adequate level of protection of the patients' personal data, Site, the Principal Investigator, the CRO, the IWRS provider, Regional laboratory and the Centralized laboratory undertake to adopt all the necessary activities to overcome such remarks to assure the full compliance with the data protection laws.

5.11.5 Archiving of the clinical trial master file and patients' personal data

Unless other EU laws require archiving for a longer period, the Sponsor, Site and the Principal Investigator shall archive the content of the clinical trial master file, including the relevant patients' personal data, for at least 25 years after the end of the clinical trial.
However, medical records shall be archived in accordance with the national laws of the country where the study is performed. The patient code pairing list (i.e. the list that where the Patient ID is linked to the patients' identification data such as name and surname), shall be archived care of the Principal Investigator.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities.
Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall undertake the responsibilities set out in this protocol.
The Sponsor appoints the Study Manager (SM) or delegates as responsible person/s for archives. Access to archives shall be restricted to those individuals.
The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the period referred to in the first paragraph. Any modification to the content of the clinical trial master file shall be traceable.

5.11.6 Data Breach

Data Breach is an incident regarding personal data security and leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed. In particular: destruction of personal data is where the data no longer exists, or no longer exists in a form that is of any use to the Site, Sponsor, CRO, Principal Investigator; Centralized Laboratory, Regional laboratory and the IWRS provider data loss is when the data may still exist, but the Site, Sponsor, CRO, Principal Investigator, Regional laboratory, Centralized Laboratory and the IWRS provider has lost control or access to it, or no longer has it in its possession; damage is where personal data has been altered, corrupted, or is no longer complete; data unavailability is where, following a data incident (such as a network outage, a natural or man-made disaster, etc.), personal data become temporarily inaccessible to the Site, Sponsor, CRO, Principal Investigator, Regional laboratory Centralized laboratory and the IWRS provider.
Anomalous Event is an event that is not part of the standard operational scope of an infrastructure, network or service and which affects, or is likely to affect, personal data; this may include theft or loss of IT devices and other physical events (e.g. an unauthorized access

to a locked storage room containing paper files with personal data), and/or electronic/IT anomalies (e.g. cyber-attacks, default or hacking of cloud services), which may in any way entail loss, unavailability, alteration, theft, copy or dissemination of personal data.

Whoever becomes aware in any way of an Anomalous Event and/or of a Data Breach (see definitions above) affecting the patients' personal data and/or personal data collected in the context of the study, shall, as appropriate, immediately (and in any case no later than 24 hours from the knowledge of an Anomalous Event and/or of a Data Breach) inform the SM, the sponsor's Data Protection Officer, who may be contacted at dpo@menarini.com, the Site and the PSI Data Protection Officer, who may be contacted at privacy@psi-cro.com and shall provide the following information:

(i) Anomalous Event / Data Breach Type (e.g. data loss, unauthorized access, loss of company device, etc.);

(ii) Person or source that first reported the Anomalous Event/ Data Breach;

(iii) Date and Time when the person who first reported the Anomalous Event / Data Breach became aware of it;

(iv) Anomalous Event / Data Breach Date and Time (actual or presumed);

(v) Place (specify if actual or alleged) where the Anomalous Event / Data Breach occurred;

(vi) Anomalous Event / Data Breach Description;

(vii) Indicate the source of the Anomalous Event / Data Breach (e.g. I.P. source) - (if relevant);

(viii) Indicate the affected infrastructure / system / application / cloud/ software / hardware / database and their location;

(ix) List or describe the processing/storage systems affected by the Anomalous Event/ Data Breach (if relevant);

(x) Number of data subjects involved (if known);

(xi) Amount of allegedly breached data

(xii) Other relevant information

Once all the above information have been provided, the Sponsor and/or the Site should have a reasonable degree of certainty that a security incident has occurred that has led to personal data being compromised.

Then, as appropriate, Sponsor and Site, each one in its respective remit, shall manage the Data Breach in accordance with the applicable data protection regulations.

For Data Breach affecting personal data of patients enrolled within the European Union, Sponsor and Site autonomously or jointly -depending on the circumstances and their privacy responsibilities as defined by the Regulation 679/2016- shall:

1. Collect the necessary evidence and information;
2. Categorize the breach;
3. Determine the risk probability and level to the rights and freedom of the concerned patients;
4. Identify and put in place appropriate remedies to minimize the impact of the Data Breach
5. Determine the notification and communication duties vis à vis the competent supervisory authority and/or the concerned patients.

5.11.7 Information notice on personal data protection and pseudo-anonymisation

Prior to patients' enrolment in the study, the Principal Investigator and/or the Site (including their personnel) shall provide each patient with adequate, law-compliant "information notices and consent forms to process personal data" as included in the ICF (or, as the case may be, through a separate, specific form) provided by the Sponsor or delegated CRO and shall collect his/her written consent to the processing of personal data according to the actual performance conditions in which the study is carried out. The Principal Investigator is responsible to archive the signed ICF in accordance with the security measures described above.
Among other things, the ICF (or the separate form) shall inform patients about:

(i) the applicable data protection legislation
(ii) what kind of data shall be collected during the study listing them in detail or by category;
(iii) the purpose of data processing (e.g. performance of the study, pharmacovigilance, registration of new drugs) and the legal basis;
(iv) whether granting the consent(s) to process personal data is a necessary or an optional condition to take part in the study;
(v) the use of data for future scientific researches / secondary use of data (if any). In such a case the future scientific purposes / secondary use shall include further medical and scientific research purposes such as studies for the registration of new medicines; studies which compare the data of this Study with other sources, etc.;
(iv) the pseudonymisation procedure and scope;
(v) who can access patients' data and under what circumstances (e.g. Principal Investigator and Site for patient management along the study, Sponsor and its vendors for collection and analysis purposes, regulatory authorities for study and marketing approval. The complete list will be available upon request);
(vi) the period of data retention/storage as defined in, including the storage of the biological sample [§ 5.11.4 and 5.11.5 above)];
(vii) to which entities/countries outside the EU patients' data will be transmitted (the complete list will be available upon request – see §5.11.9)
(viii) patients' data protection rights as defined by the EU General Data Protection Regulation 679/2016.
(ix) Data Controllers / Data Processors and the relevant contact details
(x) Sponsor's Data Protection Officer contacts (dpo@menarini.com)
(xi) in case of genetic data processing the possible findings, also with regard to unexpected findings that might be disclosed on account of the processing of the genetic data;

5.11.8 Genetic Data

No genetic data will be processed for the study purposes, except for the genetic data needed for the pregnancy follow-up.

- The collection of genetic data for performing genetic tests and screening shall be limited to the personal and family information that is absolutely indispensable for pregnancy follow-up.
- If genetic data are processed in the context of the study for pregnancy follow-up purposes (pharmacovigilance) only (i) the collection of genetic data for performing genetic tests and screening shall be limited to the personal and family information that is absolutely indispensable for pregnancy follow-up; (ii) the source, nature and mechanism for samples taking and storage will be under the pregnant health care provider and its local procedures; genetic data shall be processed pursuant to the applicable pharmacovigilance laws and regulations; genetic data shall be communicated/transmitted using high security standard. The provisions below shall be implemented as applicable from time to time.
- Without prejudice to applicable laws and regulations, except for data and results as per Section 5.10, the protocol shall be subject to confidentiality obligations that will assure the secrecy of the data for at least one year after the conclusion of the study.
- The measures to keep patients' identification data separated from biological materials and genetic information are described in Sections 5.11.4 and 5.11.5.
- Access to the premises where genetic data are stored shall be controlled by security staff and/or electronic devices also based on biometrics. Any person admitted after closing time, on whatever grounds, shall have to be identified and their data recorded.
- Preservation, use, and transportation of biological samples shall be carried out in such a manner as to also ensure their quality, integrity, availability and traceability.
- Genetic data shall be transmitted electronically by certified electronic mail after encrypting and digitally signing the information to be transmitted. Web application-based communication channels may be used if they rely on secure communication protocols and they can guarantee the digital identity of the server providing the service as well as of the client station from which the data are accessed by means of digital certificates issued by a certification authority in pursuance of the law.
- Electronically processed genetic data may be accessed provided that authentication systems are based on tokens/devices.
- Genetic data and biological samples contained in lists, registers and/or databases shall be processed with encryption techniques and/or by means of identification codes and/or any other techniques that can make them temporarily unintelligible also to the persons authorised to access them.
- In order to minimise the risks of accidental disclosure and/or unlawful/unauthorised access, patients' identities will be disclosed only when strictly necessary (e.g. to prevent a physical prejudice).
- Genetic and medical data will be processed separately from any other personal data that can identify the patients directly.
- The ICF will detail the possible findings regarding genetic data, also with regard to unexpected findings that might be disclosed as result of the test / elaboration of genetic data;

- The ICF will detail whether the data subject is allowed to limit the scope of communication of his/her genetic data and the transfer of biological samples, including their possible use for additional purposes;
- The ICF will detail the retention period of genetic data and biological samples (if different from the general retention period of other data processed in the context of the study).

5.11.9 Transfer of patients' data outside the European Union

The study performance entails transferring patients' personal data (coded data) outside the EU. To this extent, the Sponsor, the Centralized laboratory, Regional laboratory, the CRO and the IWRS provider undertake to export such data in compliance with adequate safeguards/ legal basis as required by the Regulation 679/2016 including the Commission Decisions, the Standard Contract Clauses, the Privacy Shield, patients' specific consent.
The complete list of non-EU countries where data can be exported will be available upon request.

5.11.10Exercise of patients' data privacy rights

Each study patient has the right to contact the Sponsor, the Site, the Principal Investigator, the Centralized Laboratory, the Regional laboratory, the IWRS provider and the CRO to exercise the rights afforded to the patient by the law, including the afforded ones under articles 15 to 22 of Regulation (EU) 2016/679, namely: knowing whether or not any data referring to his/ her is being processed in the context of the study; access his/her data; verify the data's content, origin, exactness, location (including, where applicable, the non EU countries where the data might be); obtain a copy of the data including their transmission to another entity indicated by the patient; ask that the data are supplemented, updated, amended; in the circumstances set forth by the law, ask that the processing of data is restricted, that data are anonymised or frozen; oppose to the processing of his/her data for legitimate reasons. Each
patient has the right to lodge a complaint with his/her local supervisory authority and/or to notify to the Data Protection Officer any use of his/her personal data the patient regards as inappropriate.
Each study patient is free to withdraw at any time from the study. In such case, each study patient may ask the Sponsor, the Site, the Principal Investigator, the Centralized Laboratory, the Regional laboratory, the CRO and the IWRS provider to destroy/delete his/her personal data including his/her biological samples, unless they have been permanently anonymized, thus preventing any further processing or analysis of his/her data. However, data and results of tests that may have been used to determine the results of the study shall not be deleted, to avoid altering or impairing altogether the results of the study.
Specific rights in relation to the processing of genetic data apply. PLEASE REFER TO §5.11.8.
If the Site, the Principal Investigator, the Centralized Laboratory, the Regional laboratory, the CRO and the IWRS provider receive a request for data privacy rights exercise, the concerned recipient shall immediately inform the Sponsor DPO by email at dpo@menarini.com

The request shall be fulfilled within the term set forth by the applicable privacy laws (normally 30 days). The Sponsor, the Site, the Principal Investigator, Regional laboratory, the Centralized Laboratory, the CRO and the IWRS provider shall implement adequate organizational measures to reply to patients within the above mentioned deadline.

5.11.11 Future research

With patients' optional and additional consent, the Sponsor and/or the Site may use the data collected during the course of the study for further medical and scientific research purposes. These may include, for example: retrospective clinical studies; clinical studies pertaining to the patients' pathology/medical condition(s) or similar conditions; studies which compare the data of this Study with those from other sources to identify the factors involved in a disease; registration of new drugs.
In the context of these additional research activities, patients' data will be processed, anonymized and transferred abroad, and may be shared with future research partners –in most cases this will prevent patients identification; however, in the unlikely event patients full identity really needs to be disclosed, the same precautions and safeguards as those described in this protocol will be implemented.

6 BACKGROUND INFORMATION

6.1 The Disease and Study Rationale

Acute Bacterial Skin and Skin Structure Infections (ABSSSI) encompass a variety of disease presentations and severities, involving the skin and underlying subcutaneous tissue, fascia, or muscle and ranging from simple superficial infections to severe necrotizing infections (*Sartelli et al. 2014*[4]). ABSSSI typically require intravenous antibiotic therapy, surgical intervention or both, and are increasingly a reason for hospitalization.

Surgical Site Infections (SSI) represent a specific chapter among the soft tissue infections. They are post-operative infections and because of their multifaceted aspects they are framed into a separate group. The Centers for Disease Control and Prevention and the European Centre for Disease Prevention and Control (CDC and ECDC, respectively) defines SSI as postoperative infection occurring within 30 days of a surgical procedure (or within one year for permanent implants).

SSI is classified as by the CDC in superficial incisional infection, deep incisional infection, and organ space infection. Superficial incisional infections are the most common type of SSI. The development of a SSI depends on contamination of the wound site at the end of a surgical procedure and specifically relates to the pathogenicity and inoculum of microorganisms present, balanced against the host's immune response.

From 2013 to 2014, in Europe, the percentage of SSI per 100 surgical procedures varied from 0.6% to 9.5% depending on the type of procedure and on the different population groups that undergo these operations and because of the different proportions of clean and contaminated operations for each operation type. Among the isolated pathogens, *Staphylococcus aureus* (17.0%) and *Escherichia coli* (16.9%) were the most commonly reported microorganisms with an expected inter-country variation. For cholecystectomy and colon surgery operations, the majority of the reported microorganisms were Enterobacteriaceae.

The ECDC released the latest annual data on antimicrobial resistance trends in 30 EU and European Economic Area (EEA) countries on 20th November 2017, confirming that methicillin-resistant *Staphylococcus aureus* (MRSA) remains a public health priority in Europe as 10 out of 30 countries reported MRSA percentages above 25% in 2016.

The presence of MRSA in SSI is independently associated with mortality compared with patients with methicillin-susceptible *Staphylococcus aureus* (MSSA). The importance of early treatment for MRSA was underscored by a retrospective study showing that patients who received therapy within two days after the date of diagnosis had a significantly shorter duration of intravenous (IV) therapy and hospital Length of Stay (LOS) than patients whose treatment was initiated later (*Nathwani D. et al, 2014*[5]). Gram-negative aetiology is also common in SSI setting as reported in the SENTRY programme (1998 – 2004), with *P. aeruginosa* being the second most important pathogen after MRSA, followed by *E. coli* (*Bassetti M et al, 2014*[6]).

It should be noted that the epidemiology of ABSSSI and SSI changes over time, with the profiles of community- and healthcare-associated causative agents constantly shifting; this is further complicated by similar shifts in the prevalence of strains showing resistance to antimicrobial agents over time.

Inappropriate antibiotic treatment is given to approximately 25% of patients, potentially prolonging hospital stay and increasing the risk of morbidity and mortality; this may occur particularly in patients with diabetes, surgical site infections, anal and perianal region infections, and compromised vascular perfusion (e.g. obese patients) where Gram-negative pathogens must also be considered when selecting initial empiric therapy (*Garau et al, 2015*[7]).
Critical medical issues are still in place in the management of patients with ABSSSI and SSI in particular, addressing empirical antimicrobial coverage, drug-drug interactions, and potential toxicities. Considerations related to drug administration include availability of IV and oral (OS) formulations for not easier IV access (e.g., in obese patients), or IV / OS switching to facilitate hospital discharge, food interaction, therapeutic drug monitoring, and fixed dose versus weight-based dosing.
The main goal of this study is to assess the efficacy and safety of delafloxacin (a fluoroquinolone with a broad spectrum *in vitro* activity, including Gram-positive, Gram-negative, atypical and anaerobes organisms available as IV and OS formulations), in comparison with best available therapy, selected among the current standard of care. Due to the multiplicity of the pathogens causative of SSI and the possibility of mixed infections, the study design also allows the possibility to add further antimicrobials to the best available therapy, among those used at each specific site, when in need of a broader coverage and upon Investigator's judgment. To strength the reliability of the study results, this clinical trial has an observer blinded design.
The financial burden of surgery is increased due to the direct costs incurred by prolonged hospitalization of the patient, diagnostic tests, and treatment. Indeed, *Broex et al., 2009*[8] demonstrated that, in European hospitals, patients who develop a SSI constitute a financial burden approximately double that of patients who do not develop a SSI. Improving the management of SSI may therefore represent an opportunity cost to hospitals by saving resources that could be spent elsewhere.
An additional objective of this study is also to collect healthcare resources consumption for the treatment of SSI in order to quantify, also from an economic point of view, the burden and highlighting potential differences in the management of these patients by introducing delafloxacin in the current armamentarium.

6.2 Investigational medicinal product: Delafloxacin N-methylglucamine salt

6.2.1 Nonclinical data

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2.2 Clinical experience

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Objective response at 48-72 hours	[redacted]		[redacted]	
	81.3, 80.7	0.8 (3.2, 4.7)	86.5, 85.4	1.2 (2.6, 4.9)
[redacted]				
[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.3 Risk benefit assessment

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

[redacted]

Taking into consideration the wide antimicrobial spectrum and comparable clinical efficacy shown by delafloxacin in the Phase II and Phase III trials versus different treatments, at least a comparable therapeutic benefit is expected for subjects who will be randomized to the delafloxacin arm versus the Reference treatment arm.

In particular, because of its spectrum of activity, pharmacokinetic and safety profile, the risk to benefit ratio of delafloxacin is anticipated to be favorable 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. 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.

7 STUDY OBJECTIVES

7.1 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.

7.2 Secondary objectives

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]

7.3 Exploratory objective

[redacted]

8 INVESTIGATIONAL PLAN

8.1 Overall study design and plan description

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 §2.1.

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 (see §8.6.2).

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: [redacted], eligibility of patients to switch to oral formulation and/or to hospital discharge (IRLOS), and actual hospital discharge (LOS).
No interim analysis is planned.

8.2 Observer blinded Design

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 as reported in §2.1) 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.

8.3 Discussion of study design, including the choice of doses and timing of administration

DELA-01 has been designed to assess the efficacy and the effectiveness of delafloxacin compared to well-known best available treatments, that have been selected to address the microbiological flora causative of post cardiothoracic and abdominal SSI, on the basis of the current international guidances (*Sartelli et al*[4], IDSA[18]). Additional therapy can also be prescribed by the Investigator to optimize the microbiological activity of Reference treatments in case of suspicion of Gram-negatives or MRSA, as described in §8.6.

The treatment duration, lasting from 5 to 14 days, and dosages have been selected based on the results of delafloxacin pivotal trials and according to the SmPCs of the Reference treatments.

Delafloxacin has been already studied and compared to the current SoC over the clinical development in double blind or double dummy designed pivotal trials.
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. 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 requirements[15] for ABSSSI.
Testing of non-inferiority of delafloxacin vs BAT is also in compliance with current international guidelines[19] 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.

8.4 Selection of Study Population

At least 600 male and female subjects, 18 years of age or older, with clinical evidence of superficial or deep incisional cardiothoracic / related leg or abdominal SSI, will be randomized in the study. After providing informed consent, the eligibility of the patients to enter the study will be assessed according to inclusion and exclusion criteria to be evaluated at Screening and confirmed at Visit 1.

8.4.1 Inclusion criteria

Eligible patients shall meet all the following criteria at Screening:

1. Male or female patients aged more than 18 years.
2. Patients with a history of cardiothoracic / related leg or abdominal surgery, occurred within 30 days and no implant is left in place, and a diagnosis of SSI according to the CDC definition[1], namely:

   Superficial Incisional Surgical Site Infection, involving only skin and subcutaneous tissue of the incision, and at least one of the following local findings:
   - purulent drainage from the superficial incision;
   - organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision;
   - superficial incision is deliberately explored by surgeon AND the patient has at least one of the following signs or symptoms of infection:
     - pain or tenderness,
     - localized swelling,
     - redness or heat;

- diagnosis of superficial incisional SSI made by the Investigator.

Or

Deep Incisional Surgical Site Infection, involving deep soft tissues (e.g. fascia and muscle layers) at the incision site and at least one of the following findings:

- purulent drainage from the deep incision but not from the organ / space component of the surgical site;
- a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms of infection:
  - fever (> 38 °C),
  - localized pain or tenderness;
- an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination;
- diagnosis of deep incisional SSI made by the Investigator.

3. The severity of infection requires an IV treatment and patient hospitalization according to the Investigator's judgment.
4. [redacted]

8.4.2 Exclusion criteria

Patients who meet any of the following criteria at Screening are not eligible to the study:

1. Previous IV antimicrobial therapy exceeding 24 hour duration administered during 72 hours prior to the first dose of study treatment.
2. Any infection expected to require systemic antimicrobial agents other than study treatment(s) (§ 2.1).

3. Medical history of significant hypersensitivity or allergic reaction or contraindication to the pharmacological classes of study treatment(s) or excipients of their formulation according to the Investigator's judgment.
4. Medical history of known or suspected central nervous system (CNS) disorders (e.g., severe cerebral arteriosclerosis, epilepsy).
5. Medical history of myasthenia gravis.
6. Medical history of *C. difficile* diarrhea.
7. [redacted]
8. Organ-space infection.
9. Complicated Intra-Abdominal Infection (cIAI).
10. Any chronic or underlying skin condition at the site of infection that may complicate the assessment of clinical response (e.g., atopic dermatitis or eczema) or any skin condition that, in the opinion of the Investigator, would interfere with the SSI healing.
11. [redacted].
12. Patients with known underlying diseases leading to deep immunosuppressive status (e.g., HIV/Acquired Immune Deficiency Syndrome-AIDS, malignancies and recent chemotherapy) that, in the opinion of the Investigator, would compromise the clinical response.
13. [redacted]
14. Patients with end-stage renal disease on hemodialysis or peritoneal dialysis or creatinine clearance (CrCl) < 15 mL/min using the Cockcroft-Gault formula.
15. [redacted]

8.4.3 Study treatment restrictions

As with other quinolones, concurrent administration of oral delafloxacin with magnesium, aluminum, or calcium antacids, as well as metal cations such as iron, and multivitamins preparations with zinc or didanosine chewable/buffered tablets should be avoided. Oral delafloxacin should be taken 2 hours before or 6 hours after taking these products. For the intravenous formulation, it is not allowed to administer delafloxacin along with any solution containing multivalent cations, e.g., calcium and magnesium, through the same intravenous line.

Study restrictions for the Reference treatments (and additional therapies, if any) must strictly follow the instructions reported on the relative SmPC.

8.4.4 Withdrawal of patients from therapy or from study

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 (§8.7.7 and §8.7.10).

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

8.5 Identity of the investigational product(s)

8.5.1 Description of investigational medicinal product(s)

Delafloxacin IV drug product

The delafloxacin drug product for IV infusion is provided in vials as freeze-dried powder for solution for IV infusion. One vial contains 433 mg delafloxacin meglumine which corresponds to 300 mg delafloxacin free acid and the following ingredients: sulfobutyl ether sodium beta-cyclodextrin, and ethylene-diamine-tetra-acetate disodium (EDTA, amount as acid). After reconstitution with 10.5 mL of 0.9% saline solution in the vial, the drug concentration is 25 mg/mL in an aqueous solution of 12.0 mL. All inactive excipients used in the formulation are of compendial grade. The reconstituted powder must not be frozen and may be stored for up to 24 hours under refrigerated (2-8°C) or controlled room temperature (20-25 °C) and then further diluted for IV infusion. The reconstituted powder will be further diluted in a total volume of 250 mL with 0.9% saline solution into IV bag before administration according to the dose scheme. Preparation must be done under controlled and appropriate aseptic conditions.

Delafloxacin oral drug product

The delafloxacin drug product for OS administration is provided as tablets. One tablet contains 649 mg of delafloxacin meglumine which corresponds to 450 mg delafloxacin free-acid and the following inactive ingredients: microcrystalline cellulose, povidone, crospovidone, sodium bicarbonate, sodium phosphate monobasic, citric acid and magnesium stearate. All inactive excipients used in the formulation are of compendial grade.

Reference drug products

Authorized market preparations will be used for Reference treatments.
Reconstitution should follow the instructions reported in the respective SmPC.

- Vancomycin
  Strength: After reconstitution each vial contains 1 g vancomycin (as hydrochloride salt)
  Formulation: Powder for solution for infusion
  Route: IV infusion

- Linezolid
  Strength: 1 mL contains 2 mg linezolid
  Formulation: Solution for infusion
  Route: IV infusion

- Linezolid
  Strength: 1 tablet contains 600 mg linezolid
  Formulation: tablets
  Route: OS administration

- Piperacillin-Tazobactam
  Strength: After reconstitution each vial contains 4 g piperacillin (as sodium salt) and 0.5 g tazobactam (as sodium salt)
  Formulation: Powder for solution for infusion
  Route: IV infusion

- Tigecycline
  Strength: After reconstitution each vial contains 50 mg tigecycline
  Formulation: Powder for solution for infusion
  Route: IV infusion

Additional therapies to add on to the Reference treatment arm as per Investigator's choice are to be selected among the SoC at the site and as locally available.

8.5.2 Packaging, labelling, and storage

The packaging and labelling of study medication will be under Sponsor's responsibility. Each study treatment will be provided in treatment boxes (kit) covering 5 treatment days to be dispensed at Randomization and later on for treatments longer than 5 days.

Delafloxacin IV drug product
The delafloxacin drug product for IV infusion will be provided in single-use glass vials with a stopper and an aluminium crimp seal with a flip-off top (primary packaging). Each vial will be labelled individually. As secondary packaging the vials will be provided in labelled boxes. All labels will be in compliance with the valid international and corresponding national requirements. The labels will report instructions on how to administer and store the IMP in local language of all countries involved in the study. The storage recommendation for the IMP is "Store at 20 to 25°C; excursions permitted to 15°C to 30°C".

Delafloxacin oral drug product
The delafloxacin oral drug product will be packaged in blisters (primary packaging) which are permanently fixed in blister cards (secondary packaging). The IMP will be labelled in compliance with the valid international and corresponding national requirements. The label

will report instructions on how to administer and store the IMP in local language of all countries involved in the study. The storage recommendation for the delafloxacin tablets is "Store at 20 to 25°C; excursions permitted to 15°C to 30°C".

Reference Treatments
Reference treatments will be provided using authorized market preparations. The market product will not be modified except for re-packaging (secondary packaging and labelling). No additional substances or materials apart from secondary packaging materials will be added to the product. All labels will be in compliance with the valid international and corresponding national requirements.

Storage conditions
At the study site, all the IMP must be kept in a secure area inaccessible to unauthorised individuals. In case the medication will be handed over to the patient the Investigator will instruct the patient to keep the IMP according to the storage conditions given on the label. Additional information is provided in the clinical trial medication (CTM) manual which is filed in the Investigator's site file.

8.5.3 Drug accountability

Upon receipt of IMP, study site personnel or designed pharmacist will open the shipment package, verify the contents as stated on the enclosed shipping form, and confirm the receipt through the IWRS.
The IWRS will be used to record the IMP delivery to the study site and the inventory at the site, including dates, quantities, batch / serial numbers and expiry dates. Each IMP kit will have a unique code number (treatment box number). The assignment of the IMP kit to a patient (patient number) will be also done through IWRS.
The Investigator will be responsible for entering in the source documents and in the eCRF the treatment box number relative to the first IMP box (Randomization, Day 1) and any subsequent kit boxes delivered (one kit box covers 5 treatment days) or in case of switching from IV to oral formulation.

Study sites will maintain drug accountability forms to document the dispensed and returned IMP. In case IMP is given to outpatients, they will be instructed to return to the site used or unused oral IMP box at each Visit.
The peel-off labels of IMP will be stuck on the drug accountability paper forms.

8.5.4 Destruction of surplus medication

Throughout the study and at the end of the study, all remaining study treatments will be reconciled at the clinical site under the responsibility of the Investigator.
No later than at the Site Close-out Visit, the used and unused delafloxacin kits and Reference treatments kits shall be returned to the Sponsor for destruction, provided this is not in conflict

with any national export legislation. Any local destruction of the study treatment requires a certificate of destruction, indicating the batch number and the box number.

8.6 Treatments

8.6.1 Treatment administration - frequency and duration of application

After confirmation of eligibility, patients will be randomly allocated to one of the following treatment (please refer to §2.1):

Test Treatment
Delafloxacin 300 mg IV given every 12 hours, with the option to switch to delafloxacin 450 mg OS every 12 hours as soon as patient meets the eligibility criteria to switch to oral formulation as defined in §0, at per blinded observer's assessment.

Reference Treatments for cardiothoracic / related leg SSI (and additional therapy)

- Vancomycin, 15 mg/kg given IV every 12 hours **OR**
- Linezolid, 600 mg IV given every 12 hours, with the option to switch to linezolid 600 mg OS every 12 hours as soon as patient meets the eligibility criteria to switch to oral formulation as defined in 0, at per blinded observer's assessment.

In case of suspicion of Gram-negative in the cardiothoracic SSI, the Investigator shall indicate an additional therapy as per local SoC (with the only exclusion of quinolones) to be assigned together with the Reference treatment (see Schematic study design 2.1).

Reference Treatments for abdominal SSI and (additional therapy)

- Piperacillin / tazobactam, 4 g / 0.5 g IV given every 8 hours **OR**
- Tigecycline, 100 mg IV loading dose, followed by 50 mg IV given every 12 hours.

In case of suspicion of MRSA in the abdominal SSI, if the pre-selected treatment is piperacillin/tazobactam, the Investigator shall indicate an additional therapy as per local SoC (with the only exclusion of quinolones) to be assigned together with the Reference treatment (see Schematic study design 2.1).

Delafloxacin infusion will last 60 minutes. For Reference treatments (and additional therapy, if any), the infusion duration should reflect the instructions reported in the relevant SmPC.

All treatments will be given for 5 to 14 days, based on the Investigator's judgment.

Results of microbiological culture will drive the decision to discontinue or not the additional therapy; however, study treatment should not be discontinued based solely upon microbiological results, being driven by the Investigator clinical judgment.

Please refer to §8.6.4 for any dosage modifications and to §8.4.3 for study treatment restrictions.

8.6.2 Randomization and IMP dispensing

Eligible patients will be randomly assigned in a 1:1 ratio to receive Test or Reference treatments and stratified by site of infection (at least approximately 180 patients either for the cardiothoracic / related leg or abdominal SSI) and superficial or deep infections.
Eligible patients will be randomized at Visit 1 (Day 1) to Test or Reference arm through the IWRS system according to the Randomization list generated by Sponsor or delegate. If the patient is randomized to the Reference arm, the Investigator shall confirm in the IWRS the treatment he/she has preselected out of the two possible Reference treatments for each type of SSI before Randomization.

Re-supply of IMP kits, either for prolonging the IV therapy after 5 days or in case of switch to the oral one (only for delafloxacin and linezolid), will be managed through IWRS by unblinded site staff personnel who will record in IWRS also the end of treatment.

At the time of discharge, patients who are treated with the oral formulation of delafloxacin or linezolid (and are in need to continue the treatment) will receive one kit of oral formulation (covering maximum 5 treatment days) to continue at home –as per Investigator's prescription. They will return to the site as per Investigator's prescription (and in any case within the 5 days of oral treatment covered by the dispensed box). If treatment is in need to be prolonged further (up to an overall maximum duration of 14 days), a new kit covering a maximum of 5 treatment days will be supplied if needed.

8.6.3 Treatment compliance

Study drugs will be dispensed at the study site under the conditions defined in the present protocol and will be administered by the unblinded site staff. The date and time of each study drug administration will be recorded in the source documents and eCRF.
At time of discharge, if patient is still on treatment with oral formulation, he/she will be provided with a paper diary to record daily the tablets intake as per Investigator's prescription.
The site staff should recommend the patient to be strictly adherent with the treatment prescription and verify patient treatment compliance during the following visits by performing drug accountability. Outpatients will be required to bring study drug boxes (used and unused) and completed paper diary at each site visit.

8.6.4 Dosage Adjustment / Modification

Dosing adjustment/modification have to be performed respectively at Randomization and along the study treatment, whenever clinically indicated as per Investigator's judgment, based on creatinine clearance levels calculated according to the Cockcroft-Gault formula.

Men: [(140 - age (years)) x Weight (kg)]/[72 x serum creatinine (mg/dL)]

Women: 0.85 x value calculated by the above formula.

Please refer to the table below for the dosage adjustment/modification.

Treatment	eGFR (mL/min)			
	15 ≤ClCr<20	20 ≤ClCr<30	30 ≤ClCr≤40	40 <ClCr<49
Delafloxacin	200 mg IV every 12h No dosage adjustment required for oral formulation	200 mg IV every 12h No dosage adjustment required for oral formulation	No dosage adjustment	No dosage adjustment
Vancomycin	Dose and dose-interval based on serum vancomycin trough levels and residual renal function as per SmPC*.	15 mg/kg every 24h	15 mg/kg every 24h	15 mg/kg every 24h
Linezolid	No dosage adjustment	No dosage adjustment	No dosage adjustment	No dosage adjustment
Piperacillin/ Tazobactam	Maximum dose suggested: 4 g / 0.5 g every 12h	Maximum dose suggested: 4 g / 0.5 g every 8h	Maximum dose suggested: 4 g / 0.5 g every 8h	No dosage adjustment
Tigecycline	No dosage adjustment	No dosage adjustment	No dosage adjustment	No dosage adjustment

*Individual adjustments of the vancomycin dose or infusion duration should be guided by the results of serum trough levels, with the intent to maintain a minimum trough concentration of > 15 μg/mL up to a maximum trough concentration of 20 μg/mL.

8.6.5 Prior and Concomitant medications and Wound Dressing

8.6.5.1 Prior and Concomitant Medications

All medications, including dietary supplements and nonprescription medications, taken since 30 days before the Screening Visit and until first treatment intake, will be recorded in the eCRF as prior medications.

NOTE: Patients treated with previous IV antimicrobial therapy exceeding 24 hour duration administered during 72 hours prior to start study treatment are not eligible to the study.

All medications, including dietary supplements and nonprescription medications -except topical medications with nonspecific antimicrobial activity- taken since the first treatment intake will be recorded in the eCRF as concomitant medications at each study visit.
Short-acting antipyretic treatment for fever (> 38°C) and/or relief of symptoms associated with fever is allowed. Short-acting antipyretics include acetaminophen/paracetamol and nonsteroidal anti-inflammatory drugs.

NOTE: Additional antibiotic therapies given in case of suspicion of Gram-negative or MRSA involvement (see §8.6.1), will be recorded in a dedicated form of the e-CRF.

8.6.5.2 Prohibited Medications

Antimicrobial treatments other than randomized study treatments and additional therapies, as reported in §8.6.1, are prohibited.
Starting from 2 weeks before Screening and up to the LFU Visit, the use of systemic corticosteroids for more than 10 days at a dose equivalent to > 15 mg prednisone per day is prohibited.
ONLY in case of linezolid administration the use of medicinal product which inhibits monoamine oxidases A or B (e.g., phenelzine, isocarboxazid) in the 2 weeks prior to Screening till the LFU Visit is prohibited.
Topical use of antibacterial agents (eg, mupirocin, retapamulin, fusidic acid) are not allowed for the local infection site care.

8.6.5.3 Wound Care Management

Wound care management of the SSI, including any surgical procedures, will be performed as per local standard practice with the following restriction:

- No topical solution or dressing containing specific antibacterial agents (eg, mupirocin, retapamulin, fusidic acid) shall be used; only topical solution with nonspecific activity (e.g povidone - iodine) may be used.
- No major debridement procedures, or other major surgical procedures to treat the infection on the SSI area are allowed after Randomization.
- Hyperbaric oxygen therapy is not allowed.

The following procedures are allowed:

- Daily dressing changes to the SSI.

- Use of routine packing with local anesthetic, as per SoC, will be allowed if deemed necessary by the Investigator, so long as the packing does not contain an antimicrobial compound.
- Minor bedside procedures, such as debridement and / or vacuum-assisted wound closure, that are part of routine care.

At each visit, and until the patient remains hospitalized, the Investigator will record in eCRF the wound care measures adopted since the previous visit and if any of the prohibited procedures have been performed.

NOTE: If a major surgical procedure is deemed necessary to treat/eliminate the infection, then the patient will be withdrawn from the study and will be considered as clinical failure.

8.7 Study visits, procedures and assessments

The study encompasses up to 8 site visits (depending upon the individual duration of study treatment) and ending with the Late Follow Up Visit that represents the End of Study Visit.

Each patient will undergo the study procedures described below and summarized in the study flowchart (§2.2). Along the study period, any planned and unplanned procedure (e.g. specialist visit, laboratory or radiologic examinations) will be documented and recorded in eCRF.

8.7.1 Pre-screening and Informed Consent process

Pre-screening of potential patients in person or by reviewing medical history / medication to determine their initial eligibility for a study is a common strategy in the recruitment process and can be done before informed consent is obtained.
The Investigator will be trained to encourage patients, at time of hospital discharge after surgical intervention, in coming back to the site in case they should experience any signs or symptoms of SSI.
Before performing any study procedures, all potential eligible patients will sign an Informed Consent Form (ICF) after receiving any clarification by the Investigator. The Investigator will sign the ICF as well.

8.7.2 Screening Visit

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.

The following procedures shall be performed after the patient provides informed consent:

- Check of Inclusion / Exclusion Criteria (§8.4.1 and §8.4.2)
- Collection of demographic data and medical history (§8.7.12.1)
- Physical examination (§8.7.12.2)
- Recording of prior medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, if any (§8.6.5.3)
- Gram stain and microbiological culture of infection site specimen (§8.7.11.3)
- Blood culture (§8.7.11.3)
- Vital signs (§8.7.12.2)
- 12-lead electrocardiogram (ECG) (§8.7.12.5)
- Blood sampling for safety laboratory tests (haematology, biochemistry, coagulation, virology) (§8.7.12.3)
- [redacted]
- Urinalysis (§8.7.12.3)
- Serum (or plasma) and urine pregnancy test, if applicable (§8.7.12.3)
- Recording of any Clinical Event, not associated to any drug intake (§8.8.1.2) and/or any Adverse Event associated to any drug intake (§8.8.1.1) that occurs for the first time or worsens after the signature of the ICF and prior to Investigational Medicinal Product (IMP) administration, if any.

8.7.3 Randomization and Treatment Administration - Visit 1 (Day 1)

Visit 1 has to be scheduled within 1 day from Screening, with the following procedures to be performed prior to first administration of study treatment:

- Instructions and completion of the Short Form-36 (SF-36v2) Health Survey questionnaire (§8.7.11.6), to be performed as first procedure
- Re-check of Inclusion and Exclusion criteria (§8.4.1 and §8.4.2)
- Recording of prior and concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)
- Gram stain and microbiological culture of infection site specimen (§8.7.11.3), if clinically indicated
- Blood culture, if the previous culture was positive or if clinically indicated (§8.7.11.3)
- Vital signs (§8.7.12.2)
- Recording of any Clinical Event, not associated to any drug intake (§8.8.1.2) and/or recording of any Adverse Event associated to any drug intake (§8.8.1.1) that occurs for the first time or worsens after the signature of the ICF and prior to IMP administration, if any
- Investigator’s choice of Reference treatment plus any additional therapy, if needed (§2.1)
- Assignment of the randomized treatment as per IWRS (§8.6.2)

- Administration of study medication.

NOTE-1: If Visit 1 falls on the same day of Screening, all the procedures done at Screening should not be repeated.

NOTE-2: In case of vancomycin assignment, vancomycin trough levels shall be monitored after 3 doses (steady state), at Visit 3 and whenever clinically indicated, for dose or duration of infusion adjustment[2]. See §8.6.4 for further details.

8.7.4 Day 2 Onwards Daily Assessments

Starting from Day 2 up to maximum the End Of Treatment, laboratory and clinical parameters/assessment reported below will be evaluated **DAILY** by the blinded observer who will be responsible to define:

- Eligibility of the patient to switch from IV to the oral formulation (§0).

- Eligibility of the patient to be discharge relevant for assessment of the Hospital Infection-Related Length of Stay-IRLOS (§0).

For the eligibility to IV/OS switch and/or IRLOS (to be assessed as much as possible approximately at the same time and within 12:00), the following procedures shall be daily performed:

- Vital signs: BP, HR and Body Temperature (maximum T° recorded from the last 24h)
- Blood sampling for haematology (WBC count only)
- Assessment of patient ability to tolerate PO diet and no gastrointestinal absorption problem
- Wound status idoneous for home care management

NOTE 1- At Visit 2 and Visit 3, vital signs and WBC count are also contemplated and shall be performed only once.

NOTE-2: date and time of the actual switch to oral formulation (i.e. first intake of the oral formulation), will be recorded by the Investigator. Assignment of delafloxacin or linezolid oral kit will be performed through IWRS by unblinded site staff.

NOTE-3: date and time of the actual hospital discharge (i.e. the time when the letter of discharge is issued) will be recorded by the Investigator upon occurrence along the study up to End of Study Visit.

NOTE-4: 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.

8.7.5 Visit 2 (Day 3 – 4)

The following procedures shall be performed between 48hand72h after first dose administration.

Outpatients (i.e. patients already discharged from the hospital) shall return to the site for the study visit.

- Recording of AEs occurred since previous visit, if any (§8.8.2)
- Recording of concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)
- Gram stain and microbiological culture of infection site specimen, if clinically indicated (§8.7.11.3)
- Blood culture if the previous culture was positive or if clinically indicated (§8.7.11.3)
- Vital signs (§8.7.12.2)
- Blood sampling for safety laboratory test (haematology, biochemistry, coagulation, (§8.7.12.3)
- [redacted]
- Urinalysis (§8.7.12.3).

In case of early treatment withdrawal, patients should undergo the EOT Visit, and should be followed as described in §8.4.4.

NOTE: The infection site specimen for microbiological culture should be collected before initiation of any alternative antibacterial therapy.

8.7.6 Visit 3 (Day 7)

The following procedures shall be performed at Day 7 if the patient is still on treatment.
Outpatients (i.e. patients already discharged from the hospital) shall return to the site for the study visit.

- Patient's completion of the SF-36v2 Health Survey (§8.7.11.6), to be performed as first procedure
- Recording of AEs occurred, since previous visit, if any (§8.8.2)
- Recording of concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)

- Gram stain and microbiological culture of infection site specimen, if clinically indicated (§8.7.11.3)
- Blood culture if the previous culture was positive or if clinically indicated (§0)
- Vital signs (§8.7.12.2)
- Blood sampling for safety laboratory test (haematology, biochemistry, coagulation) (§8.7.12.3)
- [redacted]
- Urinalysis (§8.7.12.3)
- Therapeutic Drug Monitoring for vancomycin, if appropriate (§8.6.4)

In case of early treatment withdrawal, patients should undergo the EOT Visit, and should be followed as described in §8.4.4.

NOTE: The infection site specimen for microbiological culture should be collected before initiation of any alternative antibacterial therapy.

8.7.7 End of Treatment - EOT Visit

The following procedures shall be performed at EOT Visit (within 1 day after last dose administration).
Outpatients (i.e. patients already discharged from the hospital) shall return to the site for the study visit as per Investigator's prescription.

- Patient's completion of the SF-36v2 Health Survey (§8.7.11.6), to be performed as first procedure
- Contact IWRS to report treatment completion status (§8.6.2)
- Recording of AEs occurred, since previous visit, if any (§8.8.2)
- Recording of concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)
- Gram stain and microbiological culture of infection site specimen (§8.7.11.3)
- Blood culture if the previous culture was positive or if clinically indicated (§8.7.11.3)
- Physical examination (§8.7.12.2)
- Vital signs (§8.7.12.2)
- 12-lead ECG (§8.7.12.5)
- Blood sampling for safety laboratory test (haematology, biochemistry, coagulation, (§8.7.12.3)
- [redacted]
- Urinalysis (§8.7.12.3)
- Serum (or plasma) pregnancy test, if applicable (§8.7.12.3)
- Assessment of clinical response (§8.7.11.2).

In case of the EOT Visit is performed for early treatment withdrawal, patients should be followed as described in §8.4.4.

8.7.8 Test of Cure -TOC Visit

The following procedures shall be performed at TOC Visit (7 - 14 days after last dose). Outpatients (i.e. patients already discharged from the hospital) shall return to the site for the study visit.

- Patient's completion of the SF-36v2 Health Survey (§8.7.11.6), to be performed as first procedure
- Recording of AEs occurred, since previous visit, if any (§8.8.2)
- Recording of concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)
- Gram stain and microbiological culture of infection site specimen (§8.7.11.3)
- Blood culture if the previous culture was positive or if clinically indicated (§8.7.11.3)
- Vital signs (§8.7.12.2)
- 12-lead ECG (§8.7.12.5)
- Blood sampling for safety laboratory tests (haematology and biochemistry) (§8.7.12.3)
- Urinalysis (§8.7.12.3)
- Assessment of clinical response (§8.7.11.2).

8.7.9 Follow-up Visit or Phone Call

Recording of AEs and concomitant medications will be performed 21 days (± 2 days) after the last dose. Outpatients (i.e. patients already discharged from the hospital) will receive a follow-up telephone call to collect this information or will be invited to the site.

8.7.10 Late Follow-up /End of Study Visit

The following procedures shall be performed at LFU Visit (28 - 30 days after last dose). Outpatients (i.e. patients already discharged from the hospital) shall return to the site for the study visit. LFU Visit represents the End of Study Visit.

- Patient's completion of the SF-36v2 Health Survey (§8.7.11.6), to be performed as first procedure
- Recording of AEs occurred, since previous visit, if any (§8.8.2)
- Recording of concomitant medications (§8.6.5.1)
- Infection site assessment (§8.7.11.1)
- Documentation of SSI wound care management, since the previous visit, if any (§8.6.5.3)

- Assessment of clinical response (§8.7.11.2).

8.7.11 Assessment of Efficacy

8.7.11.1 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; mm)
  - lymphangitis
  - lymphadenopathy (with number and anatomical site of lymph nodes)

8.7.11.2 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.

8.7.11.3 Microbiological Assessment

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 leucocytes (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 bacterial isolates (under ambient condition on transport medium) and two back-up bacterial isolates (frozen) 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 with broth microdilution. 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.

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.
Gram stain: two Gram stain slides will be prepared from every positive blood culture bottle. One slide should be stained and evaluated at the Local/Regional microbiology laboratory and both slides read and unread will be sent to Central laboratory.
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 isolates (under ambient condition on transport medium) and two back-up isolates (frozen, on dry ice) 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.

8.7.11.4 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(s) 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".

The following pathogens are examples of primary pathogens that will be used to determine the microbiological responses in the study. The typical bacterial pathogens include but may not be limited to:
Gram-positive organisms
Staphylococcus aureus (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates)
Staphylococcus haemolyticus
Staphylococcus hominis
Staphylococcus lugdunensis
Streptococcus agalactiae
Streptococcus anginosus Group (including Streptococcus anginosus, Streptococcus intermedius, and Streptococcus constellatus)
Streptococcus dysagalactiae
Streptococcus mitis Group (including Streptococcus cristatus, Streptococcus gordonii, Streptococcus oralis, Streptococcus mitis, and Streptococcus sanguinis)
Streptococcus pyogenes
Enterococci, incl. vancomycin-resistant strains
Gram-negative organisms
Enterobacteriaceae, including multidrug-resistant strains
Pseudomonas aeruginosa, Pseudomonas spp.

Acinetobacter baumannii, Acinetobacter spp.
Anaerobes

8.7.11.5 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.

8.7.11.6 Patient reported outcome questionnaire

The SF-36v2® Health Survey is a short-form health survey with 36 questions, with one-week recall period, that yields scores for psychometrically-based physical component summary and mental component summary and for eight health domains (i.e. physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health). Patients will complete the questionnaire by indicating his/her health state by ticking (or placing a cross) in the box against the most appropriate statement at each question on paper format. The Investigator or delegate will report the collected answers in the eCRF.
Questionnaire has to be administered at the study site at Visit 1, Visit 3 (if performed), EOT, TOC and LFU Visits prior to any other study visit procedure.

[redacted]

8.7.12 Assessment of Safety

8.7.12.1 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 §8.7.11.1) should be recorded on the Infection Site Assessment pages of the eCRF.

8.7.12.2 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.

8.7.12.3 Clinical Laboratory Evaluation

Safety laboratory testing will be performed by a local laboratory at the timepoints specified in the Study Flow Chart (§2.2). 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 (HbA1c) 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.

8.7.12.4 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.

8.7.12.5 12-Lead ECG

Standard 12-lead ECG will be performed at Screening, at EOT and TOC Visits as summarized in the study flowchart (§2.2), 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.

8.7.13 Study endpoints

8.7.13.1 Primary efficacy endpoint

The primary efficacy end-point is the Clinical Success defined as the clinical response of "Cure" or "Improved" at TOC (7 - 14 days after last dose) in the ITT Intent-to-Treat (ITT) and the Clinical Evaluable (CE) populations.

8.7.13.2 Secondary efficacy endpoints

The study secondary endpoints are:

a) [redacted]

d) Eligibility to switch to oral formulation according to the blinded observer's assessment as per criteria reported in §0;
e) Hospital IRLOS (Infection Related Length of Stay), in the ITT and CE populations, beginning with first dose of study treatment and ending when the patient is considered eligible to discharge (up to maximum EOT) according to the blinded observer's assessment as per criteria reported in §0;
f) Hospital LOS (Length of Stay), in the ITT and CE populations, beginning with the diagnosis of SSI (Screening) and ending with actual hospital discharge;
g) Microbiological response at EOT and TOC Visits in the MITT and the Microbiologically Evaluable (ME) populations;
h) [redacted]

[redacted]

[redacted]

[redacted]

8.7.13.4 Safety endpoints

The study will assess:

- Incidence, intensity (severity), seriousness and treatment-causality of TEAEs (i.e. AEs that occurred after the first study drug intake).
- Frequency of clinically significant changes in vital signs, 12-lead ECG and laboratory parameters (haematology, biochemistry, coagulation and urinalysis), post-dose versus baseline.

NOTE: The latest assessments performed before first study treatment administration will represent the baseline.

8.7.13.5 [redacted]

8.8 Adverse events definitions, monitoring / recording and management

8.8.1 Definition

8.8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered with a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

8.8.1.2 Clinical Event

Any adverse clinical condition not associated to a drug intake that occurs for the first time or worsens after signing the informed consent but prior to IMP administration will be classified as "Clinical Event".

8.8.1.3 Treatment -Emergent Adverse Event

Any AE that occurs for the first time or it worsens in terms of seriousness or severity after the first study drug intake will be classified as Treatment -Emergent Adverse Event (TEAE).

8.8.1.4 Drug relationship

The relationship between an AE and study drug(s) will be judged according to the following categories:

1. **Certain:** The AE occurs in a plausible time relation to the administration of the drug and cannot be explained by a concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2. **Probable:** The AE occurs in a reasonable time relation to the administration of the drug, it is unlikely to be attributed to a concurrent disease or other drugs or chemicals and it follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information (AE reappearance after drug reintroduction) is not required to fulfill this definition.
3. **Possible:** The AE occurs with a reasonable time relation to the administration of the drug, but it could also be explained by a concurrent disease or other drugs or chemicals. Information on drug withdrawal (dechallenge) may be lacking or unclear.
4. **Unassessable:** The relationship cannot be judged, because of the information is insufficient or contradictory and cannot be supplemented or verified.
5. **Unlikely:** A causal relationship cannot be definitively ruled out, but
   - other drugs, chemicals, or underlying disease provide plausible explanations

   and / or
   - the temporal relation to the administration of the drug makes a causal relation improbable (but not impossible).
6. **Not Related:** Any of the following are present:
   - existence of a clear alternative explanation
     and / or
   - unreasonable temporal relationship between drug and event
     and / or
   - non-plausibility

8.8.1.5 Adverse Drug Reactions

An adverse drug reaction (ADR) is any untoward and unintended response to an IMP that is related to any dose administered.

The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

An ADR is considered any AE for which the relationship is considered as:

- Certain
- Probable
- Possible
- Unassessable

An AE is not considered as ADR when the relationship is judged as:

- Unlikely
- Not related

8.8.1.6 Seriousness

An AE/ADR is considered as Serious when:

- results in death;
- is life - threatening;
  NOTE: Life - threatening is considered any AE in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity;
- is a congenital anomaly / birth defect;
- is another medically important condition that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. Any suspected transmission of an infectious agent via a medicinal product is considered serious and should be assessed under the category of medically important events in the absence of other seriousness criteria.

An AE/ADR is considered **non-serious** when it does not fulfill the conditions for the definition of SAE / ADR.

NOTE: neither prolonged hospitalization only due to SSI nor planned surgery should be regarded as SAE.

8.8.1.7 Adverse Event / Adverse Drug Reaction intensity (severity)

The intensity level of a serious or a non-serious AE or ADR is attributed according to the following definitions:

- **Mild**: does not interfere with routine activities; in case of laboratory tests, when there is a mild abnormality.
- **Moderate**: interferes with the routine activities; in case of laboratory tests, when there is a moderate abnormality.
- **Severe**: makes it impossible to perform routine activities; in case of laboratory tests, when there is a significant abnormality.

8.8.1.8 Adverse Event / Adverse Drug Reaction expectedness

An AE/ADR is considered **unexpected** when the nature, severity, or outcome of the AE/ADR **is not** consistent with the information provided in the reference safety document.

NOTE: For the test product, the safety reference document for assessment of expectedness will be the Investigator's Brochure for delafloxacin in force at the time of the event. For the reference products, the safety reference document will be the Section 4.2 of the respective SmPC.

8.8.1.9 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAE judged by the Investigator or the Sponsor as drug-related (§8.8.1.5), and considered as unexpected qualifies as a SUSAR.

SUSARs are subject to expedited reporting, as specified in §8.8.2.1 as having a "Reasonable Possibility" of relationship with the IMP.

8.8.1.10 Individual Case Safety Report

Format and content provided to describe one or several AEs or a disease experience that occurs to an individual patient at a particular point of time.

8.8.2 Collection, recording and reporting of adverse events

At each visit the Investigator will collect and assess any occurred subjective or objective AE, and clinical event occurred to each patient after his/her signature of the informed consent.

The Investigator should manage as AE any laboratory test abnormality (newly occurring after the IMP administration or worsening of previously known abnormalities) considered as clinically significant (CS): i.e. values significantly above or under normal range or which require an intervention or diagnostic tests, or may result in the IMP discontinuation.

Any AE communicated by the patient or by the patient's relatives or delegates through phone calls, letters or emails will also be recorded and assessed. In these cases the Investigator will try to obtain medical confirmation and assessment of the occurred AE.

When an AE has occurred, the **Investigator shall record on the respective eCRF - AE recording page any event, both serious and non-serious, whether or not thought to be drug - related,** observed in or reported by the patient (or relatives / delegates), specifying the judgment on the causal relationship with the study treatment. When the Investigator confirms, on the eCRF - Case page, that all the collected information on any Individual Case Safety Report (ICSR) (serious or not, related or not) has been entered in the eCRF, an e-mail notification will be sent to the Sponsor.

The Investigator is expected to record also any AE occurring during the study follow-up period until the LFU Visit (28 - 30 days after last dose).

Any available information and diagnostic measure (laboratory and instrumental tests, procedures, etc.) shall be recorded in the eCRF-AE pages.

When relevant, also the eCRF pages concerning medical history, concomitant medication, and laboratory test will be retrieved by the Sponsor's Study Drug Safety Manager (SDSM).

8.8.2.1 Management of Serious Adverse Events (SAEs)

Reporting duties of the Investigator

The Investigator must report all the collected information on any ICSR with SAE (whether or not deemed related to the investigational drug) in the eCRF - AE pages, **no later than 24 hours** after the first knowledge of the occurrence of the event.

Once the information is validated in the eCRF - AE page, a notification e-mail will be automatically generated and sent to the Sponsor's SDSM (Study Drug Safety Manager), so that the SAE can be retrieved.

The Investigator will be provided with the paper CRF - AE pages to be used only in case of breakdown of the eCRF System. In such case, the Investigator will be responsible for sending the paper CRF-AE pages and inserting the data in eCRF as soon as the system works again.
Whenever the paper CRF - AE page is used, it must be submitted by e-mail to the Sponsor's SDSM:

For the initial SAE the Investigator should enter in the eCRF or on the paper CRF-AE page (only if the eCRF does not work) all the available information.
When the paper CRF AE pages are used, also the following fields should be reported in CRF AE pages:

- Patient ID (patient number)
- Reporters name and telephone number for clarifications

$$responder\ rate \quad \frac{number\ of\ responder}{number\ of\ responder \quad number\ of\ nonresponder}$$

The Sponsor's confirmation of reception of the SAE report must be kept in the patient's records.
Any questions which arise during the processing and medical review of the SAE will be managed by means of electronic queries (i.e. queries in the eCRF). In case of breakdown of the eCRF System, queries will be sent by e-mail.
Any information provided by the Investigator as a query reply or as a follow-up SAE report will be processed in the same way as the initial SAE report within the required timeframe.
When relevant, also the eCRF pages concerning medical history, concomitant medication, and laboratory tests will be retrieved by the Sponsor's SDSM.
Any further information and supporting documentation that become available (copies of laboratory reports, tests, procedures, autopsy evidence of the cause of death, etc.) shall be provided no later than 24 hours after the knowledge, by the Investigator to the Sponsor's SDSM by email.

The Investigator must also comply with the local applicable obligation(s) on the reporting of ADRs to the local concerned RA / EC.

Reporting duties of the Sponsor
The Sponsor shall ensure that all relevant information about any SUSAR will be expeditiously reported to the CAs and EC (following general and local rules and procedures), with these deadlines after the first knowledge, intended as the day when the Sponsor or the CRO receives the notification of the SUSAR:

- Fatal and life threatening unexpected cases, no later than 7 days;
- Other unexpected serious cases, no later than 15 days.

The Sponsor shall ensure that all relevant new information and supporting documentation that subsequently become available, will be also expeditiously reported as follow-up information no later than 15 days.
Furthermore, the following safety issues will be subjected to expedited management for the identification of possible necessary actions:

- SAEs associated with the trial procedures
- Potential clinically significant findings emerging from non-clinical studies
- An anticipated end or suspension for safety reasons of another trial with the same study drug

When appropriate and applicable the Sponsor will provide the adequate information also to the Investigators.

8.8.2.2 Management of Non-Serious Adverse Events
The Investigator must record all the available information concerning any ICSR with non-serious adverse events (NSAE) (whether or not deemed related to the investigational drug) in the corresponding section of the eCRF, **within 5 calendar days** after the first knowledge of the occurrence of the case.

When a new AE is entered, a notification e-mail will be automatically generated and sent to the SDSM, so the NSAE can be retrieved.
When relevant, also the CRF pages concerning medical history, concomitant medication, and laboratory test will be retrieved by the SDSM.

8.8.3 Management of any laboratory abnormalities

Any laboratory test abnormality which is considered by the Investigator as CS is to be recorded and managed as NSAE or SAE if it matches with any seriousness criteria (§8.8.2 for AE collection).

8.8.4 Management of pregnancy exposure cases

The Investigator is expected to record in the provided "Pregnancy Exposure Report Form" any case of pregnancy exposure occurring in a female patient or in a male patient's partner, during the treatment and follow-up period until the LFU Visit (28 - 30 days after last dose) provided that the female patient or the patient's partner enrolled in the study has signed the related pregnancy ICF.
The initial "Pregnancy Exposure Report Form" will be sent by email to the SDSM within 5 days after being made aware of the pregnancy. The Investigator is requested to follow each case of pregnancy exposure until the outcome. The follow-up of the "Pregnancy Exposure Report Form" will be completed with data of the outcome and sent to the SDSM within 5 days after knowledge of the delivery. The mentioned form will be distributed to the sites to be used for this purpose.

Pregnant women are excluded from enrolment onto the study; in case a patient becomes pregnant during the study drug administration period, she shall be discontinued from treatment.
If the pregnancy results in an abnormal outcome (miscarriage or new-born with congenital abnormality and/or stillbirth), the follow-up of the "Pregnancy Exposure Report Form" will be completed and sent to the Sponsor within 24 hours and the abnormal outcome, will be recorded in the eCRF as a SAE and managed as above described (see §8.8.2.1). If the eCRF is not available anymore, the paper CRF - AE page (or any other support for reporting if the paper form is not available either) will be used as a back-up.

8.8.5 Annual Safety Reporting

Once a year throughout the clinical trial, the Sponsor will assure the submission to the concerned national CAs and ECs of a safety report (Development Safety Update Report, DSUR), taking into account all new safety information received during the reporting period.

8.8.6 Breaking of the Randomization Code

Not applicable.

8.8.7 Serious and Non-serious Adverse Events Follow-up

After the LFU Visit, the Investigator is not requested to actively follow-up the patient unless ongoing SAEs or NSAEs of special interest are present. In these cases, the event will be followed until the event disappears or the patient's conditions stabilize. However, if the Investigator becomes aware of a SAE with a suspected causal relationship to the study treatment that occurs after the end of the clinical trial in a patient treated by him or her, the Investigator shall, without undue delay, report the SAE to the Sponsor. These SAEs occurred after LFU Visit should be also recorded in the eCRF until it is available. If the eCRF is not available, the paper SAE form will be used as a backup (or any other support for reporting if the paper form is not available either).
Additionally, patients who discontinued the treatment for any safety reason will be also followed until the event disappears, the patient's conditions stabilize, or until recovery from all toxic effects and longer in case of expected delayed toxicity.

9 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.1 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 Reference treatment arm in terms of clinical response (Clinical Success) rate with a non-inferiority margin of 10% and 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.

9.2 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: all subjects in the ITT population who meet the following criteria:

- 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
- Did not receive any concomitant, systemic antibacterial therapy except for lack of efficacy
- Had no protocol deviations that would affect assessment of efficacy at the reference visit.

CE populations will be defined at EOT, TOC, LFU timepoints and for eligibility to switch to oral formulation, IRLOS and LOS.

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.

9.3 Statistical analysis

9.3.1 Descriptive statistics

All study variables will be presented by treatment and overall, by using the appropriate descriptive statistics according to the variable nature, unless otherwise specified:

- Continuous variables: number of non-missing observations, arithmetic mean, standard deviation, minimum, median, maximum.
- Categorical variables: number of non-missing observations and column percentages (N, %).

All statistical analyses, unless otherwise specified, will be based on 2-sided 95% CIs around the difference in treatment outcomes.

9.3.2 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:

$$= \qquad +$$

All the statistical comparisons will be a test for non-inferiority of delafloxacin versus the Reference treatment arm at a 10% non-inferiority margin (unless otherwise specified), 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.
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 noninferior 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:

$H0: P_d - P_r \leq 0$

$H_a: P_d - P_r > 0$

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. The relative p-value will be produced by using a Chi^2-Test.

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 CE populations, while for superiority only on the ITT population.

9.3.3 Secondary efficacy analysis

All the secondary efficacy endpoints will be descriptively analyzed and tested, when applicable, for non-inferiority with the possibility to switch for superiority through an ad hoc inferential analysis, as reported below:

- 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 §0 are met. Percentages are statistically analyzed analogously to the primary efficacy variable, in the ITT and CE populations. Additionally, time to eligibility to discharge will be visually assessed by Kaplan-Meier curves and the relative p-value will be obtained by a Log-rank test, in the ITT and CE population.
- 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 visually assessed by Kaplan-Meier curves and the relative p-value will be obtained by a Log-rank test, in the ITT and CE population.
- 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 §0 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 visually assessed by Kaplan-Meier curves and the relative p-value will be obtained by a Log-rank test, in the ITT and CE populations.
- Microbiological efficacy responses at EOT and TOC, as defined in §0, 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.
- [redacted]

[redacted]

[redacted]

9.3.4 [redacted]

[redacted]

[redacted]

9.3.5 Subgroup analysis

The most relevant subgroups that will be analyzed (if applicable) are:

- 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 $PaCO_2$ <32 mm Hg
  - abnormal white blood cell count (>12,000/mm^3 or <4,000/ mm^3 or >10% bands)

[redacted]

9.3.6 [redacted]

[redacted]

[redacted]

[redacted]

9.3.8 Interim analysis and stopping rules

No interim analysis is planned for this study.

9.3.9 Data imputations

A missing clinical response will be imputed as defined in §8.7.11.2
No missing responses are expected for the microbiological response.

9.4 Protocol violations and Data Review

Categories of protocol violations will be assigned to each potential protocol violation and will be integrated in the SAP.

For the primary efficacy analysis, a Data Review Meeting (DRM) will take place at the end of the study in order to evaluate and accept the data management report, discuss remaining issues (outstanding queries, unresolved errors), and to confirm and approve relevant protocol violations. Patients who experience relevant protocol violations, accordingly to what is described in §9.2, will be excluded from the CE population.
After final DRM takes place and the database is considered cleaned, the database will be locked.

9.5 Statistical analysis plan

The SAP will be finalized before the study initiation. The SAP will describe in detail study endpoints and the statistical analyses to be performed, including, if any, also additional endpoints and analyses not planned in the protocol.
In case major changes in the original primary endpoint or in the original primary analyses will occur during the study, these changes will be the subject of a substantial protocol amendment.
Minor deviations (e.g. not involving changes in the primary endpoint and analysis) which might occur during the study will be detailed only in the SAP.
All statistical analyses not pre-specified and run after data locked will be considered additional / post-hoc analyses.

10 DATA QUALITY MANAGEMENT

10.1 Data collection

Data collection activities will be carried out under the responsibility of the Sponsor. Patient data will be collected using the data capture systems described below. Patients will be identified by the patient study identification number (patient ID), assigned at the Screening Visit.

[redacted]

The data will then be processed, evaluated, and stored in pseudonymised form in accordance with applicable data protection regulations.

10.1.1 Electronic case report forms

Clinical data collected during the study at sites will be recorded in an eCRF using Medidata RAVE which is a validated system. The eCRF will be developed based on this study protocol under the responsibility of the Sponsor that will also perform user acceptance test of the eCRF in order to ensure the protocol adherence.
The eCRF will be made available to the study personnel by means of the iMedidata interface which is a validated system. The accounts will be individual and password-protected. The blinded observer will have a restricted access to eCRF in order to preserve the blind condition.
The Investigator or designee will be responsible for entering study data into the eCRF in accordance to the eCRF Completion Guidelines provided by the Sponsor. In order to improve the quality of data collection and cleaning, data shall be entered into the eCRF as closely as possible to the time when they become available and not later than within 5 working days. The eCRF data will not be considered as source data (see §10.3).
Investigators will ensure the accuracy, completeness and consistency of data entered signing electronically the eCRF using the personal password.
An audit trail within the system will track all changes made to the data.

10.1.2 IWRS

IWRS system ClinPhone RTMS, provided by Parexel International, is a validated system used by the site personnel for the patient screening (including assignment of the patient number), Randomization, kit assignment, patient status change.
The implementation of the system for this study will be detailed in the RTMS specification document. Sponsor will perform the user acceptance test of the implementation.
Site staff, excluding the blinded observer, will be provided with a personal user name and password to access to IWRS.

An IWRS user manual will be provided to site personnel.
Some data such as patient ID and visit dates, collected through IWRS system, could be automatically integrated in eCRF. The integration process will be detailed in a specific integration document. All the above mentioned documents will be provided by Parexel International.

10.1.3 Patient reported outcome questionnaire

The Optum™ SF-36v2® Health Survey asks 36 questions that yield an eight-scale profile of functional health and well-being, as well as two psychometrically based physical and mental health summary measures. The questionnaire will be administered to the patients on paper format, the Investigator or delegate will report the collected answers in the eCRF.

10.1.4 Patient Diary

At the time of discharge, the patient, if still on treatment with the oral formulation of the therapy, will receive a paper diary to record date and time of each tablet intake. The patient has to bring the diary to the site at the next study visit and the completed diary pages have to be checked and collected by the Investigator. The Investigator or designee is responsible for entering data recorded in the diary into the e-CRF.

10.1.5 Centralized Laboratory / Examination data

Local/Regional and Centralized microbiology laboratory data will be managed according to laboratory SOPs. Centralized laboratory data and relevant Local/Regional laboratory data will be transferred from Centralized laboratory to Menarini Ricerche S.p.A., Clinical Sciences Department. The transfer process will be detailed in a specific transfer document, agreed between Centralized laboratory and Sponsor.Descriptive statistical analysis will be performed on these data. The data will be also made available to the external Expert for microbiological response analysis (§8.7.11.4). The results of the analysis will be recorded by the Expert in eCRF.

10.1.6 Data capture systems versions and validation documentation

Versions of the data capture systems can change during the study. The Sponsor will maintain a list of the data capture system versions used and the validation documentation of each version. The list and the validation documentation will be provided to the site at the Site Initiation Visit (SIV) and will be updated at any data capture system version change.

10.2 Clinical data management

Data Management will be carried out under the responsibility of Sponsor. eCRF data will be electronically verified through the use of on-line and off-line checks. Discrepancies in the data will be resolved by means of electronic queries. Data will be locked by the Data Manager

when all activities for the trial, including medical revision of the data, are complete and no more entries are expected.

Data from sources other than eCRF will be provided to the Data Manager on an agreed scheduled basis. The Data Manager has the responsibility to reconcile data captured in the eCRF, with external data sources. Discrepancies, found in the reconciliation of the data, will be addressed by means of queries.

A clear overview of all clinical data management activities will be given in the Data Management Plan.

10.3 Source data

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial.
Original documents and data records include, but are not limited to hospital / patients' medical records, laboratory notes, ECG records, patients' identification forms, SF-36v2 questionnaires, patient diary and pharmacy dispensing records.
Study sites will also maintain a paper drug accountability forms for the CTM to document dispensed and returned CTM per patient.
Moreover, the blinded observer's judgment about patient eligibility to switch to oral formulation and to discharge as well as the related data will be collected through a paper worksheet, which will represent the source data of the assessment to be recorded in eCRF.
Source data should be held available for perusal by the Sponsor representatives for the study or to other authorized persons such as auditors and inspectors of Regulatory Authorities.
Direct access to source data is defined as the permission to examine, analyze, verify and reproduce any records and reports that are important for evaluation of a clinical trial. Any party allowed to direct access to study source data and documents should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary information.
Data should be consistent with the source documents and discrepancies, if any, should be explained in writing by amending the source documents or with additional documentation, if needed. All the original documentation pertinent to the study procedures must be available for review in each patient's record.

10.4 Quality control / quality assurance

10.4.1 Study Monitoring

This trial will be monitored in accordance with the ICH Note for Guidance on GCP. Monitoring will be carried out by PSI CRO AG. This study will follow the CRO quality risk management process, which is made up of systematic implementation of overall risk assessment, critical processes and data identification, risk definition, evaluation and response planning, risk monitoring and control, and risk communication and reporting. Based on

overall initial risk assessment for the study, the project Risk Management Plan will be developed. The project Risk Management Plan will contain risk based monitoring strategy, which will provide guidance on blend of onsite, offsite and central monitoring. Throughout the study, the Central Monitoring Manager will be responsible for Central Monitoring, performing periodic review of the risks, follow-up on the identified issues, and ensuring that the process of risks monitoring and review is appropriately documented; the detailed description of the Central Monitoring Manager activities will be included into the Monitoring Plan. Central monitoring will be executed by risk based monitoring tool. The site monitor will perform on site and off site visits to the trial sites throughout the study conduct. Facilities, study drug, storage area, eCRF, patient's source data, and all study documentation will be inspected/reviewed by the site monitor for adherence to the protocol and GCP. At each on site visit, the monitor will review eCRFs for completion and accuracy. Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any revealed discrepancies will be reviewed with the Investigator and his/her staff. The Investigator agrees to allow access to all study related materials needed for the proper review of study conduct and to assist the monitor during monitoring visits and during data cleaning process. Monitoring procedures will be based on risk based monitoring, particularly focusing on critical data, critical processes and subject safety, for example, informed consents, adherence to inclusion/ exclusion criteria, drug accountability, documentation of SAEs and proper recording of efficacy and safety measurements. All monitoring activities including risk based approach will be described in detail in the study-specific monitoring plan.

10.4.2 Quality Assurance

Independent study audit(s) and / or inspection(s) may take place at any time during or after the trial. The audit / inspection can be carried by the Quality Assurance (QA) of the CRO, the QA provider independent from the Sponsor or a CA. At all times, the confidentiality of subject related documents will be maintained.

11 PREMATURE TERMINATION OF THE WHOLE STUDY

The whole trial may be discontinued at the discretion of the Sponsor in the event of any of the following:

- New information leading to unfavorable risk-benefit judgment of the investigational products due to:
  - Occurrence of significantly previously unknown AEs or unexpectedly high intensity or incidence of known AEs
  - New evidence of unfavorable safety or efficacy findings (from clinical or non-clinical examinations, e.g. toxicology)
- The Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons or based on emerged data which may impact on the rationale to perform the study
- Discontinuation of development of the IMP

CAs and IECs will be informed about the discontinuation of the trial in accordance with applicable regulations.

12 END OF CLINICAL TRIAL AND ARCHIVING

The clinical study will end with the collection and analysis of study data and the issue of the Clinical Study Report. All essential documents will be archived by the Sponsor according to the relevant SOP.

12.1 Archiving of electronic documentation / data

As described in §5.5, duplicate electronic media such as CDs / DVDs (one for routine access and one for back-up) containing the patient data in PDF format (e.g. eCRFs, questionnaires) for each site will be prepared by the Sponsor or a delegate for archiving purposes. The electronic media, of a not re-printable type, will be appropriately labelled recording the files / data included. The files should contain at least the eData copy clearly reporting the system name, study code and the eCRF used; for eCRF data also the electronic signature and the associated audit trails have to be included.
The Investigator should verify whether the provided electronic media represent a complete copy of eCRFs generated during the study relevant for the site. The Investigator has to confirm the receipt and correctness of the material by signing a dedicated form provided by the Sponsor, the signed form has to be collected and archived in the eTMF.
Two copies of the same electronic media prepared for the sites or cumulative electronic media with the same content will be archived by the Sponsor. In addition the Sponsor is responsible to create 2 electronic media (one for routine access and one for back-up) containing an integrated SAS database with all study data e.g. eCRF, IWRS, centralized laboratory), with appropriate refreshment procedures.

Investigators and Sponsor will be also responsible to refresh their electronic media approximately every 7 years to ensure long term archiving of files / data.

13 REFERENCES

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2. EMA/645879/2017- EMA recommends changes to prescribing information for vancomycin antibiotics. 21 September 2017.

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17. [redacted]

18. Practice Guidelines for the Diagnosis and Management of Skin and Doft Tissue Infections: 2014 Update by the Infectious Diseases Society of America

19. Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. CPMP/EWP/558/95 rev 2. December, 2011.