# Randomized study comparing different durations of antibiotic treatment for diabetic foot infections

**Final Protocol: 2 July 2016**

**Classification of Study: Class A**

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## 1. PROTOCOL SYNOPSIS

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| **OBJECTIVES** | **Primary Objective**<br>• To determine the non-inferiority of 3 weeks of antibiotic treatment compared to 6 weeks for diabetic foot toe osteomyelitis, and 10 days compared to 20 days for non-bacteraemic diabetic foot soft tissue infections (including erysipelas). |
| **DESIGN** | This is a randomized, unblinded, single-centre study. After eventual surgical debridement (not amputation), patients will be randomized to receive 1 of 2 targeted antibiotic regimens, in the ratio 1:1.<br>For diabetic toe osteomyelitis, the patients will be randomized between a 3 and a 6 week's arm, for soft tissue infections between 10 and 20 days. The final assessments used in the primary efficacy analysis will be obtained at the test-of-cure (TOC) visit approximately 60 days after treatment is stopped. |
| **NUMBER PATIENTS** | Approximately 120 subjects will be enrolled (60 for osteomyelitis and 60 for soft tissue infections). |
| **STUDY SITE** | University of Geneva Hospitals. Others centers might participate. |
| **PATIENT POPULATION** | **Inclusion criteria**<br>1. Is aged ≥ 18<br>2. Has diabetes mellitus, according to the American Diabetes Association (ADA) criteria.<br>3. Has at least one visible inflammation with the following clinical manifestations of a moderate or severe infection based on the Infectious Disease Society of America (IDSA) guidelines for the "Diagnosis and Treatment of Diabetic Foot Infections".<br>Local Infection is defined as having ≥ 2 manifestations of inflammation (local welling or induration, erythema, local tenderness or pain, local warmth, purulent discharge (thick, opaque to white or sanguineous secretion).<br>Moderate infection is defined as: local infection (as described above) with erythema > 2cm, or involving structures deeper than skin and subcutaneous tissues and no systemic signs.<br>4. Has received appropriate surgical intervention to remove all necrotic tissue or tenotomy.<br>5. Osteomyelitis limited to bone contact, inflammation and cortical lesions in X-ray.<br><br>**Exclusion criteria**<br>6. Has a diabetic foot infection with implanted device.<br>7. Has received > 96 hours of potentially effective systemic antibiotic therapy and the wounds are clinically improving. If a patient is not improving or deep-tissue culture results indicate that the infecting pathogen is not susceptible to that antibiotic, the patient may be enrolled at any time.<br>8. Patient wants or accepts proposed amputation of infection and/or ischemia. |

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| | 9. Destructive osteomyelitis with fractures, sequestra, shattering upon bone contact, and radiological vanishing of bone beyond the cortical level.<br>10. Concomitant infections requiring more than 14 days of other antibiotic therapy. |
| **TREATMENT GROUPS** | <u>For diabetic toe osteomyelitis</u><br>***Treatment A:*** 3 weeks of targeted antibiotic therapy<br>***Treatment B:*** 6 weeks of targeted antibiotic therapy<br><u>For diabetic foot soft tissue infection</u><br>***Treatment A:*** 10 days of antibiotic therapy<br>***Treatment B:*** 20 days of antibiotic therapy |
| **TEST ARTICLE** | No placebo. All antibiotic prescription will be according to international guidelines (IDSA guidelines) and recommendations and are freely available on the Swiss market. |
| **STUDY CONDUCT** | At enrollment (Day 1), the investigator will prescribe empiric antibiotic treatment based on instructions provided in the protocol and determine the most appropriate route of administration (oral or IV) according to the patient's condition. Patients will be randomized to 1of the 2 study treatments in the ratio 1:1 with stratification between patient populations with osteomyelitis and soft tissue infections.<br>**Treatment Period and Visits**<br>Patients will be treated for approximately 10 to 42 days. If a patient achieves clinical cure (defined by Tx Visit 4), the investigator will stop study treatment at that visit. The treatment period includes the following study visits:<br>***Tx visit 1*** – Enrollment (Day 1)<br>***Tx visit 2*** – Day 8 (+/- 4 days)<br>***Tx visit 3*** – Day 20 (+/- 4 days)<br>***Tx visit 4*** – Day 40 (+/- 4 days) (only if still receiving study treatment after Tx visit 3)<br>**Follow-Up Visit**<br>Approximately 60 days after the EOT visit, patients will attend the primary Test-of-Cure (TOC) visit. |
| **STUDY DURATION** | Patients' participation in the study will include the treatment period of up to 28 days and the follow-up period of up to approximately 60 days after treatment has stopped. |
| **EFFICACY VARIABLES** | **Efficacy Variables**<br><u>Primary</u><br>• The primary efficacy variable is the percent of patients with a clinical outcome of "clinical cure" at the TOC visit<br>• Adverse events of antibiotic therapy |

# 1. INTRODUCTION

## 1.1 Background and Rationale

Diabetic foot infections (DFI) are frequent and are associated with a high burden of morbidity, costs, recurrence risk or new episodes of infections. About two-third of recurrent DFI may reveal other microorganisms than in the previous period, suggesting new episodes of infection due to the underlying problem, and/or selection by prior antimicrobial therapy. Osteomyelitis in the diabetic toe is almost always established by contiguous spread of infection from a chronic ulcer. It occurs in up to 15% of patients with a diabetic foot ulcer[1] and about 20% of all DFI (and over half of severe infections) involve bone at presentation.[2] The severity of a diabetic foot infection is based on the local and systemic signs and symptoms of infection and has been categorically defined in the Infectious Disease Society of America guidelines for the "Diagnosis and Treatment of Diabetic Foot Infections" (IDSA guidelines).[3]

Knowing the potential for poor outcomes, many clinicians have tended to treat DFIs with a long duration of antibiotic therapy, with many side effects, development and spreading of antibiotic resistance, and associated costs.[4,5] Data from recent comparative trials has shown that 1-2 weeks is sufficient for most soft tissue infections, and 4 to 6 weeks appears adequate in those with (unresected) infected bone.[6] Retrospective reviews over the past two decades have demonstrated that about two-thirds of selected patients with diabetic foot osteomyelitis can achieve remission with antibiotic therapy alone (i.e., without bone resection). One recent randomized trial found that treatment with only antibiotic therapy (given for 90 days) gave similar clinical outcomes to treatment with conservative surgery (removal only of the infected bone) along with just a short course of antibiotic therapy.[7] Another randomized trial compared a 6-week against 12-week course of antibiotic therapy, without concomitant surgery, for diabetic foot osteomyelitis[8] and also found similar outcomes.

Likewise, the optimal antibiotic duration for any skin and soft tissue infection is unknown. According to some databases of University of Geneva Hospitals, among 378 skin and soft tissue infections in 346, overall cure was achieved in 330 episodes (87%) after a median antibiotic administration of 15 days. In multivariate Cox regression analysis, duration of antibiotic therapy (HR 1.0, 95%CI 0.96-1.02) did not influence treatment failure among patients with positive MRSA carriage.[9]

Our study intends to optimize the duration of antibiotic therapy in DFI; for skin and soft tissue infections as well as for diabetic toe osteomyelitis that is not amputated.

## 1.2 Summary of Potential Risks and Benefits

A potential risk of participation in this study is experiencing a recurrence or a new episode of diabetic foot infection.

The potential benefit of participation in this study is receiving effective short-term antibiotic therapy to promote or accelerate clinical cure of the infections, with less side effects.

## 2. ETHICS

This study will be conducted in compliance with the Declaration of Helsinki and its amendments, the International Conference on Harmonisation (ICH) principles of Good Clinical Practice, and other Swiss regulations, as appropriate. It is the responsibility of the Investigator and collaborators to ensure that written informed consent is obtained from the patient before any activity or procedure is undertaken that is not part of routine care.

## 3. OBJECTIVES

To determine the efficacy of 3 weeks of targeted antibiotic therapy compared to 6 weeks for non amputated diabetic toe osteomyelitis; and 10 days compared to 20 days for diabetic foot soft tissue infections.

## 4. STUDY DESIGN

This is a randomized, unblinded, single-centre study conducted in 2 sustrata of patients with diabetic foot infections: Toe osteomyelitis and skin and soft tissue infections. Patients will be randomized to receive 1 of 2 systemic antibiotic durations; 3 versus 6 weeks for osteomyelitis, and 10 versus 20 days for skin and soft tissue infections. Patients will be treated for approximately 10 to 242 days and, if treated as outpatients, will return to the clinic for safety and efficacy assessments. The final assessments used in the primary efficacy analysis will be obtained at the test-of-cure (TOC) visit approximately 60 days after treatment is stopped.

## 5. PATIENT POPULATION

### 5.1 Selection of Study Population

120 subjects will be enrolled; 60 for osteomyelitis and 60 for soft tissue infections.

#### 5.1.1 Study Criteria

**Inclusion criteria**

- Is aged ≥ 18 years.
- Has diabetes mellitus, according to the American Diabetes Association (ADA) criteria.
- Has at least one visible inflammation with the following clinical manifestations of a moderate or severe infection based on the Infectious Disease Society of America (IDSA) guidelines for the “Diagnosis and Treatment of Diabetic Foot Infections”.
- Local Infection is defined as having ≥ 2 manifestations of inflammation (local welling or induration, erythema, local tenderness or pain, local warmth, purulent discharge (thick, opaque to white or sanguineous secretion).

- Moderate infection is defined as: local infection (as described above) with erythema > 2cm, or involving structures deeper than skin and subcutaneous tissues and no systemic signs.
- Has received appropriate surgical intervention to remove all necrotic tissue or tenotomy.
- Osteomyelitis limited to bone contact, inflammation and cortical lesions in X-ray.

**Exclusion criteria**

- Has a diabetic foot infection with implanted device.
- Has received > 96 hours of potentially effective systemic antibiotic therapy and the wounds are clinically improving. If a patient is not improving or deep-tissue culture results indicate that the infecting pathogen is not susceptible to that antibiotic, the patient may be enrolled at any time.
- Patient wants or accepts proposed amputation of infection and/or ischemia.
- Destructive osteomyelitis with fractures, sequestra, shattering upon bone contact, and radiological vanishing of bone beyond the cortical level.
- Concomitant clinical infections requiring more than 14 days of (other) antibiotic therapy.

### 5.1.2 Removal of Patients from Therapy

All patients are free to withdraw from participation in this study at any time, for any reason, and without prejudice. A patient who withdraws consent by refusing to continue with study procedures/observations will be terminated from the study. The reason for withdrawal of consent should be clearly documented wherever possible.

The investigator should make every effort to address non-compliance issues and ensure that relevant study data are obtained from patients whenever possible.

To enable collection of follow-up data, the investigator may stop study treatment at any time without withdrawing the patient from the study (e.g. the patient experiences intolerable or unacceptable AEs possibly related to study treatment and where such treatment cannot be modified within the confines of the protocol).

On rare occasions, the investigator may terminate a patient from the study to protect the patient's best interest. If a patient is withdrawn before completing the study, the reason for withdrawal will be entered in the case report form (CRF). Whenever possible and reasonable, the evaluations that are required at the next scheduled visit will be performed at early termination.

## 6. TREATMENTS

Antibiotic treatment starts after surgical debridement (if not amputated). For osteomyelitis cases, bone biopsy will be performed first. Re-vascularisation, off-loading, and local care are permitted and encouraged throughout the study and the follow-up

period. The antibiotic choice will be according to IDSA guidelines[3] and the clinical pathway for diabetic foot infections of University of Geneva Hospitals; with agents freely available on the Swiss market and in our hospital. There is no protocol for the switch from intravenous to oral therapy, which is at the discretion of the treating physician. Equally, the choice of the molecule, among those recommended, is not standardized in the study protocol.

### 6.1.1 Standard Diabetic Ulcer Care

Standard diabetic ulcer care for all patients will include wound debridement (during hospitalization or at clinic visits and only if clinically indicated ), daily care with dressing changes to all ulcers (target and non-target), pressure off loading and diabetes control.

## 6.2 Prior and Concomitant Therapy

Potentially effective successful antibiotic therapy beyond 48 hours prior to screening is not permitted. A 72 hour window is permitted, if the evolution is not successful. There is no time window if the patient requires a new antibiotic agent based on microbiological results, independently of the duration of prior antibiotic therapy with the ineffective antimicrobial agent.

# 7. STUDY PROCEDURES

## 7.1 Treatment Period

Patients will be treated for approximately 10-42 days. If a patient achieves clinical cure (defined in Section 7.1.2) by Treatment (Tx) visit 3 or 4, the investigator will stop study treatment at that visit. The treatment period includes the following study visits:

***Tx visit 1*** – Enrollment (Day 1)

***Tx visit 2*** – Day 8 (+/- 4 days)

***Tx visit 3*** – Day 14 (+/- 4 days)

***Tx visit 4*** – Day 40 (+/- 4 days) (only if still receiving study treatment after Tx visit 3)

The ***End-of-treatment (EOT) visit*** is defined as the patient's last visit (Tx visit 2, 3, 4, or Early-termination visit) at which study treatment is stopped for any reason.

### 7.1.1 Treatment Visit 1 (Enrollment [Day 1])

Screening procedures will be performed at Tx visit 1. Patients will sign an Informed Consent Form (ICF) before any study-related procedures are performed. Patients will be assessed by an investigator and the diagnosis of infected foot ulcer will be confirmed in accordance with the appropriate inclusion criteria.

**Screening Procedures**:

1. Obtain written informed consent.
2. Assign a screening number.
3. Record medical history and demographics.

4. Measure and record height and weight.
5. Perform physical examination [simple review of systems, weight, and vital signs {sitting systolic and diastolic blood pressure (BP), heart rate, respiratory rate and body temperature}].
6. Perform appropriate wound debridement (as clinically indicated) including appropriate bone biopsy (in patients with osteomyelitis; with the foot surgeon.)
7. Obtain suitable tissue specimens for bacterial cultures (aerobic and anaerobic) from the base of the target infection using biopsy or tissue curettage. Wound aspiration may be used if deemed appropriate. Swabs are not suitable for diagnostic culture.
8. Determine the total DFI wound score and its sub-totals (Appendix V, Section 10.2).
9. Review inclusion/exclusion criteria.

***Study procedures can commence if the patient meets all study entry requirements (except those related to clinical laboratory testing which are normally reviewed at Treatment Visit 2).***

**Study Procedures**

1. Collect samples of for routine clinical laboratory tests (hematology, serum chemistry and Hemoglobin A1c).
2. Record the anatomical location of the target infection and determine infection severity (moderate or severe).
3. Perform standard X-ray and clinical and angiologic assessment of the vascular status.
4. Determine the most appropriate route of administration (oral or IV) and empoirical choice of the agent according to the severity of the infection and according to IDSA guidelines, local clinical, pathway recommendations, and the patient's co-morbidities and (pseudo)allergies.
5. Randomize the patient via an electronic database or sealed envelops.
6. If the patient has any ulcer on the bottom of the foot, fit a removable cast walker (RCW) or similar device to provide off-loading.
7. Remind patient that he or she should continue to receive diabetic clinical management according to the local clinical pathway and IDSA guidelines.

### 7.1.2 Treatment Visit 2

Outpatients will return to the clinic (assessments can be performed in the hospital for inpatients), where the following assessments will be performed:

1. Record any concomitant medications as well as any additional interventions required (except wound or bone debridement performed as part of standard care).

2. Review clinical lab results from previous visit. If any results fall outside of the permitted inclusion criteria, the patient should be early terminated from the study and excluded from the mITT population.
3. Adaptation of (empirical) antibiotic therapy, if not done before.
4. Perform physical examination [simple review of systems, weight and vital signs (sitting BP, heart rate, respiratory rate and body temperature)].
5. Assess adverse events of long-term antibiotic therapy.
6. Administer appropriate ulcer debridement and cleansing.
7. Only if clinically indicated (e.g. worsening infection), obtain tissue specimens for bacterial cultures (aerobic and anaerobic) from the base of the target infection using biopsy or curettage. Wound aspiration may be used if deemed appropriate. Swabs are not suitable for diagnostic culture.
8. Assess the clinical status of the target infection and complete the DFI wound score. With reference to the general wound parameter components of the DFI wound score recorded at baseline and any additional signs and symptoms of infection, determine clinical outcome according to the following definitions:

   ***Clinical Cure***: Resolution of all clinical signs and symptoms of infection.

   ***Clinical Improvement***: Improvement of at least 1 AND no worsening of any clinical signs and symptoms of infection.

   ***No Improvement***: No improvement and no worsening of any clinical signs and symptoms of infection.

   ***Worsening***: Worsening of 1 or more clinical signs and symptoms of infection.
9. Collect blood samples for routine clinical laboratory tests (hematology and serum chemistry).
10. If the patient has any ulcer on the bottom of the foot, fit a RCW or similar device to provide off-loading.
11. For inpatients, ensure that test article and sufficient ulcer care supplies are available in the hospital. Prescribe systemic antibiotic as appropriate. If an inpatient is discharged before the next scheduled visit, dispense appropriate test article and sufficient ulcer care supplies to last until the next scheduled visit. Prescribe systemic antibiotic(s) to last the remaining duration of the expected treatment period

### 7.1.3 Treatment Visits 3 and End of Treatment

Outpatients will return to the clinic (assessments can be performed in the hospital for inpatients), where the following assessments will be performed:

1. Record any concomitant medications as well as any additional interventions (except wound or bone debridement performed as part of standard care).
2. Review clinical lab results from previous visit.

3. Perform physical examination [simple review of systems, weight and vital signs (sitting BP, heart rate, respiratory rate and body temperature)].
4. Assess adverse events of long-term antibiotic therapy.
5. Administer appropriate ulcer debridement and cleansing.
6. Only if clinically indicated (eg, worsening infection), obtain tissue specimens for bacterial cultures (aerobic and anaerobic) from the base of the target ulcer using biopsy or curettage. Wound aspiration may be used if deemed appropriate. Swabs are not suitable for diagnostic culture.
7. Assess the clinical status of the target infection and complete the DFI wound score. With reference to the general wound parameter components of the DFI wound score recorded at baseline and any additional signs and symptoms of infection, determine clinical outcome according to the following definitions:

   ***Clinical Cure***: Resolution of all clinical signs and symptoms of infection.

   ***Clinical Improvement***: Improvement of at least 1 AND no worsening of any clinical signs and symptoms of infection.

   ***No Improvement***: No improvement and no worsening of any clinical signs and symptoms of infection.

   ***Worsening***: Worsening of 1 or more clinical signs and symptoms of infection.
8. Determine whether treatment will be stopped, continued or changed. If new culture results are available assess whether additional/alternative antibiotic coverage is needed according to the antibiotic decision tree. If treatment will not be continued, this is the EOT visit and appropriate assessments should be performed (ie, tissue samples as instructed per Tx visit 5), otherwise proceed as follows:
9. Collect blood samples for routine clinical laboratory tests (hematology and serum chemistry).
10. If the patient has any ulcer on the bottom of the foot, fit a RCW or similar device to provide off-loading.
11. For inpatients, ensure that test article and sufficient ulcer care supplies are available in the hospital. Prescribe systemic antibiotic as appropriate. If an inpatient is discharged before the next scheduled visit, dispense appropriate test article and sufficient ulcer care supplies to last until the next scheduled visit. Prescribe systemic antibiotic(s) to last the remaining duration of the expected treatment period

### 7.1.4 Test-of-Cure (TOC) Visit

Every effort will be made to ensure that final efficacy assessments (ie, primary outcome data) are available for all subjects. Outpatients should return to the clinic (assessments can be performed in the hospital for inpatients), where the following assessments will be performed:

1. Record any concomitant medications as well as any additional interventions required (except wound or bone debridement performed as part of standard care).

2. Review clinical lab results from the EOT visit.
3. Record a digital photographic image of the target ulcer with a ruler in the field of view.
4. Perform an X-ray control.
5. Administer appropriate ulcer debridement (as clinically indicated) including appropriate bone debridement (in patients with osteomyelitis) and cleansing.
6. Obtain tissue specimens (if suitable culture material is available) for bacterial cultures (aerobic and anaerobic) from the base of the target ulcer using biopsy or curettage. Wound aspiration may be used if deemed appropriate. Swabs are not suitable for diagnostic culture.
7. Assess the clinical status of the target ulcer and complete the DFI wound score. With reference to the general wound parameter components of the DFI wound score recorded at baseline and any additional signs and symptoms of infection, determine clinical outcome according to the following definitions:

   ***Clinical Cure***: Resolution of all clinical signs and symptoms of infection.

   ***Clinical Improvement***: Improvement of at least 1 AND no worsening of any clinical signs and symptoms of infection.

   ***No Improvement***: No improvement and no worsening of any clinical signs and symptoms of infection.

   ***Worsening***: Worsening of 1 or more clinical signs and symptoms of infection.
8. Determine and record the DFI wound score for any non-target ulcers (as assigned at baseline).

### 7.1.5 Early Termination

Patients who withdraw consent or who, in the opinion of the investigator, are no longer able or eligible to participate in the study (including patients who require antibiotic therapy beyond Tx visit 5) will be early terminated. Where possible, such patients will complete an ***Early-termination visit*** to undergo all assessments applicable to the corresponding (or next) scheduled study visit.

## 7.2 Assessments

### 7.2.1 Clinical Assessments of Infection

Patients will be assessed for clinical outcome by the investigator at each treatment visit (interim assessments) and at the TOC visit (final/primary assessment). The Investigator will assess clinical outcome by comparing the clinical condition of the target ulcer to that at baseline according to the following criteria:

<u>Clinical Outcome Definitions</u>

- ***Clinical Cure***: Resolution of all clinical signs and symptoms of infection.

- ***Clinical Improvement***: Improvement of at least 1 AND no worsening of any clinical signs and symptoms of infection.
- ***No Improvement***: No improvement and no worsening of any clinical signs and symptoms of infection.
- ***Worsening***: Worsening of 1 or more clinical signs and symptoms of infection.

Every effort will be made to ensure that final efficacy assessments are available for all subjects in the mITT population.

### 7.2.2 Microbiological Assessments

Aerobic and anaerobic cultures of ulcers will be performed by a local lab at baseline, the EOT visit (and/or at early termination), and at the TOC visit. Cultures may also be obtained at other Tx visits if clinically indicated (e.g. worsening of infection). Suitable culture material must be obtained using biopsy or curettage at the base of the target ulcer, or by needle aspiration. Swab cultures of ulcer surfaces are not permitted. If suitable culture material is not available due to healing of the ulcer, this will be documented by the investigator.

From the baseline culture results, the investigator will determine the baseline pathogen(s) (defined as any microorganism presumed responsible for, or contributing to, the infection) for each patient's target infection.

The eradication/persistence of each baseline pathogen will be determined on the basis of culture results reported by the local laboratory. If a patient's culture result is missing for the EOT visit or the TOC visit, the baseline pathogen will be presumed eradicated if a) ulcer closure is achieved, b) as a result of ulcer healing there is a lack of suitable tissue sample/culturable material (as documented by the investigator), or c) the culture result is otherwise missing and pathogen eradication was achieved in the last available culture result. In all other circumstances, baseline pathogen persistence (ie, not eradication) will be presumed.

According to the documented or presumed eradication of a patient's baseline pathogen(s), the following definitions apply:

- A patient with "baseline pathogen eradication" is defined as a patient with eradication of all baseline pathogens.
- A patient with "baseline pathogen improvement" is defined as a patient with eradication of at least 1 but not all baseline pathogens.
- A patient with "baseline pathogen response" is defined as a patient with "baseline pathogen eradication" or "baseline pathogen improvement".

According to the patient's baseline pathogen eradication/response at the TOC visit and taking account of the patient's final clinical outcome at the TOC visit, the patient's microbiological outcome will be assigned according to the following definitions [*Note:* If there is no culture result at the TOC visit, no microbiological outcome will be assigned unless a) ulcer closure is achieved, or b) as a result of ulcer healing there is a lack of

suitable tissue sample/culturable material (as documented by the investigator), in which case a microbiological outcome of "microbiological success" will be presumed]:

### 7.2.3 Wound Assessments

At each study visit, the target infection will be assessed for ulcer closure and DFI wound score (total, general wound parameters sub-total, and wound measurement parameters sub-total). The DFI wound score is included as Appendix.

#### 7.2.3.1 Physical Examination

A physical examination [simple review of systems, weight and vital signs (sitting systolic and diastolic BP, heart rate, respiratory rate and body temperature)] will be performed at all treatment visits.

#### 7.2.3.2 Vital Signs

Vital signs, including sitting BP, pulse, respiratory rate and body temperature will be measured after the patient has been in a sitting position for 5 minutes. Vital signs will be measured at every visit during the treatment period and at the TOC visit.

#### 7.2.3.3 Clinical Laboratory Tests

The following clinical laboratory tests will be performed at every visit during the treatment period and at the TOC visit.

| **Hematology (complete blood count [CBC]):** | **Serum Chemistry:** |
|---|---|
| Hemoglobin | Creatinine |
| White blood cell (WBC) count | Glucose |
| WBC differential with Neutrophils | C-reactive protein |

## 7.3 Sample Size Determination

It is difficult to predict failure rates. Assuming a failure rate of 35% in the 6 weeks' arm and a non-inferiority margin of 10%, we estimate the necessity to enroll 120 patients (60 for osteomyelitis and 60 for soft tissue infections).

## 7.4 Statistical Analyses

Unless otherwise indicated, all testing of statistical significance will be 2-sided and a difference resulting in a *P* value of less than or equal to 0.05 will be considered statistically significant.

### 7.4.1 Analysis Populations

The **intent-to-treat (ITT)** population will consist of all randomized patients. Patients will be analyzed according to treatment group assignment regardless of whether the patient receives any study treatment or the wrong treatment. Patient disposition and baseline characteristics will be based on the ITT population.

The **per-protocol (PP)** population will consist of all randomized patients who complete

the study (or who are otherwise defined as a treatment failure) and who have not deviated significantly from the protocol. All efficacy analyses will be repeated using the PP population. Any analysis involving microbiological assessments will exclude patients without an assigned baseline pathogen.

### 7.4.2 Disposition

The numbers of patients randomized and completing the study will be tabulated overall and by treatment group. For any patient that is early terminated, the reason(s) for early termination will be tabulated overall and by treatment group. The number of patients and percentages in each analysis population will be reported.

### 7.4.3 Patient Characteristics

Demographic and baseline characteristics such as age, gender, height, weight, BMI, baseline DFI wound score and severity (according to IDSA guidelines) for the target infection, diagnosis of osteomyelitis, and any other relevant baseline information (e.g. initial administration route of systemic antibiotic, anatomical location of target infection, number of infected ulcers at baseline, initial size and number of test articles assigned) will be summarized with appropriate descriptive statistics (sample size, missing, mean, standard deviation [SD], median and minimum and maximum for continuous variables; number and percentage for categorical variables) by treatment group and overall.

### 7.4.4 Efficacy

All efficacy analyses will be performed using the mITT population and repeated with the PP population. No imputations for missing data will be performed for any primary or secondary efficacy analysis (except for the following rules governing any microbiological presumptions).

If a patient is early terminated before the TOC visit or if study treatment is otherwise stopped, no baseline pathogen eradication result will be presumed for the TOC visit. If there is no culture result at the TOC visit, no microbiological outcome will be assigned unless a) ulcer closure is achieved, or b) as a result of ulcer healing there is a lack of suitable tissue sample/culturable material (as documented by the investigator), in which case a microbiological outcome of "microbiological success" will be presumed.

For the exploratory analyses of DFI wound score and its sub-totals, the last-observation-carried-forward (LOCF) approach will be used to impute any missing data.

#### 7.4.4.1 Efficacy Definitions

For the purpose of the efficacy variables, the following definitions apply:

- "Clinical response" is defined as a clinical outcome of "clinical cure" or clinical improvement".
- "Treatment failure" is defined as either (i) a final/primary clinical outcome of "no improvement" or "worsening" at the TOC visit, or (ii) antibiotic therapy is prescribed beyond Tx visit 5.
- Adverse events of antibiotic therapy.

#### 7.4.4.2 Variables

The **primary efficacy variable** is the percent of patients with a clinical outcome of "clinical cure" at the TOC visit.

The **exploratory efficacy variables** are as follows:

- Change in DFI wound score (total, general wound parameters sub-total, and wound measurement parameters sub-total) from baseline for the target infection at each study visit.

#### 7.4.4.3 Exploratory Analyses

The change in DFI wound score (total, general wound parameters sub-total, and wound measurement parameters sub-total) will be summarized descriptively and compared across treatment groups at each study visit (including the EOT visit) using pairwise comparisons.

Sub-group analyses of the percent of patients with a clinical outcome of "clinical cure" at the TOC visit according to baseline infection severity (moderate or severe) and according to route of administration of initial antibiotic therapy prescribed on Tx visit 1 (oral or IV) will be performed. Eradication of baseline pathogens by bacterial species will be performed.

Other sub-group and exploratory analyses (as needed) may be performed using appropriate statistical methodology.

### 7.4.5 Interim Analysis

An interim analysis is planned after 6 months or the inclusion of the first 40 patients.

## 8. QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include review of protocol procedures with the investigator and associated personnel prior to the study.

### 8.1 Source Documents

All information recorded in the CRF will be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records. In some cases, the source documents may be electronic.

### 8.2 Database Lock

The database will be locked in order to protect write access after the following preconditions are fulfilled:

- All data are entered in the database
- Decisions have been made and agreed to as to the identities of all protocol violators

## 9. BUDGET, STUDY NURSE AND TIMELINE

This study needs an experienced study nurse at 10% during 2 years.
Scheduled financial expenditures (in Swiss francs) are listed below.
Additional financing sources might be sought.

| | Total | **1st year** | **2nd year** |
|---|---|---|---|
| a. Technical support | 0 | 0 | 0 |
| b. Various (and reserve) | 1'000 | 500 | 500 |
| c. Consumable material | 500 | 250 | 250 |
| d. Ethical Comittee approval | 1'000 | 1'000 | 0 |
| e. Voyages | 0 | 0 | 0 |
| f. Salary at 10% (study nurse) | 21'627 | 10'813 | 10'813 |
| g. Social charges (for Geneva) | 5'070 | 2'535 | 2'535 |
| **TOTAL Swiss francs** | **29'196** | **15'098** | **14'098** |

## 10. STUDY TERMINATION

The end of this study is defined as the date of the last follow-up visit of the last patient.

The study may be terminated prematurely for any reason and at any time in accordance with the requirements of the local Ethics Committee.

## 10. FINAL CLINICAL STUDY REPORT

The final clinical study report will be written within 1 year of completion of the clinical part of the study. This report will include a summary of the study results based on a statistical evaluation and clinical assessment. The results will be published and may be preliminarily used for various scientific congresses by any of the co-investigators.

## 12. REFERENCES


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# APPENDICES

## Allowed Antibiotic Doses

| Antibiotic | Allowed Dosing Regimens | Allowed Total Daily Dose Range |
|---|---|---|
| Levofloxacin PO | 750 mg q.24h or 500 mg q.12h | 750 to 1000 mg |
| Levofloxacin IV | 750 mg q.24h or 500 mg q.12h | 750 to 1000 mg |
| Amoxicillin/clavulanate PO | 500/125 mg q.12h. or q.8h | 1000/250 mg to 1500/375 mg |
| Amoxicillin/clavulanate IV | 1000/200 mg q.12h or q.8h | 2000/400 mg to 3000/600 mg |
| | | |
| Clindamycin PO | 300 mg or 450 mg q.6h | 1200 mg to 1800 mg |
| Linezolid PO | 600 mg q.12h | 1200 mg |
| Linezolid IV | 600 mg q.12h | 1200 mg |
| Metronidazole PO | 400 mg or 500 mg q.8h or 500 mg q.6h | 1200 mg to 2000 mg |
| Metronidazole IV | 500 mg q.8h or q.6h | 1500 mg to 2000 mg |
| Aztreonam IV | 1 g or 2 g q.12h or q.8h | 2 g to 6 g |
| Piperacillin/tazobactam IV | 3000/375 mg q.6h or 4000/500 mg q.8h | 12000/1500 mg (12 g/1.5 g) |

## 10.1 APPENDIX III Standard of Care

### Ulcer Standard of Care

The following outlines the Ulcer Standard of Care, which will be standardized at all sites and for all treatment groups:

1. Sharp surgical debridement

   Debridement will be defined as sharp surgical debridement, which includes removal of all necrotic tissue, chronic granulation tissue, bone sinus tracts, undermined borders and callus to produce a viable ulcer bed. Debridement should be carried out until healthy bleeding tissue is reached.

   If osteomyelitis has been diagnosed, surgical intervention to remove all necrotic and infected bone is required.

   All ulcers will be prepared in the following standard method:

   - All necrotic tissue should be excised until a brisk capillary bleeding from all ulcer surfaces is attained.
   - All culture specimens will be taken from deep tissue excised after the superficial tissue has been excised. The initial debridement will be performed prior to the test article application. The test article will not be applied to the ulcer bed until complete hemostasis has been attained. Further debridement will be performed as required throughout the treatment period, as determined by the investigator or designee.
   - Debridement may be performed by either the investigator or designee but should be performed by the same individual throughout the duration of the clinical study, whenever possible. If the individual who routinely performs the debridement is unavailable for any reason at any time during the study, the name of the replacement will be noted in the investigator files.

2. Maintenance of a clean, moist ulcer environment:

The ulcer and periulcer area will be cleansed to minimize bioburden and maceration. Two dressings will be applied to the target ulcer: a primary, nonadherent dressing and a secondary dressing.

- Cleansing: The investigator or designee will irrigate the ulcer with sterile normal saline solution delivered from a 10-mL syringe attached to a 20-gauge flexible angiocatheter. Sterile gauze will be used to pat the ulcer dry.
- Primary Dressing: The primary dressing will consist of the test article covered with a nonadherent, moisture permeable dressing.
- Secondary Dressing: The secondary dressing will be a saline-moistened gauze. The saline-moistened gauze will cover the nonadherent dressing and the remaining area of the ulcer.

- Roll gauze will be wrapped circumferentially to keep the dressings in place. An adhesive covering of nonirritating tape will secure the dressings.
- The dressing will be changed daily. Patients will be provided with the nonadherent dressings, commercially prepared moist saline dressings, roll gauze and nonirritating tape and will be instructed to change the dressing on the days they do not make study visits. If a primary or secondary dressing change occurs at the study site outside a protocol visit, this will be documented as an unplanned visit.

3. Pressure relief

If the ulcer is on the bottom of the foot, the patient will be fitted with an off-loading device or removable cast walker (RCW). Off-loading is defined as avoidance of all mechanical stress on the injured extremity and is essential for healing. Avoidance of weight bearing is essential. Trauma causes most plantar ulcers and ongoing trauma prevents healing. Because off-loading (not bearing ANY weight) is so critical to the healing process, patients will be instructed to wear the RCW at all times except when bathing and to use an RCW at all times when walking or standing is required. Strategies for off-loading will be standardized for all patients as follows:

All patients with an ulcer on the bottom of the foot will be fitted with an RCW or other off-loading device during the Baseline/Randomization Visit, according to the following procedure:

- The size of the walker will be determined based on the patient's correct shoe size.
- The appropriate size of the insole will be inserted into the RCW.
- Once the target ulcer has been debrided, assessed, cleansed, dressed and secured, the RCW will be applied according to the manufacturer's instructions for use.
- The investigator or designee will ensure that the patient and family members are able to unfasten, remove and reapply the RCW properly according to the manufacturer's instructions for use.

Patients will be instructed to wear the RCW at all times except when bathing. When bathing, the patient will be instructed to wear a slipper with a plastic bag worn over the slipper and tied at the ankle or higher.

## 10.2 APPENDIX Diabetic Foot Infection Wound Score

| **General Wound Parameters** | **0** | **1** | **2** | **3** |
|---|---|---|---|---|
| Purulent Drainage | Absent | | | Present |
| Non-purulent Drainage | Absent | Mild | Moderate | Severe |
| Erythema | Absent | Mild | Moderate | Severe |
| Induration | Absent | Mild | Moderate | Severe |
| Tenderness (sign) | Absent | Mild | Moderate | Severe |
| Pain (symptom) | Absent | Mild | Moderate | Severe |
| Local Warmth Increase | Absent | Mild | Moderate | Severe |
| General Wound Parameters Subtotal | | | | |

Wound Measurements

| Size ($cm^2$) | <1 | 1-2 | >2-5 | >5-10 | >10-30 | > 30 |
|---|---|---|---|---|---|---|
| | 0 | 1 | 3 | 6 | 8 | 10 |
| Depth (mm) | <5 | 5-9 | 10-20 | >20 | | |
| | 0 | 3 | 7 | 10 | | |
| Undermining (mm) | <2 | 2-5 | >5 | | | |
| | 3 | 5 | 8 | | | |
| General Wound Measurements Subtotal | | | | | | |
| **TOTAL WOUND SCORE (General Parameters Subtotal + Wound Measurements Subtotal** | | | | | | |

**Purulent drainage**: A viscous, yellowish-white or green fluid formed in infected tissue.

Graded: Absent or Present

**Non-purulent drainage:** A serous, sanguinous, or sero-sanguinous collection of fluid in the tissue surrounding the wound.

Graded:

Absent: No drainage

Mild: Scant drainage noticed on dressing (≤0.5 cm diameter) but not requiring the additional use of dressings

Moderate: Greater than scant but less than copious drainage noticed on the dressing (>0.5 to ≤2 cm diameter); possibly requiring additional dressings

Severe: Copious drainage on dressing (>2 cm diameter) requiring additional dressing changes

**Erythema:** Congestion or exudative redness surrounding the wound caused by engorgement of the capillaries in the lower layers of the skin.

Graded:

| | |
|---|---|
| Absent: | Absent |
| Mild: | Pink, barely perceptible |
| Moderate: | Pale red, defined edges |
| Severe/Extreme: | Red to dark red |

**Induration:** Inflammatory hardening or thickening of tissues; may be referred to as limb brawny edema.

Graded:

| | |
|---|---|
| Absent: | Absent |
| Mild: | Localized at the site of infection |
| Moderate: | Appears in a limited area at the site of the infection |
| Severe: | Involvement extending from the site of infection and involving a significant portion of the affected lower extremity or the entire lower extremity. |

**Tenderness (sign):** Palpation at the site of infection elicits reports of tenderness by the patient as measured by a 0 to 10 scale, with 0 being no report of tenderness upon palpation and 10 being worst or significant tenderness on palpation.

Graded:

| | |
|---|---|
| Absent: | No tenderness on palpation |
| Mild: | Tenderness upon palpation reported as ≤ 5/10 |
| Moderate: | Tenderness upon palpation reported as 6 to 8/10 |
| Severe: | Tenderness upon palpation reported as 9 to 10/10 |

**Pain:** Subjective and voluntary reporting of discomfort or the perception of pain that is experienced by the patient at the site of infection as measured by a 0 to 10 scale, with 0 being no pain and 10 being the worst pain.

Graded:

| | |
|---|---|
| Absent: | No complaints of pain |
| Mild: | Patient complains of pain ≤ 5/10 |
| Moderate: | Patient complains of pain as 6 to 8/10 |
| Severe: | Patient complains of pain as 9 to 10/10 |

**Local Warmth:** Increase relative to the uninfected contralateral foot.

Graded:

Absent

Mild

Moderate

Severe

**Wound Measurements:**

**Size ($cm^2$):** The ulcer contour traced with a fine-tipped pen on a sterile clear plastic film applied over the ulcer. For the purpose of the DFI Wound Score, the dimensions are measured and the total wound surface area estimated.

Graded: <1 ≥1 to 2 >2 to 5 >5 to 10 >10 to 30 >30 $cm^2$

**Depth (mm):** Measure the wound at its deepest part at a 90° angle to the skin. Use a sterile swab as an aid.

Graded: <5 5 to 9 10 to 20 > 20 mm

**Undermining (mm):** Measure the deepest part of any tunneling or shearing. Use a sterile swab as an aid.

Graded: <2 2 to 5 > 5 mm