

## STUDY SYNOPSIS

**Title of Study:** A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED, PARALLEL-GROUP STUDY, COMPARING TEST TOPICAL PRODUCT TO BRAND TOPICAL PRODUCT AND BOTH ACTIVE TREATMENTS TO A PLACEBO CONTROL IN THE TREATMENT OF TINEA PEDIS

**Treatment Duration:** The study treatment period will last for 14 days (2 weeks). Each Subject will participate in the study for approximately 6 weeks (Day 42,  $\pm$  4 Days) from the time the Subject signs the Informed Consent Form (ICF) through the final contact. Expected study duration is 5 to 7 months.

**Test Product:** Test topical product

**Reference Product:** Brand topical product

**Placebo Control:** Vehicle of the test topical product

**Dose and Mode of Administration:** A thin layer of gel will be applied once-daily to the affected areas plus a  $\frac{1}{2}$  inch margin of healthy surrounding skin for 2 weeks.

**Objectives:** To evaluate the therapeutic equivalence and safety of Test topical product and Brand topical product in the treatment of tinea pedis.

To demonstrate the superiority of the efficacy of the test and reference products over that of the placebo control in the treatment of tinea pedis.

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**Design:** Subjects in this randomized, double-blind, placebo controlled, parallel-group, multiple-center study will be randomly assigned in a 1:1:1 ratio to treatment with the test product, reference product or placebo control, respectively.

**Clinical Evaluations will be performed at:**

Visit 1: Screening/Baseline Visit (Day 1);  
Visit 2: End of Treatment Visit (Week 2 / Day 14  $\pm$  3 Days);  
Visit 3: Test of Cure Visit (Week 6 / Day 42  $\pm$  4 Days)

An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 3 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the Subject will continue to take part in the study), then all procedures will be performed and treated as an interim visit, with the exception of the collection of Investigational Product and Subject diaries from Subjects.

Subjects will be admitted into the study after informed consent has been obtained, a medical history and physical examination (with vital signs) have been performed and inclusion/exclusion criteria have been met. Subjects must have a clinical diagnosis of tinea pedis positive KOH test to qualify for inclusion in this study.

Each Subject will be randomly assigned in a double-blind fashion in a 1:1:1 ratio to treatment with the test product, the reference product or the placebo control.

At the screening/baseline visit, a physical examination (with vital signs) will be conducted. At each visit a target lesion on one foot will be identified as the most severe lesion and evaluated for clinical signs and symptoms. KOH and fungal culture tests will be performed for skin samples collected at the baseline and test on cure visits.

Safety will be assessed by the monitoring of all adverse events and the monitoring of any signs and symptoms of local irritation.

**Study Population:**

**Inclusion Criteria**

1. Healthy male or non pregnant female aged  $\geq 18$  years.
2. Subjects must have provided IRB approved written informed consent and sign a HIPAA authorization.
3. Female Subjects of childbearing potential (excluding women who are or premenarchal, surgically sterilized or postmenopausal for at least 1 year), in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study from the day of the first dose administration to 30 days after the last administration of study drug. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (stabilized for at least 3 months), NuvaRing® (vaginal contraceptive), Implanon™ (contraceptive implant), double barrier methods (e.g. condom and spermicide), IUD, or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. A sterile sexual partner is NOT considered an adequate form of birth control.
4. All male Subjects must agree to use accepted methods of birth control with their partners, from the day of the first dose administration to 30 days after the last administration of study drug. Abstinence is an acceptable method of birth control. Female partners should use an acceptable method of birth control as described in the above Item Number 3.
5. Subjects must be willing and able to understand and comply with the requirements of the protocol, including attendance at the required study visits.
6. Subjects must be in good health and free from any clinically significant disease, including but not limited to, conditions that may interfere with the evaluation interdigital tinea pedis.
7. The sum of the clinical signs (fissuring/cracking, erythema, maceration, and scaling) and symptoms (pruritus and burning/stinging) scores of the target lesion is at least 4, including a minimum score of at least 2 for erythema AND a minimum score of 2 for either scaling or pruritus (on a scale of 0-3, where 2 indicates moderate severity).

Clinical signs and symptoms 4-point scale:

0	none (complete absence of any signs or symptoms)
1	mild (slight)
2	moderate (definitely present)
3	severe (marked, intense)

8. Clinical diagnosis of interdigital tinea pedis with lesions localized to the interdigital spaces or predominantly interdigital, but may extend to other areas of the foot (the non-interdigital lesions should not be hyperkeratotic, i.e., characteristic of tinea pedis moccasin),
9. The presence of interdigital tinea pedis infection, confirmed by the observation of segmented fungal hyphae during a microscopic 10% potassium hydroxide (KOH) wet mount examination (potassium hydroxide mount preparation).

#### **Exclusion Criteria**

1. Female Subjects who are pregnant, nursing or planning to become pregnant during study participation.
2. Subjects with a history of hypersensitivity or allergy to luliconazole and/or any of the study medication ingredients and its excipients.
3. Use of antipruritics, including antihistamines, within 72 hours prior to the Baseline Visit.
4. Use of topical corticosteroids, antibiotics or antifungal therapies within 2 weeks prior to the Baseline Visit.
5. Use of systemic corticosteroids, antibiotics or antifungal therapy within 1 month prior to the Baseline Visit. Systemic corticosteroids do not include intranasal, inhaled, and ophthalmic corticosteroids used for the management of allergies, pulmonary disorders or other conditions.
6. Use of oral terbinafine or itraconazole within 2 months prior to the Baseline Visit.
7. Use of immunosuppressive medication or radiation therapy within 3 months prior to the Baseline Visit.
8. Any known hypersensitivity to Nafitfine HCl, or any component of the formulation.
9. Confluent, diffuse moccasin-type tinea pedis of the entire plantar surface.
10. History of significant or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that, in the Investigator's opinion, would place the study Subject at undue risk by participation or could jeopardize the integrity of the study evaluations.
11. Evidence of any concurrent dermatophytic infection of the toe nails (e.g. onychomycosis\*) or dermatological condition of the foot that, in the opinion of the Investigator, may interfere with the Investigator's evaluation of tinea pedis.  
*\* Onychomycosis, involving  $\geq 20\%$  of the area of either great toenail or involvement of more than five toenails in total*
12. Subjects with a past history of dermatophyte infections with a lack of response to antifungal therapy.
13. Has a history of uncontrolled diabetes mellitus or is immunocompromised (due to disease, e.g., HIV, or medications).
14. Subjects who have unstable medical disorders that are clinically significant or have life-threatening diseases.

15. Subjects who consume excessive amounts of alcohol (greater than two drinks per day) or use drugs of abuse (including, but not limited to, cannabinoids, cocaine and barbiturates).
16. Subjects who have participated in an investigational drug study (i.e., Subjects have been treated with an investigational drug) within 30 days prior to baseline will be excluded from study participation. Subjects who are participating in non-treatment studies such as observational studies or registry studies can be considered for inclusion.
17. Subjects who have been previously enrolled in this study.

**Number of Subjects:**

Approximately 1000 Subjects will be enrolled into the study to the following study arms:

- **Test Product:** Test topical product
- **Reference Product:** Brand topical product
- **Placebo Control:** Vehicle of the test topical product

Each site will enroll approximately between 30 and 200 subjects. Approximately equal numbers of male and female subjects will be enrolled to each of the three study arms.

**Criteria for Evaluation:****Primary Endpoint:**

The proportion of subjects with therapeutic cure at Week 6 (+/- 4 days) following 2 weeks of treatment (study day 38-46).

**Secondary Endpoint:**

The proportion of subjects with complete cure at Week 6 (+/- 4 days) following 2 weeks of treatment (study day 38-46)

Therapeutic cure is defined as both mycological cure and clinical cure.

Complete cure is defined as both mycological cure and complete clinical cure

Mycological cure is defined as a negative KOH test AND a negative fungal culture.

Clinical cure is defined as a total severity score no more than 2 with no individual severity score greater than 1, on a 4-point scale provided above. Signs and symptoms to be assessed are: fissuring/cracking, erythema, maceration, scaling, pruritus, and burning/stinging on a 4 point ordinal scale (0 = absent, 1 = mild, 2 = moderate, 3 = marked).

Complete clinical cure is defined as absence of erythema, scaling, and pruritus (grade 0 for each)

Although all tinea pedis lesions on both feet are to be treated in this study, a target lesion on one foot is to be identified as the most severe lesion and evaluated at the baseline visit and at each study visit.

Note: A positive skin fungal culture at baseline will not be an inclusion criterion due to the time lag between obtaining the culture specimen and receiving the culture results. However, a skin fungal culture will be obtained at baseline at the target site.

Testing will be performed to identify the isolates at the species level (e.g., *Trichophyton rubrum* and *Epidermophyton floccosum*)

Subjects with a pretreatment baseline skin fungal culture from the target site that is positive for *Trichophyton rubrum* or *Epidermophyton floccosum* will be included in the per protocol (PP) and modified intent to treat (mITT) populations for the primary endpoint analysis.

*Trichophyton rubrum* is the most common infecting organism in tinea pedis. Therefore, > 50% of the subjects are expected to have fungal cultures positive for *T. rubrum* upon entry into the study.

The study physicians are required to collect skin samples for KOH and Mycology Culture tests at the test-of-cure visit. In cases where the samples are not collected due to the fact that the actual infected or previously infected tissue is not available at the target site, the physician should report the target area as “Completely healed” and KOH and fungal culture is considered negative. In such cases the mycological cure will be assigned only if evidence of the healthy skin was reported, i.e., all clinical signs (fissuring/cracking, erythema, maceration, and scaling) were scored 0.

### **Statistical Methods:**

#### **Demonstration of Bioequivalence**

Bioequivalence will be established if the 90% confidence intervals of the difference of the success rates between test and reference products (T – R) is contained within the interval - 0.20 to 0.20. using the per protocol (PP) population.

#### **Demonstration of Superiority**

The test product and RLD will be compared to placebo group to test statistical superiority at  $p < 0.05$  (two-sided test), using the mITT population and the primary endpoint

#### **Analysis of Primary Endpoint**

The evaluation of the primary endpoint will be based on the proportion of subjects with a clinical response of “success” at week 6 (+/- 4 days) following 2 weeks of treatment (study day 38-46). Success is defined as therapeutic cure.

#### **Analysis of Secondary Endpoint**

The evaluation of the secondary endpoint will be based on the proportion of subjects with a complete cure at week 6 (+/- 4 days) following 2 weeks of treatment (study day 38-46).

#### **Summary of Subjects who terminate prematurely**

Reasons for premature termination will be summarized by treatment group.

#### **Concomitant medication**

The start and stop date of concomitant medication use during the study will be provided in the data set in addition to the reason for the medication use.

#### **Safety Analyses**

Safety analyses will be conducted on the safety population. Safety Incidence of all adverse events reported during the study will be summarized using the MedDRA dictionary by treatment group, body system, severity and relationship to study drug.

The report of AEs will include date of onset, description of the AE, and date of resolution. Formal statistical evaluation(s) of the comparability of the two active treatment groups will be conducted with regard to the frequency and severity of any AE that occurs in at least 5% of the Subjects in either active treatment group.

## **SAFETY AND TOLERABILITY EVALUATIONS**

### **General Safety Evaluations**

A complete medical history will be obtained for the Subject's current and past medical conditions. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity, heart attack, stroke, congestive heart failure, kidney disease, auto immune disease and gestational diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal.

Concomitant medications, in addition to the reason for the medication use, will be assessed at baseline and at each subsequent study visit. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.

A brief physical examination will be performed at baseline. The physical examination will include, at a minimum, examination of the Subject's general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart, lungs, musculoskeletal system, neurological system, lymph nodes, abdomen and extremities. The Subject's body weight will also be measured while the Subject is lightly clothed (e.g., no coat or shoes).

### **Physical Examination**

The investigator, sub-investigator or appropriately delegated designee, (Physician's Assistant, Advanced Registered Nurse Practitioner, and Registered Nurse as per local regulations) will perform a brief physical examination, prior to the Subject starting study drug.

Vital signs, including blood pressure, pulse rate, respiratory rate and oral body temperature will be documented at Visit 1. Vital signs will be measured after the Subject has rested in a seated position for at least 5 minutes.

The Subject's body weight will also be measured while the Subject is lightly clothed (e.g., no coat or shoes). Height will be measured without shoes.

### **Pregnancy Test**

All female Subjects of childbearing potential will undergo a urine pregnancy test during Visit 1 and at each subsequent study visit. All female Subjects are considered to be of childbearing potential unless they are premenarchal, have been surgically sterilized or have been postmenopausal for at least 1 year. Women of childbearing potential, in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study from the day of the first dose administration to 30 days after the last administration of study drug. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (stabilized for at least 3 months), NuvaRing® (vaginal contraceptive), Implanon™ (contraceptive implant), double barrier methods (e.g. condom and spermicide), IUD, or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. A sterile sexual partner is NOT considered an adequate form of birth control. Subjects on hormonal contraception must be stabilized on the same type for at least three months prior to enrollment in the study and must not change the method during the study. Subjects who had used hormonal contraception and stopped must have stopped no less than three months prior to the study.

### **Concomitant medications**

Concomitant medications, including the use of sunscreen, in addition to the reason for the medication use, will be assessed at baseline and at each subsequent study visit. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.

A record of concomitant medications taken by the Subject is to be obtained using generic name, if known, with the corresponding indication. The medications to be recorded will include prescription and over-the-counter (OTC) medications and dietary supplements. All medications taken on a regular basis, including aspirin and acetaminophen, should be recorded.

### **Adverse Events**

An adverse event is defined as any untoward medical occurrence (sign, symptom or laboratory finding), regardless of severity and whether or not attributed to the investigational product. All adverse events, whether observed by an Investigator or Study Coordinator or reported by the Subject, whether related to study drug or not related to study drug, shall be documented on the eCRF and Subject records, together with details, i.e. date of onset, the duration and intensity of each episode, the action taken, the relationship to the investigational product and the degree of severity, the seriousness and the outcome.

## **CLINICAL EVALUATIONS**

### **Clinical signs and symptoms**

At each visit a target lesion on one foot will be identified as the most severe lesion and evaluated for clinical signs (fissuring/cracking, erythema, maceration, and scaling) and symptoms (pruritus and burning/stinging) on a scale on the following scale:

- 0 = none (complete absence of any signs or symptoms)
- 1 = mild (slight)
- 2 = moderate (definitely present)
- 3 = severe (marked, intense)

To be included in the trial, the Subject must have the sum of the clinical signs and symptoms scores of the target lesion at least 4, including a minimum score of at least 2 for erythema AND a minimum score of 2 for either scaling or pruritus (on a scale of 0-3, where 2 indicates moderate severity).

### **KOH Wet Mount**

If the Subject's clinical signs and symptoms assessment supports evidence of tinea pedis (as outlined above), the Subject will provisionally be included in the trial based on the confirmation of a positive potassium hydroxide (KOH) wet mount preparation. Skin scrapings from the target site will be placed on a clean glass slide and a drop of 10% KOH will be added to the slide and covered with a cover slip and placed on a microscope slide. A microscopic examination of the skin scraping sample will reveal the presence or lack thereof of segmented fungal hyphae. This procedure will be conducted at the investigative site.

Only if a positive KOH wet mount is detected, the Subject will be enrolled in the study and a skin fungal culture will be obtained at the target site. Note that a positive skin fungal culture at baseline is not an

inclusion criterion due to the time lag between obtaining the culture specimen and receiving the culture results. This procedure will be repeated at Visit 3

### **Mycological Culture**

If at Visit 1 the KOH wet mount result is positive, the Subject will be enrolled in the study and a skin fungal culture will be obtained at the target site. This sample will be sent to a centralized microbiology laboratory for analysis. The skin scraping will be placed in a Dermapak® transport kit provided by the central laboratory. The kit should be sealed according to the directions on the back of the kit. The sample kit should be sent to the central laboratory as instructed in the laboratory manual provided by the Central Lab :

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For Subjects with positive cultures at baseline, this procedure will be repeated in Visit 3 only if the of the KOH wet mount results are negative at Visit 3.

If the KOH wet mount results at Visit 3 are positive then the Subject is considered to be a mycological failure and further cultures are not necessary.

Testing will be performed to identify the isolates at the species level (e.g., *Trichophyton rubrum* and *Epidermophyton floccosum*).

The study physicians are required to collect skin samples for KOH and Mycology Culture tests at the test-of-cure visit. In cases where the samples are not collected due to the fact that the actual infected or previously infected tissue is not available at the target site, the physician should report the target area as "Completely healed" and KOH and fungal culture is considered negative. In such cases the mycological cure will be assigned only if evidence of the healthy skin was reported, i.e., all clinical signs (fissuring/cracking, erythema, maceration, and scaling) were scored 0.

## **STUDY VISITS (SEE STUDY VISIT SCHEDULE)**

### **Visit 1: Baseline (Day 1)**

The following procedures will be performed at Visit 1:

1. **Written informed consent will be obtained.** Subjects must have provided IRB approved written informed consent. Prior to initiating screening for the study, Subjects will be given the approved ICF describing the study and any risks associated with participation. The Subject will be allowed as much time as needed to read and understand the information presented in the consent form. Appropriate study personnel will be available to answer any questions the Subject might have regarding the study or study-related procedures. If the Subject chooses to participate in the study, he or she will be asked to sign and date the consent form and will be provided with a copy for his or her records. In addition, the Principal Investigator or the Principal Investigator's Designee will provide a HIPAA authorization form (if applicable) for the Subject or the Subject's legally acceptable representative (i.e., parent or guardian) to review and sign. Both the ICF and the HIPAA authorization form (if



applicable) must be signed by the Subject or the Subject's legally acceptable representative (i.e., parent or guardian) before any protocol assessments can be undertaken.

2. A complete medical history will be obtained for the Subject's current and past medical conditions. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity\*, heart attack, stroke, congestive heart failure, kidney disease, and auto immune disease and gestational diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal.

\* Obesity = BMI  $\geq$ 30 (as defined by Metropolitan Life Insurance Company Chart)

3. Demographics and vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated position for 5 minutes before vital signs are obtained.
4. A brief physical examination, including height (measured in inches) and weight (measured in pounds), will be performed. At a minimum, the physical examination will include the following: assessment of general appearance, skin, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, extremities.
5. A complete list of current and past (within the previous 30 days) concomitant medications will be obtained for each Subject.
6. A urine pregnancy test will be conducted for all females of childbearing potential.
7. A target lesion on one foot will be identified as the most severe lesion and evaluated for clinical signs (fissuring/cracking, erythema, maceration, and scaling) and symptoms (pruritus and burning/stinging) on a scale on the following scale:

0 = none (complete absence of any signs or symptoms)

1 = mild (slight)

2 = moderate (definitely present)

3 = severe (marked, intense)

8. If the Subject's clinical signs and symptoms assessment supports evidence of tinea pedis (as outlined above), the skin scrapings from the target site will be placed on a clean glass slide and a drop of 10% KOH will be added to the slide and covered with a cover slip and placed on a microscope slide. A microscopic examination of the skin scraping sample will reveal the presence or lack thereof of segmented fungal hyphae. This procedure will be conducted at the investigative site.
9. If the KOH wet mount result is positive, the Subject will be enrolled in the study and a skin fungal culture will be obtained at the target site. This sample will be sent to a centralized microbiology laboratory for analysis. The skin scraping will be placed in a Dermapak® transport kit provided by the central laboratory. The kit should be sealed according to the directions on the back of the kit. The sample kit should be sent to the central laboratory as instructed in the laboratory manual provided by Central Lab :

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10. When the Subject has completed all screening procedures, compliance with the inclusion and exclusion criteria will be reviewed. After the inclusion and exclusion criteria have been confirmed, the Subject will be randomized to a treatment group. The Subject will be assigned a randomization number.
11. The following will be dispensed during Visit 1:
  - The investigational product
  - One Ivory soap bar
  - One pack of Graham PST Professional Service Towels
  - A diary card to record product use from Visit 1 to Visit 2
12. Randomized Subjects will be instructed on the correct method for the application of the Investigational Product. The first application of the Investigational Product will be performed by the Subject at home on the day of the Visit 1. The study restrictions will also be reviewed with the Subject and an instruction sheet will be issued to the Subject.
13. Randomized Subjects will be provided with a diary and instructed how and when to complete the diary. They will be told that they are to document all treatments administered, including the date and all treatments missed. In addition, Subjects will be instructed to document all AEs. Subjects will also be instructed to call the study site if they experience any severe intolerability (i.e., local skin reactions) to Investigational Product.
14. Visit 2 (Day 14  $\pm$  3 days from the date of Visit 1) will be scheduled and the Subject will be instructed to bring all Investigational Product (used, unused, and partially used) and the Subject diary to this visit.

### **Visit 2: End of Treatment (Week 2; Day 14 $\pm$ 3 Days)**

The following procedures will be performed at Visit 2:

If **baseline skin fungal culture results are unknown or final results are positive**, the following procedures will be performed at Visit 2:

1. A urine pregnancy test will be conducted for all females of childbearing potential.
2. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject.
3. A target lesion on one foot will be identified as the most severe lesion and evaluated for clinical signs (fissuring/cracking, erythema, maceration, and scaling) and symptoms (pruritus and burning/stinging) on a scale on the following scale:
  - 0 = none (complete absence of any signs or symptoms)
  - 1 = mild (slight)
  - 2 = moderate (definitely present)
  - 3 = severe (marked, intense)
4. The occurrence of all AEs will be assessed and documented.

5. The Subject's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The Subject's diary will be collected and reviewed for completion. A new diary will be issued.
6. The Subject's used Investigational Product will be returned to the third-party drug dispenser.
7. Visit 3 (Day 42 ± 4 days from the date of Visit 1) will be scheduled and the Subject will be instructed to bring the Subject diary to this visit.

It is not anticipated that Subjects will require additional supplies during this visit; additional supplies will be dispensed if required.

If **baseline skin fungal culture final results are negative**: the Subject will be terminated from the trial and the following procedures will be performed:

1. A urine pregnancy test will be conducted for all females of childbearing potential.
2. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject.
3. The occurrence of all AEs will be assessed and documented.
4. The Subject's used Investigational Product will be returned to the third-party drug dispenser.

### **Visit 3: Test of Cure (Week 6; Day 42 ± 4 Days) / Early Discontinuation**

The following procedures will be performed at Visit 3:

If **baseline skin fungal culture final results are negative**: the visit will be performed by telephone before the scheduled Visit 3 date. The following information will be collected:

1. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject.
2. The occurrence of all AEs will be assessed and documented.

If **baseline skin fungal culture final results are positive**: the following procedures will be performed at Visit 3:

1. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject.
2. The occurrence of all AEs will be assessed and documented.
3. The Subject's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The Subject's diary will be collected and reviewed for completion.
4. A target lesion on one foot will be identified as the most severe lesion and evaluated for clinical signs (fissuring/cracking, erythema, maceration, and scaling) and symptoms (pruritus and burning/stinging) on a scale on the following scale:

0 = none (complete absence of any signs or symptoms)

1 = mild (slight)

2 = moderate (definitely present)

3 = severe (marked, intense)

5. The skin sample from the target site will be collected for for KOH and Mycology Culture tests. This sample will be sent to a centralized microbiology laboratory for analysis. The skin scraping will be placed in a Dermapak® transport kit provided by the central laboratory. The kit should be sealed according to the directions on the back of the kit. The sample kit should be sent to the central laboratory as instructed in the laboratory manual provided by Central Lab :

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The study physicians are required to collect skin samples for KOH and Mycology Culture tests at the test-of-cure visit. In cases where the samples are not collected due to the fact that the actual infected or previously infected tissue is not available at the target site, the physician should report the target area as “Completely healed” and KOH and fungal culture is considered negative. In such cases the mycological cure will be assigned only if evidence of the healthy skin was reported, i.e., all clinical signs (fissuring/cracking, erythema, maceration, and scaling) were scored 0.

For Subjects required **early discontinuation**, the following procedures should be performed at Visit 3.

1. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject.
2. The occurrence of all AEs will be assessed and documented.

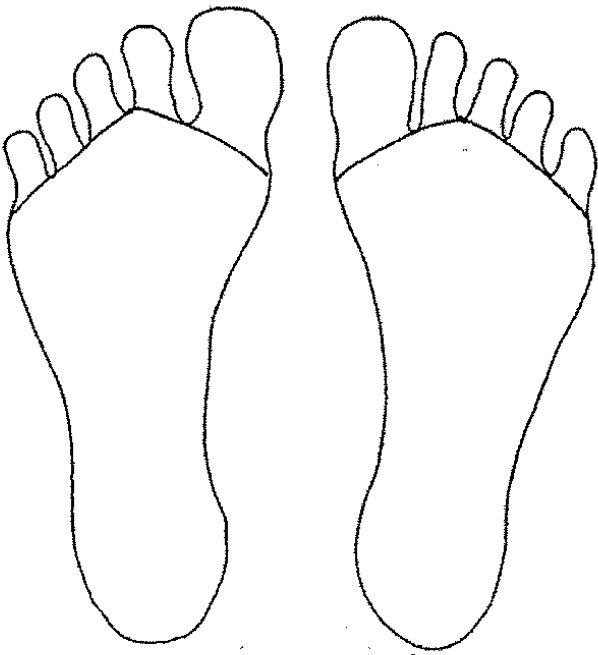
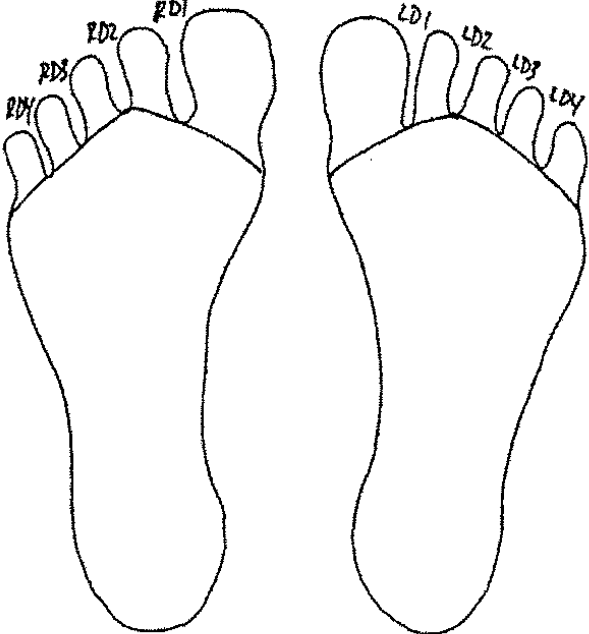
### **Unscheduled Visits and Early Discontinuation Visit**

An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator’s opinion it is warranted. If the Unscheduled Visit is due to an AE, the Principal Investigator will determine whether additional visits are needed.

If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and required procedures scheduled for Visit 3 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the Subject will continue to take part in the study), then all procedures scheduled for that interim visit will be performed, with the exception of the collection of Investigational Product and Subject diaries from Subjects.

If the Subject’s condition has worsened to the degree that it is unsafe for the Subject to continue in the study, the Subject may be discontinued from the study as treatment failure and a standard of care treatment may be advised at the Principal Investigator’s discretion.

**INTERDIGITAL TINEA PEDIS DIAGRAM FOR SELECTION OF THE TARGET LESION**

Tinea Pedis Assessment	Key
<p><b>On the diagram below, shade all affected areas on both feet and mark the interdigital area with the most severe involvement likely to produce a fungal isolate (Target Site) with an X. Select only one site.</b></p>  <p style="text-align: center;">Plantar View</p> <p style="display: flex; justify-content: space-around;"> <span>Right</span> <span>Left</span> </p>	<p><b>Use for reference to document Target Site location on the CRF.</b></p>  <p style="text-align: center;">Plantar View</p> <p style="display: flex; justify-content: space-around;"> <span>Right</span> <span>Left</span> </p>