

CONFIDENTIAL PROTOCOL

A Randomized, Double-Blind, Vehicle-Controlled, Parallel-Design, Multiple-Site Clinical Study to Evaluate the Therapeutic Equivalence of Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd) to Ketoconazole Cream 2% (G&W Laboratories Inc.) in the Treatment of Tinea Pedis

COVER PAGE

PROTOCOL

Rev. 1.0

November 8, 2018

NCT03824912

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Protocol Number: 71875502

Novum Study Number: 71875502

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1.0 TITLE PAGE

Drug Product	Ketoconazole Cream 2%
Population	Approximately 830 males and non-pregnant females, 18 years of age and older, with a clinical diagnosis of tinea pedis
Study Design	A randomized, double-blind, vehicle-controlled, parallel-group, multiple-site bioequivalence study with clinical endpoints
Sponsor	Encube Ethicals Pvt Ltd
Protocol Number	71875502
Novum Study Number	71875502
Protocol Date	11/08/2018

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2.0 KEY STUDY PERSONNEL AND FACILITIES

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3.0 SIGNATURE PAGE

We, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study. The study will be performed according to this protocol, all applicable Food and Drug Administration (FDA) regulations, International Conference on Harmonisation (ICH) guidelines and Good Clinical Practice (GCP) standards.

Gail Gongas
Vice President, Clinical Trials and Data Management
Novum Pharmaceutical Research Services

Date

Christian P. Urrea, MD
Medical Monitor, Clinical Trials
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Chief Scientific Officer
Novum Pharmaceutical Research Services

Date

Dr. Lalatendu Panigrahi
Chief Scientific Officer
Encube Ethicals Pvt Ltd

Date

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PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct protocol 71875502 Rev 0 in accordance with FDA regulations, ICH guidelines and GCPs. I understand that no deviations from the protocol may be made without the prior permission of the Sponsor (Encube Ethicals Pvt Ltd) or Novum Pharmaceutical Research Services, the company managing the study.

Principal Investigator

Date

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5.0 SYNOPSIS

Protocol Number	71875502
Title	A Randomized, Double-Blind, Vehicle-Controlled, Parallel-Design, Multiple-Site Clinical Study to Evaluate the Therapeutic Equivalence of Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd) to Ketoconazole Cream 2% (G&W Laboratories Inc.) in the Treatment of Tinea Pedis
Objectives	<p>The objectives of this study are to:</p> <ol style="list-style-type: none">1. Evaluate the therapeutic equivalence of a generic Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd) to the Reference product, Ketoconazole Cream 2% (G&W Laboratories Inc.) in the treatment of tinea pedis.2. Demonstrate the superiority of the clinical effect of the Test and Reference (active) products over that of the Placebo (vehicle) in the treatment of tinea pedis.3. Compare the safety of the Test, Reference and Placebo products in the treatment of tinea pedis.
Sponsor	Encube Ethicals Pvt Ltd
Study Products	<ul style="list-style-type: none">• Test: Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)• Reference: Ketoconazole Cream 2% (G&W Laboratories Inc.); Registrant: Teva Pharmaceuticals USA Inc.)• Placebo: Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)
Route of Administration	Topical
Treatment Randomization	2:2:1 (Test: Reference: Placebo)
Dosage Regimen	Patients will be instructed to apply sufficient study product to cover affected and immediate surrounding areas once daily for 42 ± 4 days. Each patient is expected to receive 42 ± 4 doses.
Patient Population	Approximately 830 males and non-pregnant females, 18 years of age and older, with a microbiologically-confirmed clinical diagnosis of tinea pedis
Study Design	A randomized, double-blind, vehicle-controlled, parallel-group, multiple-site bioequivalence study with clinical endpoints
Study Conduct	Eligible patients will be randomized in a 2:2:1 ratio to one of three treatments (Test, Reference or Placebo) at Visit 1. Patients will complete three clinic visits as follows: <ul style="list-style-type: none">• Visit 1 (Day 1): Screening/Baseline• Visit 2 (Day 42 ± 4): End of Treatment• Visit 3 (Day 56 ± 4): Test-of-Cure/End of Study

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	<p>Patients will be instructed to apply the study product to the affected and immediate surrounding areas once daily for a total of 42 ± 4 days starting on the day of enrollment (i.e., Day 1). The last dose should be applied on the day of Visit 2 (Day 42 ± 4). Evaluations will be performed in accordance with the study schematic. Safety assessments will include monitoring of adverse events (AEs), vital signs measurement, and urine pregnancy tests (for females of childbearing potential). Clinical assessments will include the potassium hydroxide (KOH) wet mount, mycological culture, and rating of signs and symptoms. The Investigator should identify the most severe lesion (i.e., target lesion) at baseline. Although the study product should be applied to all infected areas (both feet), only the target lesion will be evaluated for analysis.</p>
Inclusion Criteria	<ol style="list-style-type: none">1. Healthy male or non-pregnant, non-lactating female, ≥ 18 years of age.2. Signed informed consent form (ICF) that meets all criteria of current Food and Drug Administration regulations.3. Female patient of childbearing potential must not be pregnant or lactating at Visit 1 (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin).4. Female patient of childbearing potential must agree to the use of a reliable method of contraception throughout the study (e.g., total abstinence, intrauterine device, a double-barrier method, oral, transdermal, injected, or implanted non-hormonal or hormonal contraceptive) throughout the study. A sterile sexual partner is not considered an adequate form of birth control. If the female is using any estrogen or oral contraceptive therapy, the same product must have been taken for at least one month before Visit 1.5. Have clinical diagnosis of 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).6. The presence of tinea pedis infection provisionally confirmed at baseline by a positive KOH wet mount preparation (i.e., skin scrapings from the target site are placed on a microscope slide with a drop of 10% KOH, and microscopic examination reveals segmented fungal hyphae).7. The sum of clinical signs and symptoms scores of the target lesion ≥ 4. See Appendix A for scoring scale:<ol style="list-style-type: none">a. Signs: Fissuring/cracking, erythema, maceration and scalingb. Symptoms: pruritus and burning/stingingIn addition the target lesion must have a minimum score ≥ 2 for erythema and a minimum score ≥ 2 for either pruritus or scaling.

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Exclusion Criteria	<ol style="list-style-type: none">1. Females who are pregnant, lactating or planning to become pregnant during the study period.2. History of or current psoriasis, Lichen planus or contact dermatitis involving the feet within the previous 12 months.3. History of dermatophyte infections with a lack of response to antifungal therapy (recurrent tinea pedis [i.e., more than 3 infections in the past 12 months] that were unresponsive to previous antifungal therapy).4. History of allergy, hypersensitivity, or intolerance to ketoconazole, other imidazoles, sulfites or any other component of the study product.5. Confluent, diffuse moccasin-type tinea pedis of the entire plantar surface.6. Current uncontrolled diabetes.7. Presence of any other infection of the foot or other disease process that, in the Investigator's opinion, may interfere with the evaluation of the patient's tinea pedis.8. Known history of or current impaired wound healing, presence of peripheral vascular disease and/or trophic changes of the lower limbs to an extent that, in the opinion of the Investigator, would make the patient unsuitable for the study or compromise patient's safety.9. Significant history or current evidence of chronic infectious disease, system disorder, organ disorder, immunosuppression (due to disease or therapy, including history of organ transplant), or other medical condition that, in the Investigator's opinion, would place the patient at undue risk by participating or compromise the integrity of the study data.10. Use of antipruritics, including antihistamines, within 72 hours before Visit 1.11. Use of topical corticosteroids, topical antibiotics or topical antifungal therapy (e.g., clotrimazole, econazole, fluconazole) within 2 weeks before Visit 1.12. Use of systemic (e.g., oral or injectable) antibiotics, systemic antifungal therapy, or systemic corticosteroids within 30 days before Visit 1. The use of intranasal, inhaled or ophthalmic corticosteroids for acute or chronic conditions (e.g., allergic conjunctivitis, asthma/chronic obstructive pulmonary disease maintenance) is acceptable to the extent that, in the opinion of the Investigator, does not compromise safety of patient or integrity of data.13. Use of oral terbinafine or itraconazole within 2 months before Visit 1.14. Use of immunosuppressive medication or radiation therapy within 3 months before Visit 1.15. Receipt of any drug as part of a research study within 30 days before
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	<p>Visit 1.</p> <p>16. Previous participation in this study.</p> <p>17. Employee of the Investigator or research center or their immediate family members.</p> <p>18. Inability to understand the requirements of the study and the relative information or are unable or unwilling to comply with the study protocol.</p>
Efficacy Variables	The primary and secondary efficacy variables are the outcome of the KOH test (negative or positive), outcome of the mycological culture (negative or positive), and signs and symptoms scores.
Efficacy Endpoints	<p><u>Primary Efficacy Endpoint</u></p> <p>The primary efficacy endpoint is the proportion of patients in each treatment group with a Therapeutic Cure of tinea pedis at the test-of-cure visit conducted two weeks after the end of treatment (Day 56 ± 4).</p> <p><u>Secondary Efficacy Endpoints</u></p> <p>The secondary efficacy endpoints are:</p> <ul style="list-style-type: none">• The proportion of patients in each treatment group with a Clinical Cure at Day 56 ± 4.• The proportion of patients in each treatment group with a Mycological Cure at Day 56 ± 4. <p><u>Definitions</u></p> <ol style="list-style-type: none">1. <u>Therapeutic Cure:</u> To be considered a Therapeutic Cure, the patient must have both Clinical and Mycological Cure of tinea pedis.2. <u>Therapeutic Failure:</u> A patient will be considered a Therapeutic Failure if:<ol style="list-style-type: none">a. the patient is a Clinical or Mycological Failureb. the patient was considered to have an insufficient therapeutic responsec. the patient used topical drug therapy for irritation or pruritus on the feet after the treatment phase of the study3. <u>Clinical Cure:</u> To be considered a clinical cure the patient's total severity score must be ≤ 2 with no individual severity score > 1.4. <u>Clinical Failure:</u> A patient will be considered a Clinical Failure if the patient's total severity score is > 2 <u>or</u> any individual score is > 1.5. <u>Mycological Cure:</u> To be considered a mycological cure the patient must have a negative KOH test <u>and</u> a negative fungal culture.6. <u>Mycological Failure:</u> A patient will be considered a Mycological Failure if the patient's KOH test is positive <u>or</u> the patient's fungal culture is positive.

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Evaluation of Therapeutic Equivalence and Superiority	<p><u>Therapeutic Equivalence</u></p> <p>Therapeutic equivalence will be evaluated for the primary endpoint in the per-protocol (PP) population. If the 90% confidence interval (calculated using Yates' continuity correction) on the absolute difference between the proportion of patients with a Therapeutic Cure in the Test and Reference groups ($p_T - p_R$) is contained within the range [-20%, +20%] then therapeutic equivalence of the Test product to the Reference product will be considered to have been demonstrated.</p> <p>The same statistical approach will be conducted for analyses of the secondary endpoints in the PP population.</p> <p>To declare therapeutic equivalence of the Test product to the Reference product, equivalence must be demonstrated for only the primary endpoint in the PP population.</p> <p>Patients who are missing mycological culture data at the test-of-cure visit will not be included in the analysis for the secondary endpoint of Mycological Cure.</p> <p><u>Superiority to Placebo</u></p> <p>Superiority of the Test and Reference products against the Placebo product for the primary endpoint will be evaluated in the modified Intent-to-Treat (mITT) population using, if necessary, last observation carried forward (LOCF) as described in section 11.3.2. If the proportions of patients with a Therapeutic Cure in the Test and the Reference product groups are numerically and statistically superior to that of the Placebo ($p < 0.05$; using a two-sided Cochran-Mantel-Haenszel [CMH] test, stratified by clinical site) then superiority of the Test and Reference products over Placebo will be concluded.</p> <p>The same statistical approach will be conducted for analyses of the secondary endpoints in the mITT population.</p> <p>To declare superiority of the Test and Reference products over Placebo, their superiority must be demonstrated for only the primary endpoint in the mITT population.</p> <p><u>Treatment-by-Site Interaction and Pooling of Clinical Sites</u></p> <p>As this is a multiple-site study, the interaction of treatment-by-site may be evaluated for the primary efficacy endpoint in the PP population for equivalence testing. The treatment-by-site interaction will be evaluated by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level ($p < 0.05$, 2-sided). A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site, so as to avoid bias in the stratification of the sites in the CMH test and in the estimation of a treatment-by-site interaction effect. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients</p>
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	<p>in the PP population at the site with the highest enrolling rate in the PP population. If the treatment-by-site interaction term is found to be statistically significant ($p < 0.05$) for the primary endpoint, then the interaction term will also be assessed for clinical relevance before pooling the data across sites. This will include examination of Therapeutic Cure rates at each site where sample sizes per treatment may be influential in the assessment of the interaction. The treatment-by-site interaction may also be evaluated for the analyses of the secondary endpoints in the PP population for equivalence testing if the treatment-by-site interaction is found to be significant in the primary analysis.</p>
Safety Analysis	<p>Adverse events (AEs) will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 21.0 or higher and summarized by treatment group. Summary tables comparing the type, date of onset, date of resolution, incidence, severity, relationship to the study product, outcome, and action taken will be prepared by treatment group. If sufficient data exist, then AE frequencies will be compared among the three treatments using Fisher's exact test; if this test is statistically significant at the 5% significance level, then a pairwise Fisher's exact test comparing Test and Reference will be conducted.</p> <p>Signs and symptoms of tinea pedis will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be discontinued from further participation in the study and given alternative therapy for their condition.</p> <p>Concomitant medication use will be tabulated by patient.</p>
Sample Size Determination	<p>For the primary endpoint analysis (proportion of patients in the PP population with a Therapeutic Cure at the test-of-cure visit), sample size is estimated for therapeutic equivalence of the Test to the Reference product and superiority of each of the active treatments groups over Placebo. The sample size estimations are based on previous studies conducted for ketoconazole cream.¹</p> <p>In the PP population, the proportion of patients with a Therapeutic Cure in the Reference group is expected to be 50%. Assuming that the Therapeutic Cure rate for the Test treatment group is an absolute difference of 5% lower than the Reference Responder rate (i.e., $p_T - p_R = -5\%$), a sample size of 172 patients in each active group in the PP population will provide approximately 85% power to demonstrate therapeutic equivalence (i.e., the 90% confidence interval [Yates' continuity-corrected] on the $p_T - p_R$ difference is within a defined equivalence range [-20%, +20%]).</p> <p>The Therapeutic Cure rates for the Placebo and active treatment groups at the test-of-cure visit are anticipated to be approximately 10% and at least 40% (Test = 40%, Reference = 45%), respectively, in the mITT population.</p>

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	<p>Using a 2:1 (Active: Placebo) randomization scheme, and assuming the conversion rate from mITT to PP will be approximately 80%, 216 patients in each active treatment group (Test and Reference) and 108 patients in the Placebo group of the mITT population will provide at least 99% power to demonstrate superiority of active treatments over Placebo ($p < 0.05$; using two-sided, continuity-corrected Z-test and a pooled response rate for the standard error of the difference in proportions).</p> <p>Under the above assumptions, the overall study power to demonstrate therapeutic equivalence and superiority is estimated to be at least 85% ($100\% \times 0.85 \times 0.999$), assuming 100% correlation between the two superiority tests.</p> <p>To allow for approximately 35% of patients who may have negative fungal cultures post-randomization, drop out from the study or are otherwise non-evaluable, approximately 830 patients may be randomized (332 in each active group and 166 in the Placebo group) to yield 540 patients in the mITT population.</p> <p>More than 50% of the patients should have baseline fungal cultures that test positive for <i>T. rubrum</i>. If fewer than 50% of enrolled patients have a positive <i>T. rubrum</i> culture or the number of patients with negative fungal cultures is more than anticipated, then additional patients may be enrolled to ensure that at least 430 (172:172:86) patients are eligible in the PP population, of which > 50% have a positive <i>T. rubrum</i> culture at baseline.</p>
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6.0 STUDY SCHEMATIC

PROCEDURE	VISIT 1 (Day 1) Screening/ Baseline	VISIT 2 (Day 42 ± 4 Days)* End of Treatment	VISIT 3 (Day 56 ± 4 Days) Test-of-Cure/ End of Study
Informed Consent	X		
Medical History and Demographics	X		
Perform Pregnancy Test**	X	X	X
Record Vital Signs	X	X	X
Review and Assessment of Concomitant Medications	X	X	X
Review and Assessment of Adverse Events		X	X
Designate Target Lesion	X		
Assess Local Signs and Symptoms	X	X	X
Collect Sample for KOH Wet Mount	X		X [†]
Inclusion/Exclusion Criteria Review	X		
Collect Sample for Mycological Culture [‡]	X		X
Dispense Study Product	X		
Provide Patient Diary	X	X	
Collect/Review Patient Diary		X	X
Collect Study Product		X	X [§]
Discharge from Study			X

*Dosing regimen is once daily for 42 ± 4 days starting on the day of enrollment (Day 1) through the day of Visit 2 (Day 42 ± 4).

**For females of childbearing potential

†KOH sample will not be collected if baseline culture is negative.

‡Mycological culture sample will not be sent if KOH is negative at baseline or positive at Visit 3. See Appendix B.

§Study product will be collected at Visit 3 if it is not returned at Visit 2.

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7.0 LIST OF ABBREVIATIONS AND TERMS

ADaM	Analysis Dataset Model
AE	Adverse Event
C	Celsius
CDISC	Clinical Data Interchange Consortium
CMH	Cochran-Mantel-Haenszel
CRO	Clinical Research Organization
eCRF	electronic Case Report Form
eCTD	electronic Common Technical Document
F	Fahrenheit
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practices
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IRB	Institutional Review Board
KOH	Potassium Hydroxide
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
mL	Milliliter
OTC	Over-The-Counter
PP	Per-Protocol
RS	Reference Standard
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model

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A Randomized, Double-Blind, Vehicle-Controlled, Parallel-Design, Multiple-Site Clinical Study to Evaluate the Therapeutic Equivalence of Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd) to Ketoconazole Cream 2% (G&W Laboratories Inc.) in the Treatment of Tinea Pedis

8.0 INTRODUCTION

8.1 Disease Being Treated

Tinea pedis is a superficial fungal infection (dermatophytosis) of the foot caused by one or more of the following genera of dermatophytes: *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Epidermophyton floccosum*.² The dermatophytes require keratin for growth and thus their invasion is restricted to hair, nails and the stratum corneum of the skin.

It is estimated that an individual's lifetime risk of acquiring a tinea infection on some part of the body, is approximately 10-20%, affecting up to 70% of the world's population at some point. Occurrences of fungal infection overall appear to be increasing, with an estimated 29-59 million people experiencing at least one mycotic infection per any given year, in the United States alone.^{3,4}

Tinea pedis is one of the most common dermatophytoses and is most frequently caused by *T. rubrum*.^{5,6} Skin affected by tinea pedis is usually pruritic, and other symptoms can include burning, erythema, scaling, fissuring/cracking and bulla formation of the skin around the toes or plantar surface of the feet. Athlete's foot is the common name for tinea pedis, as the infection is typically spread through the use of common bathing and changing areas, such as sports locker rooms.

8.2 Availability and Efficacy of Already Approved Therapies

There are a number of prescription and over-the-counter (OTC) therapies available for the treatment of tinea pedis. For mild cases, improved foot hygiene may be sufficient to control the signs and symptoms. Depending on the severity of infection, tinea pedis can be treated with oral or topical antifungal agents, or a combination of both when necessary. Oral antifungal agents may be used in very severe cases, such as those with the involvement of larger body areas or in conjunction with other superficial fungal infections. Treatment with topical agents can last up to six weeks depending on the recommendation of the manufacturer.

Topical antifungal agents are currently considered the most effective and safest forms of treatment. The two principal pharmacologic groups used to treat dermatophyte infections are the allylamines, which include naftifine and terbinafine, and the azoles, which include econazole, oxiconazole and clotrimazole.^{7,8}

8.3 Scientific and Statistical Considerations

Ketoconazole is not considered to be sufficiently absorbed from the skin to provide measurable systemic concentrations.⁹ The 21 Code of Federal Regulations Sections 320.24 (Revised April 1, 2014) requires that in-vivo pharmacokinetic testing in humans is the preferred method in evaluating bioequivalence. However, circumstances for which measurement of the active moieties in biological fluids is not possible, a pharmacodynamic response study indicative of clinical efficacy can be considered.^{10,11} Therefore, a comparative clinical endpoint study is considered the most appropriate method to evaluate the clinical (therapeutic) effect of two ketoconazole topical cream formulations.

Sample size estimations for this study are based on studies conducted for Teva Pharmaceuticals Abbreviated New Drug Application (ANDA) #075-581 for Ketoconazole Cream 2%.¹

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8.4 Justification for Use of Placebo

Tinea pedis is a very common infection that affects the superficial layers of the epidermis and is limited in its extension. Symptoms are primarily dermatological and present no serious risk to the patient. It is not uncommon for an infection to go unnoticed and untreated for an extended period of time.¹² Patients receiving placebo would not be harmed by the lack of active treatment and would still benefit by participating and being compliant with the hygiene procedure as described in the protocol. By complying with the inclusion and exclusion criteria, all participating patients are expected to be overall healthy and not suffering from conditions that could increase the risk of complications from an underlying tinea infection on the feet.

Furthermore, and as per the Food and Drug Administration (FDA) guidance, a Placebo group is included to confirm the sensitivity of the study and minimize the possibility of a false positive result of bioequivalence.¹³ Therefore, in addition to demonstrating therapeutic equivalence between Test and Reference products, both active products must show statistical superiority to the Placebo.¹⁴

8.5 Risks and Benefits

The risks and benefits to patients enrolled in clinical research studies that include a Placebo treatment group must be carefully considered based on three main criteria, namely: the disease being treated, the availability, efficacy and safety of approved therapies, and the scientific and statistical requirements of the desired outcome of the research study. The Office of Human Rights Protection, a Division of the United States Federal Government's Department of Health and Human Services, has issued a detailed guidebook to Institutional Review Boards (IRBs) that includes discussion on the use of placebos in clinical studies.¹⁵

Qualified patients have a 20% chance they may be randomized to Placebo. Randomized patients will be treated with study product for 42 ± 4 days. Although the potential for any drug-related side effects of significance occurring during the study is low, the risk is higher in the two active treatment groups than in the Placebo group.

All patients enrolled in this study will receive the benefit of free specialized medical care beyond standard medical treatment that would be expected through most health insurance plans. In addition, the patient will receive a stipend for participation to cover costs and expenses associated with trips to the medical facility.

9.0 STUDY OBJECTIVES

The objectives of this study are to:

1. Evaluate the therapeutic equivalence of a generic Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd) to the Reference product, Ketoconazole Cream 2% (G&W Laboratories Inc.) in the treatment of tinea pedis.
2. Demonstrate the superiority of the clinical effect of the Test and Reference (active) products over that of the Placebo (vehicle) in the treatment of tinea pedis.
3. Compare the safety of the Test, Reference and Placebo products in the treatment of tinea pedis.

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10.0 INVESTIGATIONAL PLAN

10.1 Study Design and Plan Description

This randomized, double-blind, vehicle-controlled, parallel-group, multiple-site study has been designed to evaluate the clinical (therapeutic) effect of a generic Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd) compared to the Orange Book Reference Standard (RS) product, Ketoconazole Cream 2% (G&W Laboratories Inc.) in patients with tinea pedis. Additionally, both the Test and Reference (i.e., the RS) treatments will be tested for superiority to a Placebo.

Before any study-specific procedures are performed, all patients will read and sign the IRB-approved informed consent form (ICF).

Approximately 830 eligible patients, 18 years of age and older, will be randomized in a 2:2:1 ratio (Test: Reference: Placebo) to one of the three study products as follows:

- **Test:** Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
- **Reference:** Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
- **Placebo:** Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

Patients will complete three clinic visits as follows:

- Visit 1 (Day 1): Screening/Baseline
- Visit 2 (Day 42 ± 4): End of Treatment
- Visit 3 (Day 56 ± 4): Test-of-Cure/End of Study

Patients will be instructed to apply the study product to affected and immediate surrounding areas once daily for a total of 42 ± 4 days starting on the day of enrollment (i.e., Day 1). The last dose should be applied on the day of Visit 2 (Day 42 ± 4). Evaluations will be performed in accordance with the study schematic. Safety assessments will include monitoring of adverse events (AEs), vital signs measurement, and urine pregnancy tests (for females of childbearing potential). Clinical assessments will include the potassium hydroxide (KOH) wet mount, mycological culture, and rating of signs and symptoms. The Investigator should identify the most severe lesion (i.e., target lesion) at baseline. Although the study product should be applied to all infected areas (both feet), only the target lesion will be evaluated for analysis.

10.2 Selection of Study Design

This protocol is designed based on the FDA draft guidance for Ketoconazole Topical Cream released in March 2010.¹³

Statistical analyses of the clinical data will be based on recommendations in the FDA Guidances.^{13,16}

10.3 Selection of Study Population

10.3.1 Inclusion Criteria

1. Healthy male or non-pregnant, non-lactating female, ≥ 18 years of age.

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2. Signed ICF that meets all criteria of current FDA regulations.
3. Female patient of childbearing potential must not be pregnant or lactating at Visit 1 (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin).
4. Female patient of childbearing potential must agree to the use of a reliable method of contraception throughout the study (e.g., total abstinence, intrauterine device, a double-barrier method, oral, transdermal, injected, or implanted non-hormonal or hormonal contraceptive) throughout the study. A sterile sexual partner is not considered an adequate form of birth control. If the female is using any estrogen or oral contraceptive therapy, the same product must have been taken for at least one month before Visit 1.
5. Have clinical diagnosis of 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).
6. The presence of tinea pedis infection provisionally confirmed at baseline by a positive KOH wet mount preparation (i.e., skin scrapings from the target site are placed on a microscope slide with a drop of 10% KOH, and microscopic examination reveals segmented fungal hyphae).
7. The sum of clinical signs and symptoms scores of the target lesion ≥ 4 . See Appendix A for scoring scale:
 - a. **Signs:** Fissuring/cracking, erythema, maceration and scaling
 - b. **Symptoms:** pruritus and burning/stinging

In addition the target lesion must have a minimum score ≥ 2 for erythema and a minimum score ≥ 2 for either pruritus or scaling.

10.3.2 Exclusion Criteria

1. Females who are pregnant, lactating or planning to become pregnant during the study period.
2. History of or current psoriasis, Lichen planus or contact dermatitis involving the feet within the previous 12 months.
3. History of dermatophyte infections with a lack of response to antifungal therapy (recurrent tinea pedis [i.e., more than 3 infections in the past 12 months] that were unresponsive to previous antifungal therapy).
4. History of allergy, hypersensitivity, or intolerance to ketoconazole, other imidazoles, sulfites or any other component of the study product.
5. Confluent, diffuse moccasin-type tinea pedis of the entire plantar surface.
6. Current uncontrolled diabetes.
7. Presence of any other infection of the foot or other disease process that, in the Investigator's opinion, may interfere with the evaluation of the patient's tinea pedis.

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8. Known history of or current impaired wound healing, presence of peripheral vascular disease and/or trophic changes of the lower limbs to an extent that, in the opinion of the Investigator, would make the patient unsuitable for the study or compromise patient's safety.
9. Significant history or current evidence of chronic infectious disease, system disorder, organ disorder, immunosuppression (due to disease or therapy, including history of organ transplant), or other medical condition that, in the Investigator's opinion, would place the patient at undue risk by participating or compromise the integrity of the study data.
10. Use of antipruritics, including antihistamines, within 72 hours before Visit 1.
11. Use of topical corticosteroids, topical antibiotics or topical antifungal therapy (e.g., clotrimazole, econazole, fluconazole) within 2 weeks before Visit 1.
12. Use of systemic (e.g., oral or injectable) antibiotics, systemic antifungal therapy, or systemic corticosteroids within 30 days before Visit 1. The use of intranasal, inhaled or ophthalmic corticosteroids for acute or chronic conditions (e.g., allergic conjunctivitis, asthma/chronic obstructive pulmonary disease maintenance) is acceptable to the extent that, in the opinion of the Investigator, does not compromise safety of patient or integrity of data.
13. Use of oral terbinafine or itraconazole within 2 months before Visit 1.
14. Use of immunosuppressive medication or radiation therapy within 3 months before Visit 1.
15. Receipt of any drug as part of a research study within 30 days before Visit 1.
16. Previous participation in this study.
17. Employee of the Investigator or research center or their immediate family members.
18. Inability to understand the requirements of the study and the relative information or are unable or unwilling to comply with the study protocol.

10.3.3 Restrictions During the Study

The following concomitant medications will not be allowed while enrolled in the study:

- Any topical products applied to the treatment area
- Any systemic (e.g., oral or injectable) antibiotics or anti-fungals
- Systemic corticosteroids or immunosuppressive drugs.
- Anti-pruritics, including antihistamines, within 24 hours of study visits.

Patients will be instructed not to use any occlusive wrappings or dressings over the treatment area during the study.

The use of hormonal contraceptives should not be initiated or changed during the study.

10.3.4 Removal of Patients from the Study

Patients will be informed that they are free to withdraw from the study at any time. If necessary, the Investigator may withdraw a patient from the study to protect the health of that patient. The clinical report will include all reasons for early withdrawals.

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Reasons for removal may include the following:

- Patient withdrew consent.
- Significant AE that led the Investigator or patient to withdraw for safety reasons.
- Non-compliance with protocol requirements (e.g., use of restricted medication, not following dosing procedures, failure to make scheduled study visits in a timely fashion).
- Pregnancy
- Negative baseline culture results
- Development of an intercurrent condition or complication that could affect the safety of the patient or the validity of evaluation of the patient's clinical state to an extent considered significant by the Investigator
- Significant worsening of tinea pedis such that the Investigator and/or patient believe it is in the best interest of the patient to withdraw from the study and be provided alternative treatment.
- Patient enrolls in another clinical trial, or is found to have previously enrolled in this clinical trial.

Patients who withdraw or are removed from the study will not be replaced.

10.4 Treatments

10.4.1 Identity of Investigational Product

The following products will be used in the study:

- **Test:** Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd)
- **Reference:** Ketoconazole Cream 2% (G&W Laboratories Inc.; Registrant: Teva Pharmaceuticals USA Inc.)
- **Placebo:** Placebo Cream (Test vehicle) (Encube Ethicals Pvt Ltd)

10.4.2 Method of Assigning Patients to Treatment Groups

All randomized study product will be blinded and packaged in sealed boxes by an independent packaging company. Randomization will be pre-planned according to a computer-generated randomization schedule. The randomization will be generated in blocks, each containing five patients' worth of study product (2 Test, 2 Reference, and 1 Placebo).

The randomization number will be a unique four-digit number. Patient numbers will be assigned immediately before dispensing of study product and in ascending sequential order, beginning with the lowest available number at the study site. Each patient kit and each dispensed study tube should include the four-digit patient number on the label.

At the end of the study, after all the clinical data have been entered and the study database has been locked, a copy of the randomization schedule will be sent to the statistician.

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10.4.3 Study Blind

The study product will be randomized, packaged and blinded by an independent packaging company. The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the patient assignment. Each study site will have at least one Independent Dispenser. The role of the Independent Dispenser is to dispense and collect study product to/from the patients, maintain dispensing records and ensure the study product logs are complete and accurate.

The patient will be requested not to discuss the appearance of the study product with the Investigator or study staff outside of the Independent Dispenser. A perforated or two-part label will be attached to the study product supplies for each patient. Both pieces of the label should include the following information:

- Protocol number
- Randomization number
- Space for patient's initials
- Statement that the product is for investigational use only
- Space for dispensing date and the Sponsor's name

One part of the label will remain attached to the box. The other part will be removed before dispensing and attached to patient's source documentation.

To ensure information that could potentially bias handling of data is not disclosed, the clinical packaging company will hold the randomization scheme until database lock. A perforated tear-off label containing the unblinding information will be placed in the patient's chart, to be opened in case of medical emergency only and should be kept at the site with the study documents when the study is completed.

Whenever possible, the Novum Medical Monitor must be contacted before breaking the blind for any patient. The unblinding labels should be stored in a secure location at all times and maintained at the site for all randomized patients after the completion of the study.

At the end of the study, after the database has been locked, each site will be sent a sealed envelope containing the full study randomization that should be retained with the study documents in the event of an FDA inspection.

10.4.4 Treatment Administration

At Visit 1, eligible patients will receive three 30 g tubes of randomized study product (i.e., Test, Reference, or Placebo). Patients will be instructed to use sufficient amount of the study product to cover all affected and immediate surrounding areas on the feet once daily for a total of 42 ± 4 days, starting on the day of enrollment (i.e., Day 1). The last dose should be applied on the day of Visit 2. It is important that patients adhere to the entire dosing regimen, even in the eventuality of a rapid relief of the symptoms.

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Patients will be instructed to cleanse their feet with warm water and soap, dry feet completely before applying the study product. Patients should avoid bathing, showering or washing the treated areas of the feet for at least 4 hours after applying the study product. In addition, all patients will be provided with verbal advice on basic foot hygiene (e.g., change socks regularly, try and keep feet as dry as possible during the day, wash feet thoroughly after using communal bathing, showering areas).

Each patient will be provided with a dosing diary in which they will be required to record dosing dates and times. The dosing diary should be brought to Visit 2 so that the study staff may check compliance and filed in the patient's source documentation. At the end of the study they will be retained in the patient's file as source documentation.

10.4.5 Study Product Shipment, Storage, and Retention

The study product will be shipped to each Investigator's site from a central location. The Principal Investigator at each site is responsible for ensuring that all study products are stored in locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study product will be maintained in accordance with federal regulations.

Storage Conditions

Study product will be stored at controlled room temperature 20-25°C (68-77°F) in a secure place with access by authorized individuals only.

Retention

For every study product shipment received at the site, the Investigator (or designee) will randomly select at least one block of study product for retention. The selection process will ensure a sufficient amount of retention samples are retained as per Sponsor requirement. Each block selected for retention will be labeled as a retention sample and should not be dispensed to study patients. The selected retention samples will be retained by each site under FDA regulations for a minimum of five years .¹⁷

Once the site has been notified that they may do so, all unused study product and empty or partially used tubes of study product, other than that randomly selected for retention samples will be returned to the Sponsor's designee. It is important that retention samples not be returned to Novum, the Sponsor or the packaging company during or at the end of the study.

10.4.6 Compliance

Patients will be provided with a diary to record the time and date of dosing. Patients taking fewer than 75% or more than 125% of the required doses will be considered non-compliant with dosing and excluded from the PP population. Compliance with dosing will be verified by the use of the patient diaries. Compliance criteria are outlined in the table below:

For patients who have completed the study:

Study Design			Compliance Criteria	
Study Period	Treatment Duration	Scheduled Doses	Not more than 125% (doses)	Not less than 75% (doses)

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Randomized Treatment	38-46 Days	42	52	32
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For patients who are early terminated, compliance will be determined from their duration in the study, up to the time they are considered early terminated. For example, if a patient is discontinued after 20 days of participation and doses 18 times, their percent compliance is 90%.

10.5 Study Conduct

10.5.1 Visit 1 (Day 1): Screening/Baseline

1. **Informed Consent:** Patients who are willing to comply with study procedures will read, understand and sign the informed consent.
2. **Medical History and Demographics:** Collect the patient's demographic information and medical history, including tinea pedis history.
3. **Perform Pregnancy Test:** A urine pregnancy test will be required of all female patients of childbearing potential before starting treatment.
4. **Record Vital Signs:** Record the patient's vital signs (blood pressure, pulse, temperature and respiration rate).
5. **Review and Assessment of Concomitant Medications:** Review the patient's use of concomitant medication within the last six months.
6. **Designate Target Lesion:** The Investigator should identify and record the interdigital space with the most severe interdigital infection. This will be designated the target lesion and will be followed and evaluated at each visit.
7. **Assess Local Signs and Symptoms:** Clinical signs and symptoms of tinea pedis at the target lesion site will be evaluated using the static scale in Appendix A. Wherever possible, the same Investigator should attempt to perform all clinical exams at all visits for an individual patient.
8. **Collect Sample for KOH Wet Mount:** If the clinical signs and symptoms of interdigital tinea pedis are present, then samples for the KOH wet mount should be obtained from the designated target lesion site as per instructions in section 10.6.9. The KOH wet mount review should be performed by the Investigator or appropriately trained and qualified delegated staff.
9. **Inclusion/Exclusion Criteria Review:** Review inclusion/exclusion criteria and confirm patient is eligible for randomization, pending results of the fungal culture.
10. **Collect Sample for Mycological Culture:** If the patient meets all of the other inclusion/exclusion criteria then a sample will be sent to the centralized laboratory for fungal culture.
11. **Dispense Study Product:** The Independent Dispenser will dispense study product to eligible patients with along with dosing instructions.
12. **Provide Patient Diary:** The site will provide a diary to each patient with instructions on how to complete the diary.

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13. Schedule Visit 2.

10.5.2 Visit 2 (Day 42 ± 4 Days): End of Treatment

1. **Perform Pregnancy Test:** A urine pregnancy test will be required of all female patients of childbearing potential.
2. **Record Vital Signs:** The patient's vital signs will be recorded (blood pressure, pulse, temperature and respiration rate).
3. **Review and Assessment of Concomitant Medications:** Review the patient's use of any new or ongoing concomitant medications since last visit.
4. **Review and Assessment of Adverse Events:** Patients will be questioned about any health status changes/AEs since last visit. All AEs will be recorded.
5. **Assess Local Signs and Symptoms:** Clinical signs and symptoms of tinea pedis at the target lesion site identified at Visit 1 will be evaluated using the static scale in Appendix A. Wherever possible, the same Investigator should attempt to perform all clinical exams at all visits for an individual patient.
6. **Collect and Review Patient Diary:** Collect the diary from the patient and review for compliance with the protocol requirements.
7. **Collect Study Product:** Collect previously dispensed tubes of study product.
8. **Provide Patient Diary:** The site will provide a diary to each patient with instructions on how to complete the diary.
9. Schedule Visit 3.

10.5.3 Visit 3 (Day 56 ± 4 Days): Test-of-Cure/End of Study

1. **Perform Pregnancy Test:** A urine pregnancy test will be required of all female patients of childbearing potential.
2. **Record Vital Signs:** The patient's vital signs will be recorded (blood pressure, pulse, temperature and respiration rate).
3. **Review and Assessment of Concomitant Medications:** Review the patient's use of any new or ongoing concomitant medications since last visit.
4. **Review and Assessment of Adverse Events:** Patients will be questioned about any health status changes/AEs since last visit. All AEs will be recorded.
5. **Assess Local Signs and Symptoms:** Clinical signs and symptoms of tinea pedis at the target lesion site identified at Visit 1 will be evaluated using the static scale in Appendix A. Wherever possible, the same Investigator should attempt to perform all clinical exams at all visits for an individual patient.
6. **Collect Sample for KOH Wet Mount:** Patients with positive baseline culture results will have a sample for the KOH wet mount obtained from the designated target lesion site as per

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instructions in section 10.6.9. The KOH wet mount review should be performed by the Investigator or appropriately trained and qualified delegated staff.

7. **Collect Sample for Mycological Culture:** Patients with positive baseline culture results will have a sample sent to the centralized laboratory for fungal culture. Patients with a positive KOH wet mount at this visit will not have a mycological culture sample collected.
8. **Collect and Review Patient Diary:** Collect previously dispensed diary and review for compliance with the protocol.
9. **Collect Study Product:** Study product tubes that were not returned at Visit 2 will be collected.
10. Discharge from study.

10.6 Study Procedures

10.6.1 Informed Consent

At Visit 1, before performing any study-related procedures the study patient must sign the IRB-approved ICF. The ICF will be reviewed and approved by an IRB before study commencement. No patient will be entered into the study without reading, understanding, and signing an ICF. If any other language is required, translation will be performed by a certified translator.

10.6.2 Medical History and Demographics

At Visit 1, each patient will be required to provide basic demographic information: date of birth, sex, ethnicity and race. Patients will also be questioned about personal medical history, including tinea pedis history.

10.6.3 Perform Pregnancy Test

All females of childbearing potential will have a urine pregnancy test performed at each visit. The test must be negative at Visit 1 for the patient to be eligible for inclusion in the study. If the patient is female and not considered of childbearing potential, then the reason must be documented in the patient's source documents.

Any patient who becomes pregnant during the study should be discontinued and end of study procedures (Visit 3 procedures) completed. The outcome of the pregnancy should be followed by the Investigator to the conclusion of the pregnancy. The pregnancy will be reported as an AE.

10.6.4 Record Vital Signs

The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate) at each visit.

10.6.5 Review and Assessment of Concomitant Medications

At Visit 1, patients will be questioned about medication use over the previous six months. At all subsequent visits, patients will be questioned about ongoing or new concomitant medication use.

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At Visit 2, any patient who has used medications restricted by the protocol may be discontinued from the study. If discontinued, all end of study procedures (Visit 3 procedures) should be performed.

10.6.6 Review and Assessment of Adverse Events

At Visits 2 and 3, patients will be questioned regarding any changes in their medical status since their previous visit. Any significant health changes observed after dosing will be reported as AEs, as deemed appropriate by the Investigator.

10.6.7 Designate Target Lesion

At Visit 1, an examination of the feet will be performed to determine the type and severity of the infection. The clinical staff will record the affected areas in the source document. They will identify the foot and interdigital space with the most severe interdigital infection. This will be designated the target lesion and its location noted in the source documentation. The target lesion will be followed and evaluated at each visit.

10.6.8 Assess Local Signs and Symptoms

Using the identified target lesion the following clinical signs and symptoms will be rated:

- **Signs:** fissuring/cracking, erythema, maceration, and scaling
- **Symptoms:** pruritus and burning/stinging

The severity of each clinical symptom should be evaluated by the Investigator as either “none”, “mild”, “moderate” or “severe” using the 4-point (0-3) rating scale in Appendix A. The signs and symptoms of the target lesion should be evaluated for current severity per visit and not in comparison to any other visit or other patient.

Wherever possible, the same Investigator should attempt to perform all clinical exams at all visits for an individual patient.

To be eligible for inclusion in the study the most infected area must have a total score of at least 4, a minimum score of at least 2 for erythema, and a minimum score of at least 2 for either scaling or pruritus.

10.6.9 Collect Sample for KOH Wet Mount

If the signs and symptoms of tinea pedis meet the inclusion criteria at Visit 1, then samples for the KOH wet mount and fungal culture should be obtained from the target lesion site. After clinical assessments and before possible randomization, sufficient sample should be obtained to perform both KOH wet mount and mycological culture. The sample for the KOH wet mount should be placed onto a clean glass slide. The target lesion site should not be cleansed or sterilized before sample collection. A drop of 10% KOH should then be added to the slide and covered with a cover slip. The slide should be gently heated and then observed under the microscope. The KOH wet mount assessment will be conducted at the investigative site by the Investigator or appropriately trained and qualified delegated staff. The results of the KOH wet mount test will be entered in the patient’s source and electronic case report form (eCRF), as appropriate. Only those patients that have a positive KOH wet mount for tinea pedis (presence of

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segmented fungal hyphae under microscopic examination) at Visit 1 will have samples sent for fungal culture.

If the results of the baseline mycological culture are positive, samples for KOH will be obtained from the target lesion site at Visit 3. All efforts should be made to attempt valid skin scrapings for microscopic examinations at Visit 3, even in case of virtually healed lesions as appropriate. If the results of the baseline culture are negative, patient should be discontinued and no KOH wet mount is necessary.

10.6.10 Inclusion/Exclusion Criteria Review

At Visit 1, inclusion/exclusion criteria will be reviewed to ensure patients' eligibility for participation in the study.

10.6.11 Collect Sample for Mycological Culture

If, at Visit 1, the patient meets all of the other inclusion/exclusion criteria, including a positive KOH wet mount test, then a sample will be sent to the centralized laboratory for fungal culture. As it could take up to 28 days or more for the results of the fungal cultures to be known, the Investigator can enroll patients into the study if they meet all of the other inclusion/exclusion criteria pending the results of the fungal culture. Culture must be positive for *T. rubrum*, *T. mentagrophytes* or *E. floccosum* for the patient to be included in the modified intent-to-treat (mITT) and per-protocol (PP) populations.

The sample for the culture should be placed into the transport kit provided by the central laboratory. The kit should be sealed according to the directions on the back of the kit itself. The sample kit should be sent to the central laboratory as instructed in the laboratory manual provided by ACM-Pivotal Global Central Laboratory.

ACM Pivotal Laboratory
160 Elmgrove Park
Rochester, NY 14624
Phone: 800-525-5227

If the results of the baseline culture are positive, patients may continue in the study and samples for mycological culture will be obtained from the target lesion site at Visit 3. If the results of the baseline culture are negative, the patient should be discontinued and early termination procedures should be performed. No mycological culture sample should be collected as part of the early termination procedures.

Mycological culture samples will not be collected for patients with a positive KOH wet mount at Visit 3.

10.6.12 Dispense Study Product

An Independent Dispenser will dispense three tubes of study product at Visit 1 along with dosing instructions. The Independent Dispenser will ensure the study product logs are reported correctly.

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10.6.13 Provide Patient Diary

At Visit 1, patients will be provided with a diary to record AEs, concomitant medications and date and time of dosing. The patients will also receive on-site training on completing the diary.

At Visit 2, patients will be provided with a diary to record AEs and concomitant medications.

10.6.14 Collect and Review Patient Diary

At Visits 2 and 3, patient diaries will be collected and reviewed for compliance with the protocol.

10.6.15 Collecting Study Product

The study product will be collected by the Independent Dispenser at Visit 2 (or 3 if not returned at Visit 2) and checked to ensure no evidence of tampering with the blind has occurred. The Independent Dispenser will ensure the study product logs are reported correctly.

10.7 Adverse Events

The patients will be monitored throughout the study for any AEs. Adverse events will be collected through both solicited and unsolicited means and subsequently coded in tabular form using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or higher. The patients will be encouraged to report signs, symptoms, and any changes in health to the clinic staff. Signs and symptoms of tinea pedis will not be considered AEs unless, in the opinion of the Investigator, they have increased in severity to the extent that the Investigator believes it to be clinically significant. Severity of each AE will be determined by the staff based on observation and questioning of the patients. The Investigator will judge the relationship of the event to the study treatments. Adverse events should be followed up until they have resolved or stabilized.

10.7.1 Adverse Event Definitions

Adverse Event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease, temporally associated with the use of a medicinal (investigational) product, whether or not related to this product. This includes events not seen at baseline, or worsened even if present at baseline.

Unexpected Adverse Event: An AE where the nature or severity of is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Adverse Drug Reaction: All noxious and unintended responses to a medical product related to any dose should be considered adverse drug reactions. The response to a 'medical product' means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

10.7.2 Severity of Adverse Event

The severity of the AE will be graded by the Investigator using the following criteria as guidelines:

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- MILD: Awareness of symptom but does not interfere with routine activities.
- MODERATE: Discomfort sufficient to interfere with routine activities.
- SEVERE: Impossible to perform routine activities.

10.7.3 Relationship of Adverse Event

Relationship to the study product:

- Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility
- Related: A causal relationship between the study treatment and the AE is a reasonable possibility.

10.7.4 Patient's Participation Stopping Criteria

In the opinion of the Investigator, if the patient suffers an AE that warrants discontinuation of the study product because of interference with age-appropriate instrumental Activities of Daily Living, for example, preparing for meal, shopping for groceries or clothing, using the telephone, etc. the patient will be followed until the AE resolves or is considered stable. Any patient that discontinues the study because of an AE will be followed until resolution or stabilization of the AE.

10.8 Serious Adverse Events

10.8.1 Definition of a Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose suggests a medically significant hazard, including any event that:

- Results in death: includes all deaths, even those that appear to be completely unrelated to study treatment (e.g., car accident where patient is a passenger).
- Is life-threatening: in the view of the Investigator, the patient is at immediate risk of death at the time of the event.
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Causes congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the serious outcomes listed above (e.g., intensive treatment in an emergency room, convulsions that do not result in hospitalizations). emergency room visits that require medical or surgical intervention to prevent one of the other serious outcomes listed above are considered an SAE.

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10.8.2 Reporting Serious Adverse Events

Investigator Reporting of SAEs

Adverse events which meet the above criteria for "Serious" will be reported to Novum within 24 hours. Novum will report all SAEs to the Sponsor and IRB within 24 hours of notice whether or not they are considered expected or drug-related. All SAEs will be reported as per applicable regulations. All SAEs encountered during the study will be reported on the appropriate form and summarized in the final report.

Following is the contact information:

Christian P. Urrea, MD
Medical Monitor, Clinical Trials
Cell Phone: 412-667-1472
Phone: 412-363-3300 Ext. 597
Fax: 412-291-3171
Email: cpurrea@novumptrs.com

Or

Gail Gongas
Vice President, Clinical Trials and Data Management
Cell Phone 412-606-1603
Phone: 412-363-3300 Ext. 522
Fax: 412-291-3171

Novum will report any SAE to Sponsor:

Documentation of SAEs and follow-up information should be sent to the Sponsor within 24 hours from Novum being made aware of the SAE. Following is the contact information:

Dr. Brijesh Wadekar
Head- Clinical Trials
Encube Ethicals Pvt Ltd
Steelmade Industrial Estate, Marol Village,
Andheri (E), Mumbai – 400059, India
Phone: +91-22-6264-7009
Fax: +91-22-66935230
Email: brijesh.w@encubeethicals.com

Novum will be responsible for notifying the FDA of any SAEs. Novum must notify FDA of fatal or life-threatening SAE as soon as possible, but no later than seven calendar days from reporting the event by the Investigator.

Novum will inform all the participating Investigators of any SAEs reported at other study sites within 15 days from the initial report.

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11.0 STATISTICAL METHODS

11.1 Statistical Plan

A Statistical Analysis Plan (SAP), detailing the intended statistical analyses of the study data, will be prepared as a separate document and finalized before database lock. Any deviation from the original SAP will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused and spurious data will be included in the SAP.

All statistical analyses will be performed by Novum Pharmaceutical Research Services and conducted using SAS®, Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and Analysis Dataset Model (ADaM).

11.2 Sample Size Determination

For the primary endpoint analysis (proportion of patients in the PP population with a Therapeutic Cure at the test-of-cure visit), sample size is estimated for therapeutic equivalence of the Test to the Reference product and superiority of each of the active treatments groups over Placebo. The sample size estimations are based on previous studies conducted for ketoconazole cream.¹

In the PP population, the proportion of patients with a Therapeutic Cure in the Reference group is expected to be 50%. Assuming that the Therapeutic Cure rate for the Test treatment group is an absolute difference of 5% lower than the Reference Responder rate (i.e., $p_T - p_R = -5\%$), a sample size of 172 patients in each active group in the PP population will provide approximately 85% power to demonstrate therapeutic equivalence (i.e., the 90% confidence interval [Yates' continuity-corrected] on the $p_T - p_R$ difference is within a defined equivalence range [-20%, +20%]).

The Therapeutic Cure rates for the Placebo and active treatment groups at the test-of-cure visit are anticipated to be approximately 10% and at least 40% (Test = 40%, Reference = 45%), respectively, in the mITT population. Using a 2:1 (Active: Placebo) randomization scheme, and assuming the conversion rate from mITT to PP will be approximately 80%, 216 patients in each active treatment group (Test and Reference) and 108 patients in the Placebo group of the mITT population will provide at least 99% power to demonstrate superiority of active treatments over Placebo ($p < 0.05$; using two-sided, continuity-corrected Z-test and a pooled response rate for the standard error of the difference in proportions).

Under the above assumptions, the overall study power to demonstrate therapeutic equivalence and superiority is estimated to be at least 85% ($100\% \times 0.85 \times 0.999$), assuming 100% correlation between the two superiority tests.

To allow for approximately 35% of patients who may have negative fungal cultures post-randomization, drop out from the study or are otherwise non-evaluable, approximately 830 patients may be randomized (332 in each active group and 166 in the Placebo group) to yield 540 patients in the mITT population.

More than 50% of the patients should have baseline fungal cultures that test positive for *T. rubrum*. If fewer than 50% of enrolled patients have a positive *T. rubrum* culture or the number of patients with negative fungal cultures is more than anticipated, then additional patients may be enrolled to ensure

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that at least 430 (172:172:86) patients are eligible in the PP population, of which > 50% have a positive *T. rubrum* culture at baseline.

11.3 Study Populations

11.3.1 Per-Protocol Population

The PP population will include all randomized patients who:

- Met all inclusion and exclusion criteria.
- Made the final study visit within the protocol window of Day 56 ± 4 days (Day 52 to Day 60 inclusive) with no protocol violations that would affect the treatment evaluation.
- Did not have any significant protocol deviations.
- Were compliant with dosing between 75%-125% of the required doses.
- Had a positive baseline KOH and fungal culture for *Trichophyton rubrum*, *Trichophyton mentagrophyties* or *Epidermophyton floccosum*.

Patients discontinued from the study because of lack of treatment effect after completing at least 14 days of treatment will be included in the PP population as Therapeutic Failures provided they had a positive baseline KOH, positive baseline fungal culture, and did not have any significant protocol deviations. For these patients, there will be no mycological testing at time of discontinuation; therefore, they will be considered Therapeutic Failures in the primary analysis but the Mycological Cure data will be set to missing for the secondary endpoint.

Patients who meet the criteria above, but who also used topical drug therapy for irritation or pruritus on the feet after the treatment phase of the study will be included in the PP population as Therapeutic Failures. If no mycological testing is performed, the patients will be considered Therapeutic Failures in the primary analysis but the Mycological Cure data will be set to missing for the secondary endpoint.

All analyses performed using the PP population will be done on an observed case basis (i.e., no last observation carried forward [LOCF] will be performed).

11.3.2 Modified Intent-to-Treat Population

The mITT population will include: randomized patients who:

- Met all inclusion/exclusion criteria.
- Applied at least one dose of assigned product.
- Had at least one post-baseline evaluation.
- Had a positive baseline KOH and fungal culture for *Trichophyton rubrum*, *Trichophyton mentagrophyties* or *Epidermophyton floccosum*.

Patients discontinued early for reasons other than lack of treatment effect will be excluded from the PP population and included in the mITT population using LOCF. Patients who qualify for inclusion in the mITT population with missing endpoint data who were not discontinued for lack

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of treatment effect will also be evaluated using LOCF; that is, if a patient who was not discontinued for lack of treatment effect does not have KOH or mycological culture results at Visit 3, this patient will be evaluated for the primary and secondary endpoints using LOCF from Visit 1. Patients who discontinued because of lack of treatment will not have LOCF performed.

Patients who meet the criteria above, but who also used topical drug therapy on the feet for the treatment of irritation or pruritus after the treatment phase of the study will be included in the mITT as Therapeutic Failures. If no mycological testing is performed, these patients will be considered Therapeutic Failures in the primary analysis but the Mycological Cure data will be set to missing for the secondary endpoint. No LOCF will be performed.

11.3.3 Safety Populations

The Safety population will include all patients who are randomized and received study product.

11.4 Baseline Comparability

Baseline characteristics will be evaluated separately for the PP, mITT and Safety populations.

The following baseline demographics (determined from their initial study visit) will be evaluated:

- Age (years)
- Sex (Male/Female)
- Ethnicity (Hispanic/Non-Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native)
- Type of infection (interdigital only or interdigital with extension)
- Total baseline signs and symptoms score
- Presence or absence of onychomycosis
- Number of infections in the past 12 months
- Primary infective organism

Summary tables by treatment group will be presented. Continuous variables will be summarized using descriptive statistics (number of observations, median, minimum, maximum, mean, and standard deviation). Categorical variables will be summarized using frequencies and percentage. Baseline treatment comparisons will be presented using Chi-Square or Cochran-Mantel-Haenszel (CMH) tests for the categorical variables, and Analysis of Variance for the continuous variables.

All data will be listed by treatment and patient.

11.5 Efficacy Variables

The primary and secondary efficacy variables are the outcome of the KOH test (negative or positive), outcome of the mycological culture (negative or positive), and signs and symptoms scores.

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11.6 Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients in each treatment group with a Therapeutic Cure of tinea pedis at the test-of-cure visit two weeks after the end of treatment (Day 56 ± 4).

Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- The proportion of patients in each treatment group with a Clinical Cure at Day 56 ± 4.
- The proportion of patients in each treatment group with a Mycological Cure at Day 56 ± 4.

Definitions

1. **Therapeutic Cure**: To be considered a Therapeutic Cure, the patient must have both Clinical and Mycological Cure of tinea pedis.
2. **Therapeutic Failure**: A patient will be considered a Therapeutic Failure if:
 - a. the patient is a Clinical or Mycological Failure
 - b. the patient was considered to have an insufficient therapeutic response
 - c. the patient used topical drug therapy for irritation or pruritus on the feet after the treatment phase of the study
3. **Clinical Cure**: To be considered a clinical cure the patient's total severity score must be ≤ 2 with no individual severity score > 1 .
4. **Clinical Failure**: A patient will be considered a Clinical Failure if the patient's total severity score is > 2 or any individual score is > 1 .
5. **Mycological Cure**: To be considered a mycological cure the patient must have a negative KOH test and a negative fungal culture.
6. **Mycological Failure**: A patient will be considered a Mycological Failure if the patient's KOH test is positive or the patient's fungal culture is positive.

11.7 Efficacy Analysis

Therapeutic Equivalence

Therapeutic equivalence will be evaluated for the primary endpoint in the per-protocol (PP) population. If the 90% confidence interval (calculated using Yates' continuity correction) on the absolute difference between the proportion of patients with a Therapeutic Cure in the Test and Reference groups ($p_T - p_R$) is contained within the range [-20%, +20%] then therapeutic equivalence of the Test product to the Reference product will be considered to have been demonstrated.

The same statistical approach will be conducted for analyses of the secondary endpoints in the PP population.

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To declare therapeutic equivalence of the Test product to the Reference product, equivalence must be demonstrated for only the primary endpoint in the PP population.

Patients who are missing mycological culture data at the test-of-cure visit will not be included in the analysis for the secondary endpoint of Mycological Cure.

Superiority to Placebo

Superiority of the Test and Reference products against the Placebo product for the primary endpoint will be evaluated in the mITT population using, if necessary, LOCF as described in section 11.3.2. If the proportions of patients with a Therapeutic Cure in the Test and the Reference product groups are numerically and statistically superior to that of the Placebo ($p < 0.05$; using a two-sided Cochran-Mantel-Haenszel [CMH] test, stratified by clinical site) then superiority of the Test and Reference products over Placebo will be concluded.

The same statistical approach will be conducted for analyses of the secondary endpoints in the mITT population.

To declare superiority of the Test and Reference products over Placebo, their superiority must be demonstrated for only the primary endpoint in the mITT population.

Treatment-by-Site Interaction and Pooling of Clinical Sites

As this is a multiple-site study, the interaction of treatment-by-site may be evaluated for the primary efficacy endpoint in the PP population for equivalence testing. The treatment-by-site interaction will be evaluated by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level ($p < 0.05$, 2-sided). A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site, so as to avoid bias in the stratification of the sites in the CMH test and in the estimation of a treatment-by-site interaction effect. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients in the PP population at the site with the highest enrolling rate in the PP population. If the treatment-by-site interaction term is found to be statistically significant ($p < 0.05$) for the primary endpoint, then the interaction term will also be assessed for clinical relevance before pooling the data across sites. This will include examination of Therapeutic Cure rates at each site where sample sizes per treatment may be influential in the assessment of the interaction. The treatment-by-site interaction may also be evaluated for the analyses of the secondary endpoints in the PP population for equivalence testing if the treatment-by-site interaction is found to be significant in the primary analysis.

11.8 Safety Analysis

Adverse events (AEs) will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 21.0 or higher and summarized by treatment group. Summary tables comparing the type, date of onset, date of resolution, incidence, severity, relationship to the study product, outcome, and action taken will be prepared by treatment group. If sufficient data exist, then AE frequencies will be compared among the three treatments using Fisher's exact test; if this test is statistically significant at the 5% significance level, then a pairwise Fisher's exact test comparing Test and Reference will be conducted.

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Signs and symptoms of tinea pedis will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be discontinued from further participation in the study and given alternative therapy for their condition.

Concomitant medication use will be tabulated by patient.

12.0 REGULATORY OBLIGATIONS

12.1 Institutional Review Board

The study protocol, ICF, Investigator's Brochure, or package insert (as applicable), and any specific advertising will be submitted to and approved by an IRB before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification of the board's approval along with a description by profession and gender of the board's composition will be provided to the Sponsor.

12.2 Study Documentation

This study will be conducted in compliance with the protocol; GCPs and all applicable regulations, including the Federal Food, Drug, and Cosmetics Act, US applicable Code of Federal Regulations (title 21), parts 50, 56, 312, 320, and any IRB requirements relative to clinical studies; and the Declaration of Helsinki, June 1964, as modified by the 64th World Medical Association General Assembly, October 2013.^{10,18-20} The Investigator will permit trial-related monitoring, audits, IRB review, and regulatory inspections providing direct access to source data/documents.

12.2.1 Protocol

The Investigator indicated on FDA Form 1572 will act as the Principal Investigator at each study site. Protocols will be noted as approved by placement of the Novum Representative's signature on the cover page. The Sponsor of the study will also approve the protocol by having a study-responsible individual sign the protocol cover page. The Principal Investigator will sign the protocol signature page indicating their agreement to conduct the study according to the protocol.

12.2.2 Informed Consent

An ICF that includes all of the relevant elements currently required by FDA and local state regulations will be provided to each prospective patient before enrollment into the study. The type and method of study, tests to be administered, any potential or possible hazards, and the patient's right to withdraw from the study at any time will be explained to the patients by the Investigator or designee. Once the Investigator or designee is assured that an individual candidate understands the implications of participating in this study, the patient will be asked to give consent by signing and dating in the appropriate areas of the ICF. The Investigator or designee will also sign and date the form, along with a staff member who will sign the ICF as a witness to verify that the patient has indeed received information. If any other language is required, translation will be performed by a certified translator. A copy of the ICF and Assent (when applicable) will be provided to the patient.

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12.2.3 Protocol and Informed Consent Changes

Sponsor approved changes to the protocol or the ICF form will be implemented as revisions to the original documents and will require additional review and approval by the IRB. Revisions to the original protocol will be documented in amendments, incorporated as a preface to the new version. Any revision that substantially alters the study design or increases potential risk to the patient requires the patient's consent to continue in the study. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to the Sponsor.

12.2.4 Source Documents and Electronic Case Report Forms

All patients will be identified by initials, date of birth, and a unique patient number. Source documents will be used to record all study-related data. Source document entries will be used to complete eCRFs. A set of eCRFs will be completed for each patient randomized in the study. All data and eCRFs will be reviewed, evaluated, and signed by the Investigator.

The original source documents and a copy of the corresponding eCRFs will be retained by the Investigator. Patients who terminate early from the study will have the Visit 3 (end of study) source/eCRF completed.

12.2.5 Drug Accountability

All study product receipt, inventory, dispensing, dosing, and reconciliation records will be maintained in compliance with federal regulations. The study product will be dispensed to qualified study patients according to established procedures. At the end of the study (after the database has been locked) all used and unused study product will be returned to Sponsor or designee.

12.2.6 Retention of Reserve Samples

For every study product shipment received at the site, the Investigator (or designee) will randomly remove at least one block of study product and keep for retention. A block contains five patient kits (as the study is randomized in a 2:2:1 ratio). The randomization number of each patient kit in each block kept for retention will be noted on the drug accountability form. These retention samples should be stored under the appropriate storage conditions for a minimum of five years following the application approval or, if not approved, at least five years after the completion of the study.¹⁷

12.2.7 Pregnancies

If following initiation of study participation, it is subsequently discovered that a study patient is pregnant or may have been pregnant since the initiation of study participation (i.e., since the signing of ICF), the study product will be permanently discontinued. The Principal Investigator or designee must immediately notify the Medical Monitor of this event. Reporting timelines and Novum/Sponsor contact will be consistent with SAE reporting guidelines (i.e., pregnancies will be reported to the Sponsor/Novum within 24 hours to the contacts listed in Section 10.8.2).

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient. Other appropriate pregnancy follow-up procedures should be considered if indicated. All

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follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome will be communicated as per the above guidelines. Infants should be followed for a minimum of eight weeks after birth.

12.2.8 Reporting Safety Information to the IRB

The Investigator must promptly report to the Investigator's IRB all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs occurring during the study, regardless of the assessed causality.²⁰

12.2.9 Record Retention

All drug accountability records, eCRFs, source data and related regulatory documents must be retained for at least two years following completion of the study or Test product approval for marketing by the FDA.

12.2.10 Study Monitoring and Auditing

Novum will be responsible for monitoring the study according to Good Clinical Practice and applicable regulations. Monitoring visits are for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The clinical site will make all records associated with the study available to Novum's representative during such visits and audits.

The study may be subject to audit by the Sponsor, Sponsor Representative or by regulatory authorities. If such an audit occurs the Investigator must agree to allow access to required patient records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of study procedures.

12.2.11 End of the Trial

The end of the trial is defined as the time at which the last patient has completed their last visit in the study. Upon completion of the study, the study product will no longer be available to the patient but the Investigator can, at their discretion, discuss alternative treatments with the patient.

12.2.12 Clinical Study Report

At the end of the study a full report per requirements of Sponsor and regulatory authorities will be prepared which will include a narrative of the clinical conduct and results of the study, a statistical report including a description of the analysis performed, and other documentation as may be appropriate. The report will be in electronic format according to eCTD ICH formatting standards and guidelines.²¹

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13.0 REFERENCES

- 1 FDA. Summary Basis of Approval-Ketoconazole 2% Cream (Teva Pharmaceuticals; ANDA 75-581). (1999).
- 2 Weitzman, I. & Summerbell, R. C. The dermatophytes. *Clinical microbiology reviews* **8**, 240-259 (1995).
- 3 Drake, L. A. *et al.* Guidelines of care for superficial mycotic infections of the skin: tinea corporis, tinea cruris, tinea faciei, tinea manuum, and tinea pedis. Guidelines/Outcomes Committee. American Academy of Dermatology. *Journal of the American Academy of Dermatology* **34**, 282-286 (1996).
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CONFIDENTIAL PROTOCOL

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Evaluate the Therapeutic Equivalence of Ketoconazole Cream 2% (Encube Ethicals Pvt Ltd) to
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14.0 APPENDICES

14.1 Appendix A: Local Signs and Symptoms

The most severely affected area will be identified as the target lesion at the baseline visit and will be used for the assessments at Day 42 and Day 56 visits.

The Clinical Signs and Symptoms of tinea pedis will be rated by the Investigator as “none”, “mild,” “moderate” or “severe” using the following standardized rating scale.

0 = None (complete absence of any sign or symptom)

1 = Mild (Slight)

2 = Moderate (Definitely Present)

3 = Severe (Marked, Intense)

The following signs and symptoms will be rated at each visit:

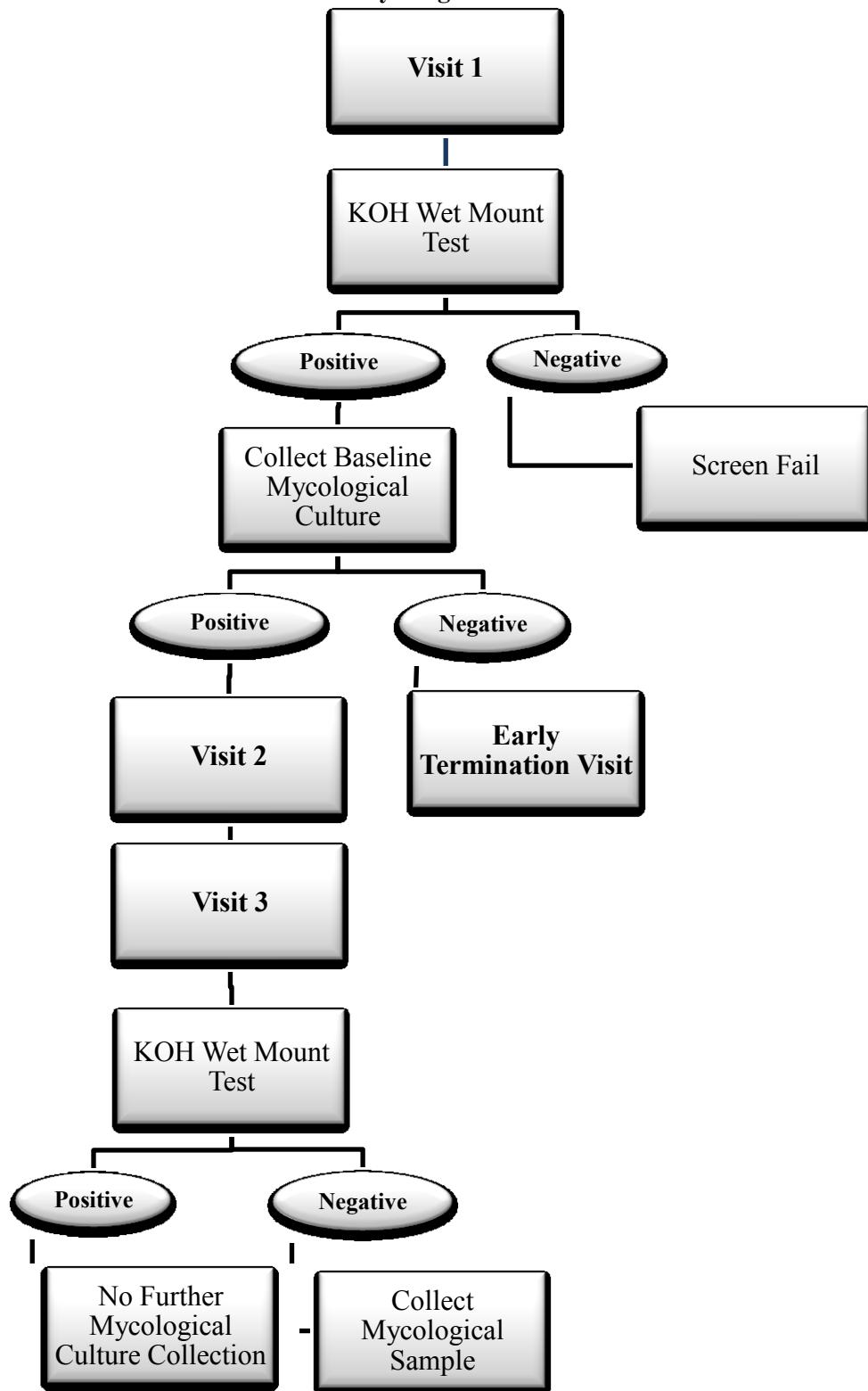
- Signs: Fissuring/cracking, erythema, maceration, and scaling
- Symptoms: Pruritus and burning/stinging

To be eligible for inclusion the most infected area must have a total score ≥ 4 for the clinical signs and symptoms at the target lesion site. In addition, the target lesion site must have a minimum score of at least 2 for erythema and a minimum score of at least 2 for either pruritus or scaling.

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14.2 Appendix B: KOH Wet Mount Test and Mycological Culture Collection Schedule



14.3 Appendix C: Ketoconazole Cream 2% Product Insert

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14.4 Appendix D: Amendments to the Protocol

Amendment	Date	
1	11/08/2018	
The following revisions were made to the protocol dated 06/13/2018:		
<ul style="list-style-type: none">Section 2.0, 3.0, and 10.8.2: Updated Medical Monitor information		