NCT02812771

Clinical Study Protocol

Efinaconazole 10% Topical Solution

Protocol V01-108A-401

A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails

Development phase of study:	4
Study design:	Multi center, open label , single-arm, safety and pharmacokinetics study
Date:	May 10, 2016
Sponsor:	Dow Pharmaceutical Sciences, a wholly owned subsidiary of Valeant Pharmaceuticals International 1330 Redwood Way, Suite C Petaluma, CA 94954

CO FIDENTIAL

Nothing herein is to be disclosed without prior approval of the sponsor.

VA LEANT
Research & Development

Protocol Review and Approvals

A Multicentcr, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics ofEfinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails

Reviewed and approved:

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[redacted]

5/12/2016
Date

5/12/16
Date

05/11/2016
Date

05-11-2016
Date

Personnel Responsible for Conducting the Study

A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails

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Principal Investigator Protocol Agreement Page

I agree:

- To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IEC) for the study protocol, written informed consent, consent form updates, subject-recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study.
- Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study.
- To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies).
- That I am thoroughly familiar with the appropriate use of the investigational products(s), as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current Investigator Brochure or equivalent document and approved product label (if applicable).
- To provide sufficient time and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions.

_____

Principal Investigator (print name)

_____ _____

Principal Investigator (signature) Date

2 Synopsis

Name of Sponsor/Company: **Dow Pharmaceuticals Sciences, a wholly owned subsidiary of Valeant Pharmaceuticals International**
Name of investigational product: Efinaconazole 10% Topical Solution
Name of active ingredient: Efinaconazole
Title of study: A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails
Number of clinical centers: Approximately 10-15 investigational centers in the United States, and the Caribbean
Objectives: The primary objectives of this study are to evaluate: 1) safety of once daily topically administered efinaconazole 10% for 48 weeks in pediatric subjects (6-16 years of age) with at least mild onychomycosis of the toenails, and 2) pharmacokinetics PK (4 weeks) of once daily topically administered efinaconazole 10% in pediatric subjects (12-16 years of age) with moderate to severe onychomycosis of the toenails.
Methodology: This is an open label, single-arm study designed to evaluate the safety and PK of a once daily topical application of efinaconazole in the treatment of pediatric subjects with mild to severe onychomycosis of the toenails. The study will include subjects 6 to 16 years of age, inclusive, but PK assessments will only be performed on subjects 12 to 16 years of age, inclusive (referred to throughout the protocol as the PK subset). All subjects must have onychomycosis of at least 1 great toenail; subjects in the PK subset must have onychomycosis of both great toenails and at least 4 other toenails. Efforts will be made to enroll subjects into the PK subset such that the subjects are evenly distributed across the required age range. For subjects not participating in the PK subset, the study will consist of 14 scheduled visits, including Screening (up to Day -42), Baseline (Day 1), 12 treatment visits (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). Subjects included in the PK subset will attend the scheduled visits up to Week 4 and an additional study visit at Day 29 for collection of the final PK blood sample. The PK assessments will be performed under maximal use conditions. Once PK assessments are complete at Day 29, the PK subset of subjects will continue treatment through week 48 with additional visits at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). At the Screening Visit, subjects and/or their parents/legal guardians will sign an informed consent/assent form and a photography consent/assent form, provide their medical histories, report their previous and concomitant medications, and be evaluated against the inclusion/exclusion criteria. Females of childbearing potential (FOCBP) will have urine pregnancy tests performed. During this visit, subjects will undergo an examination of their feet to visually ascertain the presence of onychomycosis in at least 1 great toenail for subjects not included in the PK assessments, and on both great toenails and at least 4 other toenails for subjects included in the PK assessments. Additionally, the percent involvement of the affected great toenail(s) will be recorded. A direct microscopic examination for the hyphae associated with dermatophytes

will be performed at the investigational center using potassium hydroxide (KOH) on toenail scrapings collected from the affected great toenail(s) (ie, at least 1 great toenail for all subjects and both great toenails for subjects in the PK subset). Subjects with KOH-positive toenail samples will provide additional samples from the affected great toenail(s) for KOH examination and mycological culture (conducted at a central mycology laboratory). Blood and urine specimens will be collected for serum chemistry, hematology, and urinalysis evaluations. At relevant post-Screening Visits, the target great toenail will be trimmed back to the distal groove before the clinical evaluations are performed and before photographs are taken.

At the Baseline Visit (which should be scheduled after KOH and fungal culture results have been obtained from the mycology lab), subjects and/or their parents/legal guardians will update their medical histories and concomitant medication uses, and the inclusion/exclusion criteria will be confirmed. Subjects will undergo abbreviated physical examinations, clinical laboratory evaluations, assessments of vital signs (sitting blood pressure, respiration, pulse, and temperature), and measurements of height and weight. All FOCBP will have urine pregnancy tests performed. For the purposes of efficacy assessments, 1 target great toenail will be selected from the study-eligible great toenail(s), including subjects in the PK subset for whom both great toenails must be involved. Where both great toenails are study-eligible, the toenail with the greater percent of affected area will be selected for mycologic data and for inclusion in the efficacy analysis. In the instance where the percent of affected area is the same for both study-eligible great toenails, the investigator may select either great toenail as the target toenail. The target great toenail will be identified and recorded for each subject, photographs of the target great toenail will be obtained, and a transverse notch will be inscribed in the target great toenail adjacent to the proximal toenail fold (as a marker for measuring toenail growth at subsequent visits). Assessments of all other nontarget toenails, including the other involved toenails of subjects in the PK subset, will also be conducted to assess the presence or absence of onychomycosis on each toenail. This assessment will continue throughout the study visits through week 52.

After confirming eligibility at the Baseline Visit, subjects will be enrolled in the treatment period. Subjects or their parents/legal guardians will apply the first dose of study drug to the qualified toenails at the investigational center under the supervision of designated study personnel. Any local skin reactions that occur at the study drug application site, along with any adverse events (AEs), will be recorded. Subjects or their parents/legal guardians will receive weighed study drug bottles and given verbal and written instructions for treatment application. Specifically, subjects who are not included in the PK subset will be instructed to apply the study drug to the affected toenails once daily at bedtime for 48 weeks. Subjects who are included in the PK subset will be instructed to apply the study drug to all 10 toenails once daily at bedtime for 4 weeks. Following the PK blood collections on Days 28 and 29, these subjects will be instructed to continue treatment with study drug to only the affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). All subjects or their parents/legal guardians will also receive diaries, with instructions to complete a record of all applications and to note any missed applications of the study drug.

Subjects in the PK subset will not apply study drug the night prior to the Week 4 (Day 28) visit. Following the Day 28 study procedures, subjects in the PK subset will undergo timed blood collections to assess plasma concentrations of efinaconazole and metabolites (H3 and H4). Assessments will require collection of approximately 4 mL of whole blood at each time point (approximately 20 mL total). Within 1 hour after the predose blood sample is drawn, the subjects/parents/legal guardians will apply study drug to all 10 toenails at the investigational center. Subsequent blood collections will occur 2, 4, and 12 hours postdose on Day 28. The subjects will go home after Day 28, but will not apply study drug on the night of the Day 28 visit. PK subjects will return to the investigational center the following day (Day 29) for collection of a 24-hour postdose blood sample. PK subjects will continue treatment with study drug to only the target great toenail and the other affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52).

Safety will be assessed by reviewing the occurrence of AEs and local skin reactions, assessing vital sign measurements and abbreviated physical examination findings, and noting any additions or changes in concomitant medication uses. Blood samples will be collected at Screening and Week 48 for routine safety laboratory evaluations (serum chemistry, hematology, and urinalysis); urine pregnancy tests will be obtained for all FOCBP at each study visit. Efficacy assessments will be performed throughout the study. The efficacy analyses will be based on microscopic examination and mycological culture results for the target great

toenail, the percent involvement of the target great toenail, the length of the unaffected part of the target great toenail, the growth of the target great toenail, and the number of affected nontarget toenails.

Note that growth of the target great toenail will be measured by inscribing a transverse notch, at the center of the toenail, in the toenail adjacent to the proximal toenail fold at Baseline and measuring toenail growth from that point forward. At every subsequent visit, the distance between the proximal toenail fold and the notch will be measured and recorded. A new notch will be inscribed in the toenail adjacent to the proximal toenail fold if the initially applied notch grows out during the course of the study.

A post-treatment follow-up visit will occur 4 weeks after the last treatment visit for each subject (ie, at Week 52). Subjects who discontinue from the study prior to Week 48 will complete the Week 48 study procedures.

Number of subjects planned:

Approximately 60 subjects total

Approximately 20 subjects in the PK subset

Diagnosis and criteria for inclusion:

1. Male or female subjects of any race, 6 to 16 years of age (inclusive).
    - **PK Subset:** Male or female subjects of any race, 12 to 16 years of age (inclusive).
2. Verbal and written informed consent/assent obtained from the subject and/or their parent or legal guardian.
3. Good general health, as assessed by the investigator, based on the subject's medical history, physical examination, and safety laboratory tests.
4. At least 1 great toenail (the "target great toenail") with clinically diagnosed distal lateral subungual onychomycosis involving at least 20% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. Up to 6 toenails may have onychomycosis.
    - **PK Subset:** Both great toenails with clinically diagnosed distal lateral subungual onychomycosis involving at least 50% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. Subjects must also have at least 4 toenails other than the great toenails with onychomycosis.
5. Target great toenail for all subjects, and both great toenails for subjects in the PK subset, must have evidence of toenail growth, per subject's report that monthly clipping is needed.
6. Within 42 days prior to the Baseline (Day 1) Visit, have a positive KOH examination (at the investigational center and confirmed by the mycology lab) of the target great toenail for all subjects,
7. Within 42 days prior to the Baseline (Day 1) Visit, have a positive dermatophyte culture for *Trichophyton rubrum* or *Trichophyton mentagrophytes* (at the central mycology laboratory) from the target great toenail in all subjects
    - **PK Subset:** Prior to the Baseline Visit, the great toenail designated for efficacy assessments as the target great toenail must have both a positive KOH examination (confirmed by the mycology lab) and a positive fungal culture.
8. All FOCBP must have a negative urine pregnancy test at the Screening and Baseline Visits and must agree to use an effective method of contraception throughout the study. Effective contraception is defined as use of an intrauterine device, condom with spermicide, diaphragm with spermicide, abstinence (subject is not sexually active), or stable use of a hormonal contraceptive (oral, implant, injection, or transdermal patch) for at least 3 months prior to the Baseline Visit.
9. Subjects and their parents/legal guardians are willing to comply with study instructions and return to the investigational center for all required visits (a visit schedule with the length of each visit will be provided to ensure that the subject can meet the requirements and have adequate transportation).

10. Subject and their parents/legal guardians agree that the subject will avoid the use of toenail polish, cosmetic toenail products, and pedicures during the study period.

Exclusion criteria:

1. Females who are pregnant, nursing an infant, or planning a pregnancy during the study period.
2. History of immunosuppression and/or clinical signs indicative of possible immunosuppression, as determined by the investigator, or known human immunodeficiency virus infection.
3. History of diabetes that is uncontrolled as determined by the investigator (diabetes that is controlled by diet or medication does not exclude a subject).
4. Presence of any toenail infection other than or in addition to dermatophytes, such as *Scytalidium* as determined by the investigator (candidal onychomycosis infection, concurrent with a positive dermatophyte culture, is acceptable).
5. Presence of any of the following: dermatophytoma, fungal "spikes" within 3 mm of the proximal toenail fold on the target great toenail, infection extending to the matrix, or only lateral toenail disease in the target great toenail.
6. Presence of severe moccasin tinea pedis at the Screening or Baseline Visits, as determined by the investigator (if interdigital tinea pedis requires treatment during the study, the subject must agree to use only an investigator-approved topical antifungal therapy).
7. Presence of any disease/condition that might cause toenail abnormalities or may interfere with the evaluation of the study drug as determined by the investigator (eg, open sores or ulceration on the toes of affected toenails, psoriasis, immune dysfunction, collagen-vascular diseases, lichen planus, peripheral vascular disease, or traumatic onychodystrophy due to chronic physical stimuli).
8. Any previous surgery on the target great toenail.
9. Presence of onychomycosis of the fingernail.
10. History of immunodeficiency as determined by the investigator.
11. Presence of 1-hand, 2-foot syndrome, or fingernail dermatophytosis.
12. Target great toenail (including toenail plate and any subungual debris) thicker than 3 mm at the Screening and Baseline Visits.
13. Presence of onychodystrophy that could interfere with clinical assessments as determined by the investigator.
14. History of hypersensitivity or allergic reactions to azole derivatives or any of the study drug constituents.
15. Presence of any underlying disease that, in the opinion of the investigator, could present a safety concern for the subject by participating in the study.
16. Subject has received treatment for any type of cancer in the previous 6 months, except for nonmelanoma skin cancer (eg, basal cell carcinoma or nonmetastatic squamous cell carcinoma) that was treated successfully.
17. Presence of any dermatological condition on the feet that could interfere with clinical evaluations as determined by the investigator.
18. Presence of any underlying disease or dermatological condition other than onychomycosis that requires the use of interfering topical or systemic therapy and would make evaluations inconclusive as determined by the investigator, or subject requires treatment with a topical product on the toenails other than the study drug during the study.
19. Subjects using the following topical preparations within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following topical preparations during the study:
    - Toenail polish, cosmetic toenail products, or topical prescription or over-the-counter antifungal therapy for tinea pedis: 1 day
    - Other topical prescription or over-the-counter medications to the feet or toenails (with the

exception of bland emollients): 2 weeks

- Topical prescription or over-the-counter antifungal therapy for the toenails, including devices to treat onychomycosis: 4 weeks
- Topical corticosteroids for the feet: 2 weeks

20. Subjects using the following systemic medications within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following systemic medications during the study:
    - Systemic antifungal therapy: 4 weeks
    - More than two, 2-week courses of oral corticosteroid therapy or 1 intramuscular, intravenous, or intra-articular injection of corticosteroids (nasal steroid sprays and steroid inhalers are permitted if use is stable and not expected to change during the study): 3 months
    - Systemic immunosuppressive agents: 6 months
21. Subject has previously been nonresponsive to systemic antifungal therapy for onychomycosis.
22. Subject is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
23. Use of any investigational drug or device within 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit, or concurrent participation in another clinical study with an investigational drug or device.

Investigational product, dosage and mode of administration:

Investigational Drug: Efinaconazole 10% Solution (efinaconazole)

Dosing for Subjects NOT Included in the PK Subset: Subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) (if any) once daily at bedtime. Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be given instructions regarding how to apply the study drug, ie, by completely covering the target great toenail, including the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate. The study drug will be applied to each of the other infected toenails in a similar manner.

Dosing for Subjects Included in the PK Subset:

Days 1 to 28 – Subjects and their parents/legal guardians will be instructed to apply study drug to all 10 toenails, once daily at bedtime for 4 weeks. During this period, all PK subjects will be instructed to apply the study drug by completely covering each toenail and 0.5 cm of adjacent skin, including the toenail folds, toenail bed, hyponychium, undersurface of the toenail plate. The subjects will not apply study drug the night prior to the Week 4 (Day 28) visit, nor will they apply study drug on the night of the Week 4/Day 28 Visit. Within 1 hour after the predose blood sample is drawn on Day 28, subjects and/or their parents/legal guardians will apply study drug to all 10 toenails in the manner described above at the investigational center.

Days 29 to Week 48:

After completion of the PK portion of the study, subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) once daily at bedtime. Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those

toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be given instructions regarding how to apply the study drug, ie, by completely covering the target great toenail, including the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate (if onychomycosis is present). The study drug will be applied to each of the other infected toenails in a similar manner.

Mode of Administration:

Topical application: the subjects will apply the study drug to their toenail(s), the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate. The subjects and their parents/legal guardians will be instructed to wait for the toenails to air-dry thoroughly before touching with clothing.

Duration of treatment:

48 weeks

Reference therapy, dosage and mode of administration:

Not applicable

Criteria for evaluation:

Safety:

Adverse events will be collected as spontaneous reports by the subjects and as observations by the investigators. The collection of AEs should begin following the subject's completion of the consent/assent process to participate in the study.

Local skin reactions (redness, swelling, burning, itching, and vesiculation) will be reviewed with the subject starting at the Baseline Visit (after study drug application at the investigational center) and continuing through the last study visit. The presence or absence of burning, itching, and vesiculation will be reported simply as "yes" or "no". The worst instances of redness and swelling observed since the previous study visit will be reported using a 4-point scale (where 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe).

Blood and urine samples will be collected for routine clinical laboratory tests (hematology, serum chemistry, and urinalysis) at Screening and Week 48. Any clinically significant abnormalities in safety laboratory test results that are present at the last treatment visit (Week 48/Early Termination) will be followed to resolution (ie, return to normal values or to the baseline state) or until clinically stable as determined by the investigator.

Vital sign measurements (sitting blood pressure, respiration, pulse, and temperature) will be obtained at Baseline and Weeks 12, 24, 36, and 48. An abbreviated physical examination will be performed at Baseline and Week 48; as part of the examination, height and weight will be measured at Baseline and Week 48.

Urine pregnancy tests will be performed for all FOCBP at the Screening Visit and at each subsequent study visit. If a subject becomes pregnant during the treatment period, the study drug will be discontinued immediately, the subject will be discontinued from the study, and the investigator will notify the sponsor. The pregnancy will be followed to term with the outcome reported to the sponsor.

Efficacy will be assessed to evaluate compliance with treatment as part of the safety assessment. The efficacy variables evaluated in this study include microscopic KOH examination and mycological culture outcomes of the target great toenail, percent involvement of the target great toenail, growth of the target great toenail, and assessments of the nontarget toenails.

Pharmacokinetics: Concentrations of efinaconazole and metabolites (H3 and H4), along with other relevant PK parameters, will be assessed based on blood samples collected at Days 28 and 29. The specific collection time points are predose on Day 28 and 2, 4, 12, and 24 hours postdose.

Photography:

Close-up photographs of the subject's target great toenail will be used for documentation purposes only and will not be used for determinations of eligibility or any study-related activities.

Statistical Methods:

Safety:

All subjects who receive at least 1 confirmed dose of study drug will be included in the safety analysis set. No imputations will be made for missing safety data. The primary safety objective will be considered met when approximately 40 evaluable subjects have been treated for 48 weeks.

All AEs occurring during the study will be recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are those AEs with an onset on or after the date of first study drug application. All TEAEs will be summarized by the number of subjects reporting each TEAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the Safety, PK and Non-PK populations. Each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category.

Serious adverse events (SAEs) will be summarized by the number of subjects reporting each SAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the Safety, PK and Non-PK populations.

Local skin reaction scores (redness, swelling, burning, itching, and vesiculation) at each study visit will be summarized using frequency tables for the Safety, PK and Non-PK populations. Additionally, redness and swelling severity scores will be summarized using descriptive statistics (mean, standard deviation [SD], median, and minimum and maximum). Subjects with a severity score worse than baseline will also be summarized at each postbaseline study visit. The worst score and the last score during the post-baseline period will also be summarized.

Results of safety laboratory parameters and vital sign measurements will be summarized at each study visit using descriptive statistics or frequencies and percentages, as appropriate, for the Safety, PK and Non-PK populations. Changes from baseline in safety laboratory values will be summarized by treatment group at Week 48 using descriptive statistics. In addition, changes from baseline in safety laboratory values will be summarized using shift tables according to normal ranges.

This study's primary object is to assess the safety of the study drug. Descriptive efficacy statistics for the endpoints will assist in evaluating compliance with treatment for the purposes of safety assessment.

The efficacy endpoints include the following:

- Complete Cure, defined as 0% clinical involvement of the target toenail and negative KOH and fungal culture at Week 52
- Complete or Almost Complete Cure at Week 52, defined as :S 5% toenail involvement
- Clinical Efficacy rate at Week 52, defined as an affected target great toenail area of < 10%
- Mycologic Cure rate at Week 52, defined as a negative KOH examination and a negative fungal culture of the target great toenail sample

The Complete Cure rate, the Complete or Almost Complete Cure rate, the Clinical Efficacy rate, and the Mycologic Cure rate will be presented using descriptive statistics (sample size n, frequency counts and percentages) for the Safety, PK and Non-PK populations. In addition, the growth of the target great toenail at each study visit and the change from baseline in the number of affected nontarget toenails will be descriptively summarized.

A last observation carried forward (LOCF) imputation will be used to impute missing values for the efficacy variables at Week 52. No sensitivity analyses will be conducted.

Any subjects remaining (i.e., have not been treated for 48 weeks) will be followed until completion. The final report will be amended with data on these subjects.

Pharmacokinetics:

All subjects in the PK subset who receive at least 1 confirmed dose of study drug and have any PK data on Days 28 and 29 will be included in the PK analysis set. Blood samples will be tested for plasma concentrations of efinaconazole and metabolites (H3 and H4). No imputations will be made for missing data.

Plasma concentrations that are reported as below the limit of quantitation (BLQ) in the data transfer file will be set to zero for the summaries of concentrations as well as calculation of PK parameters. Missing values will be treated as if they were never drawn. Plasma concentrations of efinaconazole and metabolite (H3 and H4) and PK parameters will be summarized using descriptive statistics (n, mean, SD, standard error of the mean [SEM], coefficient of variation [CV], median, minimum, and maximum). Geometric means will also be used to summarize C_{max}, C_{min}, $AUC_{(0\text{-}t)}$ and $AUC_{(0\text{-}24h)}$.

The mean plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will be presented graphically for Days 28 and 29 in both linear and logarithmic scales. Individual subject plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will also be created.

Plasma PK parameters for efinaconazole and metabolites (H3 and H4) will be calculated using noncompartmental analysis. The PK parameters will be calculated for each subject using actual sampling times. The maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) will be taken directly from the data.

The following PK parameters will be calculated from the individual plasma concentrations on Days 28 and 29 when possible:

- C_{max} (observed peak drug [efinaconazole and metabolites] concentration)
- T_{max} (time at which C_{max} occurs)
- C_{min} (observed minimum drug concentration)
- $AUC_{0\text{-}t}$ (area under the concentration-time curve from time 0 up to the sampling time corresponding to the last quantifiable concentration)
- $AUC_{0\text{-}24h}$ (area under the concentration-time curve from time 0 through 24 hours [corresponding to the dosing interval])

Additional PK parameters may be calculated as appropriate.

The PK objectives will be considered met when approximately 16 evaluable subjects are treated under maximal use conditions through day 28 of the PK evaluation.

Sample size calculations:

Approximately 60 subjects will be enrolled and receive treatment with study drug. Approximately 20 of the subjects will be enrolled in the PK subset. These sample sizes were based on PK and clinical considerations; no formal sample size calculation was performed. The numbers of planned subjects are considered adequate for determining the safety profile and the PK parameters of efinaconazole in a pediatric population of subjects aged 6 to 16 years with mild to severe onychomycosis of the toenails.

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4 List of Abbreviations and Definitions of Terms

Abbreviation or Specialist Term	Definition or Explanation
AE	Adverse event
AUC_{0-24h}	Area under the concentration-time curve from time 0 through 24 hours (corresponding to the dosing interval)
AUC_{0-t}	Area under the concentration-time curve from time 0 up to the sampling time corresponding to the last quantifiable concentration
C_{max}	Observed peak drug concentration
C_{min}	Observed minimum drug concentration
eCRF	Electronic case report form
Efinaconazole	Efinaconazole 10% Solution
FOCBP	Females of childbearing potential
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KOH	Potassium hydroxide
LOQ	Limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
T_{max}	Time at which the observed peak drug concentration occurs
US	United States

5 Introduction

Onychomycosis is a chronic and recurring fungal infection of the fingernails or toenails that accounts for about half of all nail disorders. Onychomycosis is usually caused by dermatophytes, either *Trichophyton rubrum* (71%) or *Trichophyton mentagrophytes* (20%). The prevalence of onychomycosis in the United States (US) may be as large as 13%, with the infection observed predominantly in elderly patients (60%) [1, 2]. Onychomycosis of the toenail can result in permanent toenail deformity and has a significant impact on quality of life due to concerns with the appearance of the toenails and interference with wearing shoes, walking, and participating in various sports activities [3, 4].

Cure rates for topical treatments have been significantly lower than currently available systemic medications [5], presumably because they bind strongly to keratin and do not adequately penetrate the nail unit. However, while effective, oral therapy is limited by safety concerns due to systemic exposure. For example, both oral itraconazole and oral terbinafine have the potential to cause drug-drug interactions and hepatotoxicity. Efinaconazole 10% Solution (efinaconazole) has a low affinity for keratin binding and has a higher binding reversibility than that of other reference drugs. Therefore, efinaconazole appears to be a promising antifungal compound for the topical treatment of onychomycosis.

Efinaconazole is a novel triazole antifungal agent that is active in vitro against a wide range of pathogenic fungi and is expected to be effective in the treatment of mild to moderate onychomycosis.

Efinaconazole has been shown to be efficacious in vitro against a panel of fungal species that invade human skin, hair, and nails including dermatophytes Trichophyton, Microsporum, Epidermophyton, and the yeast, Malassezia species, responsible for tinea unguium (onychomycosis), tinea corporis, tinea pedis, tinea capitis, and pityriasis versicolor. Efinaconazole has been shown to be fungicidal against *Candida albicans* and other Candida species responsible for the major yeast (nondermatophyte) form of onychomycosis and cutaneous candidiasis. In vitro studies against dermatophytes showed that efinaconazole was more potent than clotrimazole, but less potent than butenafine.

Efinaconazole has successfully treated experimentally induced dermal candidiasis, tinea corporis, tinea pedis, and tinea unguium in vivo in guinea pig models. It has generally out performed reference drugs in these models, and in particular out performed the marketed drugs for tinea unguium: ciclopirox olamine (approved for the topical treatment of onychomycosis in the US), amorolfine (available outside the US as a topical nail lacquer), and terbinafine (available in the US in oral form).

The safety and efficacy of once daily use of efinaconazole for the treatment of onychomycosis of the toenail were assessed in two 52-week prospective, multicenter, randomized, double-blind clinical studies. These studies were conducted in subjects 18 to 70 years of age with 20% to 50% clinical involvement of the target great toenail, without dermatophytomas or lunula (matrix) involvement (n = 870 in Study 1 and n = 781 in Study 2) [6]. These studies evaluated 48-weeks of treatment with efinaconazole relative to vehicle solution. At Week 52 (4-weeks after completion of therapy), efinaconazole was superior to vehicle solution in both studies and thus demonstrated efficacy in the treatment of onychomycosis. The most common adverse reactions (ie, reactions with incidences > 1%) reported in the studies were ingrown toenails, application site dermatitis, application site vesicles, and application site pain.

Efinaconazole was approved by the US Food and Drug Administration in June 2014 for the topical treatment of onychomycosis of the toenail(s) due to *T rubrum* and *T mentagrophytes* (Julia® [efinaconazole] topical solution, 10% [6]). The approved drug is intended for topical application to affected toenails once daily for 48 weeks. During application, the toenail, toenail folds, toenail bed, hyponychium, and undersurface of the toenail plate are to be completely covered.

The current clinical study is designed to evaluate the safety and pharmacokinetics (PK) of once daily topical application of efinaconazole in the treatment of pediatric subjects with mild to severe onychomycosis of the toenails. Application and use of the study drug is consistent with the approved package insert. The evaluations included in the current study are consistent with the evaluations conducted in the development of the approved drug.

6 Study Objectives and Purpose

The primary objectives of this study are to evaluate: 1) safety of once daily topically administered efinaconazole 10% for 48 weeks in pediatric subjects (6-16 years of age) with at least mild onychomycosis of the toenails, and 2) pharmacokinetics PK (4 weeks) of once daily topically administered efinaconazole 10% in pediatric subjects (12-16 years of age) with moderate to severe onychomycosis of the toenails.

7 Investigational Plan

7.1 Investigators and Study Administrative Structure

Approximately 10 to 15 investigational centers are planned to participate in this study. Each clinical investigator will be required to provide a copy of his/her curriculum vitae and medical license, complete a financial disclosure statement, and generate a list of study personnel who will be involved in the study, with a summary of their roles and qualifications.

The Sponsor has designated a Contract Research Organization to assume responsibility for activities related to the conduct of the study. The Sponsor also has designated central laboratories to analyze biological samples related to clinical safety, pharmacokinetics, and mycology. A listing of the organizations involved in the conduct of the study is provided under Personnel Section in the front of the protocol. A complete description of the Sponsor's and delegates' study-related roles/responsibilities, including key personnel, is contained within the Sponsor's study project plan.

7.2 Summary of Study Design

This is an open label, single-arm study designed to evaluate the safety and PK of a once daily topical application of efinaconazole in the treatment of pediatric subjects with mild to severe onychomycosis of the toenails. The study will include a total of 60 subjects, 40 of whom will be 6 to 16 years of age, inclusive, and PK assessments will be performed on approximately 20 subjects 12 to 16 years of age, inclusive (referred to throughout the protocol as the PK subset). All subjects must have onychomycosis of at least 1 great toenail; subjects in the PK subset must have onychomycosis of both great toenails and at least 4 other toenails. Efforts will be made to enroll subjects into the PK subset such that the subjects are evenly distributed across the required age range.

For subjects not participating in the PK subset, the study will consist of 14 scheduled visits, including Screening (up to Day -42), Baseline (Day 1), 12 treatment visits (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). Subjects included in the PK subset will attend the scheduled visits up to Week 4 (Day 28) and an additional study visit at Day 29 for collection of the final PK blood sample. The PK assessments will be performed under maximal use conditions. Once PK assessments are complete at Day 29, the PK subset of subjects will continue treatment through week 48 with visits at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52).

At the Screening Visit, subjects and their parents/legal guardians will sign an informed consent/assent form and a photography consent/assent form, provide their medical histories, report their previous and concomitant medications, and be evaluated against the inclusion/exclusion criteria. Females of childbearing potential (FOCBP) will have urine pregnancy tests performed. During this visit, subjects will undergo an examination of their feet to visually ascertain the presence of onychomycosis in at least 1 great toenail for subjects not included in the PK assessments, and on both great toenails and at least 4 other toenails for subjects included in the PK assessments. Additionally, the percent involvement of the affected great toenail(s) will be recorded. A direct microscopic examination for the hyphae associated with dermatophytes will be performed at the investigational center using

potassium hydroxide (KOH) on toenail scrapings collected from the affected great toenail(s) (ie, at least 1 great toenail for all subjects and both great toenails for subjects in the PK subset). Subjects with KOH-positive toenail samples will provide an additional sample from the affected great toenail(s) for KOH examination and mycological culture (conducted at a central mycology laboratory). Blood and urine specimens will be collected for serum chemistry, hematology, and urinalysis evaluations. At relevant post-Screening Visits, the target great toenail will be trimmed back to the distal groove before the clinical evaluations are performed and before photographs are taken.

If a subject fails screening, either at the Screening or Baseline visit (prior to enrollment to treatment), the subject may be rescreened at a later date. Subjects who are rescreened, will be assigned a new screening number, must be re-consented, and undergo all screening procedures per protocol.

At the Baseline Visit (which should be scheduled after KOH and fungal culture results have been obtained from the mycology lab), subjects and/or their parents/legal guardians will update their medical histories and concomitant medication uses, and the inclusion/exclusion criteria will be confirmed. Subjects will undergo abbreviated physical examinations, clinical laboratory evaluations, assessments of vital signs (sitting blood pressure, respiration, pulse, and temperature), and measurements of height and weight. All FOCBP will have urine pregnancy tests performed. For the purposes of efficacy assessments, 1 target great toenail will be selected from the study-eligible great toenail(s), including subjects in the PK subset for whom both great toenails must be involved. Where both great toenails are study-eligible, the toenail with the greater percent of affected area will be selected for mycologic data and for inclusion in the efficacy analysis. In the instance where the percent of affected area is the same for both study-eligible great toenails, the investigator may select either great toenail as the target toenail. The target great toenail will be identified and recorded for each subject, photographs of the target great toenail will be obtained, and a transverse notch will be inscribed in the target great toenail adjacent to the proximal toenail fold (as a marker for measuring toenail growth at subsequent visits). Assessments of all other nontarget toenails, including the other involved toenails of subjects in the PK subset, will also be conducted to assess the presence or absence of onychomycosis on each toenail. This assessment will continue throughout the study visits through week 52.

After confirming eligibility at the Baseline Visit (Day 1), subjects will be enrolled in the treatment period. Subjects or their parents/legal guardians will apply the first dose of study drug to the qualified toenails at the investigational center under the supervision of designated study personnel. Any local skin reactions that occur at the study drug application site, along

with any adverse events (AEs), will be recorded. Subjects and their parents/legal guardians will receive weighed study drug bottles and given verbal and written instructions for treatment application. Specifically, subjects who are not included in the PK subset will be instructed to apply the study drug to the affected toenails once daily at bedtime for 48 weeks. Subjects who are included in the PK subset will be instructed to apply the study drug to all 10 toenails once daily at bedtime for 4 weeks. Following the PK blood collections on Days 28 and 29, these subjects will be instructed to continue treatment with study drug to only the affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). All subjects or their parents/legal guardians will also receive diaries, with instructions to complete a record of all applications and to note any missed applications of the study drug.

Subjects in the PK subset will not apply study drug the night prior to the Week 4 (Day 28) visit. Following the Day 28 study procedures, subjects in the PK subset will undergo timed blood collections to assess plasma concentrations of efinaconazole and metabolites (H3 and H4). Assessments will require collection of approximately 4 mL of whole blood at each time point (approximately 20 mL total). Within 1 hour after the predose blood sample is drawn, the subjects/parents/legal guardians will apply study drug to all 10 toenails at the investigational center. Subsequent blood collections will occur 2, 4, and 12 hours postdose on Day 28. The subjects will go home after Day 28, but will not apply study drug on the night of the Day 28 visit. PK subjects will return to the investigational center the following day(Day 29) for collection of a 24-hour postdose blood sample. PK subjects will continue treatment with study drug to only the target great toenail and the other affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52).

Safety will be assessed by reviewing the occurrence of AEs and local skin reactions, assessing vital sign measurements and abbreviated physical examination findings, and noting any additions or changes in concomitant medication uses. Blood samples will be collected at Screening and Week 48 for routine safety laboratory evaluations (serum chemistry, hematology, and urinalysis); urine pregnancy tests will be obtained for all FOCBP at each study visit. Efficacy assessments will be performed throughout the study. Efficacy analyses will be based on microscopic examination and mycological culture results for the target great toenail, the percent involvement of the target great toenail, the length of the unaffected part of the target great toenail, the growth of the target great toenail, and the number of affected nontarget toenails.

A post-treatment follow-up visit will occur 4 weeks after the last treatment visit for each subject (ie, at Week 52). Subjects who discontinue from the study prior to Week 48 will complete the Week 48 study procedures.

The study design and schedule of assessments is presented in Table 1.

Table 1: Study Design and Schedule of Assessments

		Treatment Period														Post-Treatment
Visit	1-SCR	2-BL	3	3A [a]	4	5	6	7	8	9	10	11	12	13	14 [b]	15
Week	Up to Day -42	Day 1	4 (Day 28)	4 (Day 29)	8	12	16	20	24	28	32	36	40	44	48	52
PROCEDURES																
Obtain Informed Consent/Assent and Photography Consent/Assent	X															
Review Medical History	X	X [c]														
Review Previous Therapies	X	X [c]														
Review Inclusion/Exclusion Criteria	X	X [c]														
Conduct Urine Pregnancy Test (all females of childbearing potential) [d]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Clip Toenails [e]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Notch Target Great Toenail [f]		X														
Measure Target Great Toenail Growth (from the PNF to the notch) [f]			X		X	X	X	X	X	X	X	X	X	X	X	X
Conduct Target Great Toenail Assessments [g]	X	X				X			X			X			X	X
Conduct Nontarget Toenail Assessments [h]	X	X				X			X			X			X	X
Obtain Photography		X							X						X	X
Perform KOH Examination [i]	X					X			X			X			X	X
Sample for Fungal Culture[i]	X					X			X			X			X	X
Conduct Abbreviated Physical Exam [j]		X													X	
Obtain Vital Signs [k]		X				X			X			X			X	

		Treatment Period														Post-Treatment
Visit	1-SCR	2-BL	3	3A [a]	4	5	6	7	8	9	10	11	12	13	14 [b]	15
Week	Up to Day -42	Day 1	4 (Day 28)	4 (Day 29)	8	12	16	20	24	28	32	36	40	44	48	52
PROCEDURES																
Collect Blood and Urine Samples for CBC/Diff, Chemistry, and Urinalysis	X														X [1]	
Enroll Qualified Subjects		X														
Review Dosing Instructions		X	X		X	X	X	X	X	X	X	X	X	X		
Apply First Dose in Clinic		X														
Weigh/Dispense Study Drug		X	X[n]		X	X	X	X	X	X	X	X	X	X		
Apply Study Drug			◄	———	———	———	———	———	———	———	———	———	———	———	►	
Collect/Weigh Study Drug			X		X	X	X	X	X	X	X	X	X	X	X	
Review Compliance			X		X	X	X	X	X	X	X	X	X	X	X	
Dispense Diary		X	X[o]		X	X	X	X	X	X	X	X	X	X		
Collect/Review Diary			X		X	X	X	X	X	X	X	X	X	X	X	
PK Blood Sample Collection [m]			X [m]	X [m]												
Review Local Skin Reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exit Study																X

Abbreviations: BL = Baseline Visit; CBC/Diff = complete blood count/differential; KOH = potassium hydroxide; PK = pharmacokinetic; PNF = proximal toenail fold; SCR = Screening Visit

Note: Post-baseline visits are to be scheduled in reference to Visit 2 (Baseline Visit) and within a window of ± 5 days.

[a] Visit 3A (Day 29) is only to be conducted for subjects in the PK subset.

[b] All Week 48 procedures are to be completed for subjects who discontinue from the study during the treatment period (ie, Early Termination).

[c] Confirmation of evaluations conducted at the Screening Visit.

[d] Urine pregnancy tests are required to have a minimum sensitivity of 25 mIU of human chorionic gonadotropin per mL of urine.

[e] Toenails are clipped prior to conducting the assessments.

[f] The transverse notch inscribed at the Baseline Visit is enhanced, as needed, at subsequent visits to allow continued measurement of toenail growth over the course of the study. In cases where the initial notch grows out or is clipped away, a new notch is inscribed in the toenail adjacent to the proximal toenail fold and measurements of toenail growth (ie, proximal toenail fold to notch) will continue using the new notch.

[g] Assessments include calculation of the percent involvement of the toenail affected by onychomycosis and measurement of the distance from the proximal toenail fold to the proximal onychomycotic border.

[h] Assessment of nontarget nails for presence or absence of onychomycosis.

[i] At the Screening visit, KOH examination will be performed at the site. If positive, additional specimens for KOH and fungal cultures are obtained from study-eligible great toenails at the Screening Visit. At all subsequently indicated study visits, specimens for KOH examinations and fungal cultures are obtained from the target great toenail.

[j] The abbreviated physical examination at the Baseline Visit and Week 48 includes height and weight,

[k] Vital sign measurements at each visit include temperature, pulse, respirations, and sitting blood pressure.

[l] Any clinically significant laboratory abnormality present at Week 48 (or Early Termination) is to be followed to resolution or until clinically stable as determined by the investigator.

[m] A subset of enrolled subjects will be assigned to PK evaluations. At the Week 4/Day 28 Visit, subjects in the PK subset will undergo timed blood sampling on Days 28 to 29 as follows:

n Study drug should be weighed and dispense at Visit 3A for PK subjects

o Diary should be dispensed with study drug at Visit 3A for PK subjects.

Visit	3					3A
Day (Week)	28 (4)					29 (4)
PROCEDURES	Predose	~1 h Following Pre-dose Sample	2 h (± 5 min)	4 h (± 5 min)	12 h (± 15 min)	24 h (± 30 min)
PK Subset - Collect Blood for Plasma Concentrations	X [p]		X	X	X	X
PK Subset - Study Drug Application		X [q]				

[p] The predose blood sample is to be collected after all Day 28/Week 4 study procedures are completed.

[q] Study drug application on Day 28/Week 4 will occur at the investigational center within 1 hour after collecting the predose blood sample. This will be the last application of study drug to all 10 toenails for subjects in the PK subset. Post Day 28, subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s). Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal

guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s).

8 Selection and Withdrawal of Subjects

8.1 Subject Inclusion Criteria

Subjects meeting all of the following criteria will be eligible for study entry:

1. Male or female subjects of any race, 6 to 16 years of age (inclusive).
   - **PK Subset**: Male or female subjects of any race, 12 to 16 years of age (inclusive).
2. Verbal and written informed consent/assent obtained from the subject and/or their parent or legal guardian.
3. Good general health, as assessed by the investigator, based on the subject's medical history, physical examination, and safety laboratory tests.
4. At least 1 great toenail (the "target great toenail") with clinically diagnosed distal lateral subungual onychomycosis involving at least 20% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. Up to 6 toenails may have onychomycosis in subjects not participating in the PK subset.
   - **PK Subset**: Both great toenails with clinically diagnosed distal lateral subungual onychomycosis involving at least 50% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. Subjects must also have at least 4 toenails other than the great toenails with onychomycosis.
5. Target great toenail for all subjects, and both great toenails for subjects in the PK subset, must have evidence of toenail growth, per subject's report that monthly clipping is needed.
6. Within 42 days prior to the Baseline (Day 1) Visit, have a positive KOH examination (at the investigational center and confirmed by the mycology lab) of the target great toenail for all subjects
7. Within 42 days prior to the Baseline (Day 1) Visit, have a positive dermatophyte culture for *T rubrum* or *T mentagrophytes* (at the central mycology laboratory) from the target great toenail in all subjects
   - **PK Subset**: Prior to the Baseline Visit, the great toenail designated for efficacy assessments as the target great toenail must have both a positive KOH examination (confirmed by the mycology lab) and a positive fungal culture.
8. All FOCBP must have a negative urine pregnancy test at the Screening and Baseline Visits and must agree to use an effective method of contraception throughout the study. Effective contraception is defined as use of an intrauterine device, condom with spermicide, diaphragm with spermicide, abstinence (subject is not sexually

active), or stable use of a hormonal contraceptive (oral, implant, injection, or transdermal patch) for at least 3 months prior to the Baseline Visit.

9. Subjects and their parents/legal guardians are willing to comply with study instructions and return to the investigational center for all required visits (a visit schedule with the length of each visit will be provided to ensure that the subject can meet the requirements and have adequate transportation).
10. Subjects and parents/legal guardians agree that the subject will avoid the use of toenail polish, cosmetic toenail products, and pedicures during the study period.

8.2 Subject Exclusion Criteria

Subjects meeting any one of the following criteria will be excluded from the study:

1. Females who are pregnant, nursing an infant, or planning a pregnancy during the study period.
2. History of immunosuppression and/or clinical signs indicative of possible immunosuppression, as determined by the investigator, or known human immunodeficiency virus infection.
3. History of diabetes that is uncontrolled as determined by the investigator (diabetes that is controlled by diet or medication does not exclude a subject).
4. Presence of any toenail infection other than or in addition to dermatophytes, such as *Scytalidium* as determined by the investigator (candidal onychomycosis infection, concurrent with a positive dermatophyte culture, is acceptable).
5. Presence of any of the following: dermatophytoma, fungal "spikes" within 3 mm of the proximal toenail fold on the target great toenail, infection extending to the matrix, or only lateral toenail disease in the target great toenail.
6. Presence of severe moccasin tinea pedis at the Screening or Baseline Visits, as determined by the investigator (if interdigital tinea pedis requires treatment during the study, the subject must agree to use only an investigator-approved topical antifungal therapy).
7. Presence of any disease/condition that might cause toenail abnormalities or may interfere with the evaluation of the study drug as determined by the investigator (eg, open sores or ulceration on the toes of affected toenails, psoriasis, immune dysfunction, collagen-vascular diseases, lichen planus, peripheral vascular disease, or traumatic onychodystrophy due to chronic physical stimuli).
8. Any previous surgery on the target great toenail.
9. Presence of onychomycosis of the fingernail.
10. History of immunodeficiency as determined by the investigator.
11. Presence of 1-hand, 2-foot syndrome, or fingernail dermatophytosis.

12. Target great toenail (including toenail plate and any subungual debris) thicker than 3 mm at the Screening and Baseline Visits.
13. Presence of onychodystrophy that could interfere with clinical assessments as determined by the investigator.
14. History of hypersensitivity or allergic reactions to azole derivatives or any of the study drug constituents.
15. Presence of any underlying disease that, in the opinion of the investigator, could present a safety concern for the subject by participating in the study.
16. Subject has received treatment for any type of cancer in the previous 6 months, except for nonmelanoma skin cancer (eg, basal cell carcinoma or nonmetastatic squamous cell carcinoma) that was treated successfully.
17. Presence of any dermatological condition on the feet that could interfere with clinical evaluations as determined by the investigator.
18. Presence of any underlying disease or dermatological condition other than onychomycosis that requires the use of interfering topical or systemic therapy and would make evaluations inconclusive as determined by the investigator, or subject requires treatment with a topical product on the toenails other than the study drug during the study.
19. Subjects using the following topical preparations within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following topical preparations during the study:
    - Toenail polish, cosmetic toenail products, or topical prescription or over-the-counter antifungal therapy for tinea pedis: 1 day
    - Other topical prescription or over-the-counter medications to the feet or toenails (with the exception of bland emollients): 2 weeks
    - Topical prescription or over-the-counter antifungal therapy for the toenails, including devices to treat onychomycosis: 4 weeks
    - Topical corticosteroids for the feet: 2 weeks
20. Subjects using the following systemic medications within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following systemic medications during the study:
    - Systemic antifungal therapy: 4 weeks
    - More than two, 2-week courses of oral corticosteroid therapy or 1 intramuscular, intravenous, or intra-articular injection of corticosteroids (nasal steroid sprays and steroid inhalers are permitted if use is stable and not expected to change during the study): 3 months

- Systemic immunosuppressive agents: 6 months

21. Subject has previously been nonresponsive to systemic antifungal therapy for onychomycosis.
22. Subject is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
23. Use of any investigational drug or device within 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit, or concurrent participation in another clinical study with an investigational drug or device.

8.3 Subject Withdrawal Criteria

When possible, subjects who discontinue from the study prior to completing the 48-week treatment period should return to the investigational center to perform the assessments scheduled for Week 48. If appropriate, discontinued subjects may be placed on other conventional therapy upon request or whenever clinically necessary, as determined by the physician. The End of Study source documents and all relevant data should be entered into the electronic case report form (eCRF) system at the time the subject discontinues from the study.

Reasons for subject withdrawal may include, but are not limited to, the following:

- Onychomycosis progression, as determined by the investigator, which requires treatment with a prohibited therapy
- Either at the investigator's discretion for safety reasons (eg, severe adverse reactions or unauthorized concomitant therapy), or at the subject's request for personal reasons
- When the requirements of the protocol are not followed
- When a concomitant therapy likely to interfere with the results of the study is reported or required by the subject (the investigator will report all such information on the source documents/eCRFs and decide, in accordance with the Sponsor, whether the subject is to be withdrawn)
- When a subject is lost to follow-up; the investigator (or designee) will try twice to reach the subject by telephone, and will send a follow-up letter by certified mail before considering the subject as lost to follow-up; these actions will be documented in the source documents and recorded on the End of Study eCRF, with a copy of the follow-up letter maintained in the investigator's file
- If a subject becomes pregnant during the treatment period, the study drug will be discontinued immediately, the subject will be discontinued from the study, and the investigator will notify the sponsor. The pregnancy will be followed to term with the outcome reported to the sponsor.

9 Treatments Planned

9.1 Methods of Assigning Subjects to Treatment Groups

This is a single-arm, open label study. After confirming eligibility at the Baseline Visit, subjects will be enrolled in the treatment period and will receive efinaconazole in accordance with the protocol (Section 10).

9.2 Randomization and Blinding

Randomization and blinding do not apply.

PK assessments will be performed on a subset of the study population. Efforts will be made to enroll subjects into the PK subset such that they are evenly distributed across the required age range.

9.3 Treatment Compliance

Subjects and their parents/legal guardians will be dispensed an initial bottle of study drug at Baseline (Day 1). Subjects and their parents/legal guardians will be instructed on the importance of returning the subject's study drug bottle(s) at the next study visit. If a subject does not return his/her study drug bottle, he/she will be instructed to return it at his/her next study visit. A new study drug bottle will be dispensed to the subjects at each post baseline study visit through Week 44. Subjects in the PK subset will be dispensed 2 bottles of study drug at Baseline (Day 1), and will be dispensed one bottle of study drug at each subsequent study visit through Week 44. All used and unused study drug bottles will be collected at Week 48.

The investigational center staff will weigh and record each bottle of study drug before dispensing to the subject and their parent/legal guardian and following return by the subject. Bottle weights will be recorded in the individual study drug log and in the appropriate eCRF.

At each post baseline study visit, subjects and/or their parents/legal guardians will be asked to report any missed doses of study drug, and provide the date and an explanation for each missed dose. A subject who has deviated from the once daily dosing regimen will be counseled in the presence of their parent/legal guardian. The dates of any missed doses of study drug will be recorded in the subject's source document and appropriate eCRF.

9.4 Treatment Administration

Subjects and their parents/legal guardians will receive both verbal and written instructions on the application of the study drug. The subject and/or their parent/legal guardian will apply the first dose of study drug at the investigational center during the Baseline Visit. All of the remaining study drug doses will be applied by the subject at home. The subjects and their

parents/legal guardians will be instructed to wait for the toenails to air-dry thoroughly before touching with clothing.

Dosing for Subjects NOT Included in the PK Subset: Subjects and their parents/legal guardians will be instructed to apply their assigned study drug to the target great toenail and all other affected toenail(s) (if any) once daily at bedtime. Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be instructed to apply the study drug by completely covering the target great toenail, including the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate. The study drug will be applied to each of the other infected toenails in a similar manner.

Dosing for Subjects Included in the PK Subset:

Days 1 to 28 – Subjects and their parents/legal guardians will be instructed to apply study drug to all 10 toenails, once daily at bedtime. During this period, all PK subjects will be instructed to apply the study drug by completely covering each toenail and 0.5 cm of adjacent skin, including the toenail folds, toenail bed, hyponychium, undersurface of the toenail plate. The subjects will not apply study drug the night prior to the Week 4 (Day 28) visit, nor will they apply study drug on the night of the Week 4/Day 28 Visit. Within 1 hour after the predose blood sample is drawn on Day 28, subjects will apply study drug to all 10 toenails in the manner described above at the investigational center.

Days 29 to Week 48:

After completion of the PK portion of the study, subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) once daily at bedtime. Subjects and their parents/legal guardianswill be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be given instructions regarding how to apply the study drug, ie, by completely covering the target great toenail, including the

toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate (if onychomycosis is present). The study drug will be applied to each of the other infected toenails in a similar manner.

9.5 Concomitant Medications

Concomitant medications/therapies refer to all medications/therapies used by the subject during the study. During the course of the study, if appropriate, every attempt should be made to keep the dosing and regimen of concomitant medications/therapies constant, and any change to a medication/therapy during the study must be recorded. Information on concomitant medications/therapies (including indication, dosing, and start and stop dates) will be recorded in the source document and on the appropriate eCRF. All concomitant medications/therapies (including foot care products) used during the study will be recorded under Concomitant Medications.

All prior medications (those used within 30 days prior to the Screening Visit) and previous antifungal medications used by the subject, including any recent over-the-counter topical treatments (those used within 60 days prior to the Screening Visit) will be recorded under Prior Therapies in the eCRF (eg, aspirin, acetaminophen, birth control pills, vitamins, herbal products, homeopathic preparations).

During the study, all foot care products used by the subject will be recorded under Concomitant Therapies.

9.5.1 Allowed Medications/Therapies

Concomitant medications (prescription or over-the-counter) that are considered necessary for the subject's welfare and do not interfere with study assessments and evaluations will be allowed during the study at the investigator's discretion.

If, during the study, a subject requires topical antifungal therapy for tinea pedis, the investigator is to document the problem and the investigator-approved treatment on the AE and concomitant therapy eCRFs, respectively, and to ensure that the subject avoids application of the concomitant therapy to the toenails or adjacent surrounding skin surface.

9.5.2 Prohibited Medications/Therapies

No topical treatments/products will be allowed on the toes or feet other than the study drug during the study, except for investigator-approved treatments.

Use of the following topical treatments is prohibited within the indicated time prior to the Baseline Visit:

Toenail polish, cosmetic toenail products, or topical prescription or over-the-counter antifungal therapy for tinea pedis	1 day
Other topical prescription or over-the-counter medications to the feet or toenails (with the exception of bland emollients)	2 weeks
Topical prescription or over-the-counter antifungal therapy for the toenails, including devices used to treat onychomycosis	4 weeks
Topical corticosteroids for the feet	2 weeks

Use of the following systemic medications is prohibited within the indicated time prior to the Baseline Visit and for the duration of the study:

Systemic antifungal therapy	4 weeks
More than two, 2-week courses of oral corticosteroid therapy or 1 intramuscular, intravenous, or intra-articular injection of corticosteroids[a]	3 months
Systemic immunosuppressive agents	6 months

[a] Nasal steroid sprays and steroid inhalers are permitted if use is stable and not expected to change during the study.

In addition, use of any investigational drug or device within 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit, or concurrent participation in another clinical study with an investigational drug or device during the study period is not allowed.

If a specific medication/therapy has the potential to interfere with the treatment effect of the study drug or interpretation of the study results, the investigator should contact the medical monitor prior to use (if possible).

Any subject using a prohibited therapy during the course of the study that could interfere with the treatment effect of the study drug or interpretation of the study results (including, but not limited to, those listed above) may be withdrawn from the study at the discretion of the investigator and/or sponsor. However, the investigator should not withdraw a subject without first confirming it with the sponsor.

9.6 Protocol Deviations and Violations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the sponsor and the institutional review board (IRB) or independent ethics committee (IEC) and agreed to by the investigator. Deviations usually have an impact on individual subjects or a small group of subjects and do not involve inclusion/exclusion or primary endpoint criteria.

A protocol violation occurs when there is nonadherence to the protocol that results in a significant, additional risk to the subject, when the subject or investigator has failed to adhere to significant protocol requirements (inclusion/exclusion criteria) and the subject was enrolled without prior sponsor approval, or when there is nonadherence to US Food and Drug Administration regulations and/or International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline.

The investigator or designee must record and explain in the subjects' source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the sponsor for agreement, to the IRB/IEC for review and approval, and to the regulatory authorities, if required.

10 Study Drug Materials and Management

The study drug will be provided to the investigational centers by the sponsor and will be dispensed to the subject and their parent/legal guardian by the pharmacy or an appropriately qualified member of the study staff assigned by the investigator.

All laboratory kits containing materials necessary to collect blood and urine for routine clinical laboratory tests, urine pregnancy tests, fungal cultures, and PK analyses will be supplied to the investigational centers by the designated central laboratories.

10.1 Study Drug

A description of the study drug is included in Table 2.

Table 2. Study Drug Identification

	Investigational Product
Drug Name	Efinaconazole 10% solution for topical administration
Name of Active Ingredient	Efinaconazole
Manufacturer	Valeant Pharmaceuticals
Chemical Name	(2R,3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol
Chemical Formula/Molecular Weight	$C_{18}H_{22}F_2N_4O$ / 348.39 amu
Therapeutic Category	Antifungal
Appearance	Clear to yellow solution
Inactive Ingredients	Alcohol, anhydrous citric acid, butylated hydroxytoluene, C12-15 alkyl lactate, cyclomethicone, diisopropyl adipate, disodium edetate, and purified water.

10.1.1 Packaging and Labeling

Efinaconazole will be provided to the investigational centers in 10 mL bottles containing 8 mL of study drug per bottle. Individual bottles will be supplied to the investigational center. The subjects and their parents/legal guardians will be dispensed 1 bottle at the Baseline Visit and 1 bottle at each subsequent study visit through Week 44. Subjects in the PK subset will be dispensed 2 bottles of study drug at the Baseline Visit, and will be dispensed one bottle of study drug at each subsequent study visit through Week 44.

The label on each bottle of study drug will identify the product as "Efinaconazole". The label on the study drug bottles will contain the following information:

- Protocol number
- Kit number
- Product identification (Efinaconazole 10% Solution)
- Subject number_____
- Subject initials_____
- Date dispensed _____
- A statement indicating the volume of the contents as 8 mL
- Instructions to keep bottle tightly closed and store in an upright position at room temperature (20°C to 25°C [68°F to 77°F]), with excursions permitted between 15°C and 30°C (59°F and 86°F)
- Lot number/expiration date
- Sponsor name and address
- A statement indicating, "Caution: New Drug - Limited by Federal Law to Investigational Use"
- A statement indicating that the drug should be kept out of reach of children

Additional information may be included on the bottle label as necessary.

10.1.2 Storage, Handling, and Disposal of Study Drug

Study drug should be stored in a secure area at the investigational center according to local regulations, in an upright position at controlled room temperature (20°C to 25°C [68°F to 77°F]), with excursions permitted between 15°C and 30°C (59°F and 86°F).

Subjects and their parents/legal guardians will be instructed to keep their study drug bottle at room temperature, out of the reach of children, not to share the study drug with anyone else, and to use it only on the affected toenails as directed by the investigator. Subjects and their parents/legal guardians will be asked to notify the investigational center immediately if a study drug bottle is damaged or lost.

All used and unused study drug supplies will be returned to the sponsor for destruction.

10.1.3 Study Drug Preparation

Not applicable; subjects and/or their parents/legal guardians will apply the study drug directly from the study drug bottles.

10.2 Study Drug Accountability

The Investigator or designee will be responsible for keeping current and accurate records of the amount of study drug received and dispensed, and its disposition. The study drug must be stored under the appropriate conditions in a secure area and is to be dispensed only to subjects enrolled in the study, in accordance with the conditions specified in this protocol. During the course of the study, the Investigator or designee must maintain an inventory of all study drug dispensed to or returned by the subject, including subject identifiers.

A study drug accountability log will be completed by the investigator or designee to document the receipt, dispensation, and return of study drug bottles.

All supplies sent to the Investigators will be accounted for and, in no case, used in any unauthorized situation. Bottles will be weighed (with the cap on) before dispensing to and upon return by the subjects, and weights will be recorded on the pharmacy log and appropriate CRF. All used and unused supplies will be returned to sponsor/designee for destruction at the conclusion of the study.

11 Study Procedures and Evaluations

11.1 Schedule of Evaluations and Procedures

All subject information and data obtained during the study visit procedures must be recorded in the source documents, applicable study logs, and eCRFs.

11.1.1 Screening Visit (Visit 1, Up to Day -42)

After signing the informed consent/assent, subjects will undergo the screening procedures to confirm eligibility to participate in the study.

The following procedures will be conducted at this visit:

1. Review and explain the nature of the study. Provide a visit schedule with the length of each visit to ensure that the subject can meet the requirements and has adequate transportation.
2. Obtain verbal and written informed consent/assent from the subject and the subject's parent(s) or legal guardian(s) prior to performing any study-related procedures. Provide signed copies of the consent and assent forms to the subject/parent(s) or legal guardian(s).
3. Obtain photography consent/assent from subject and/or the subject's parent(s) or legal guardian(s).
4. Assign a 6-digit study number, which includes the 3-digit investigational center number plus a unique 3-digit subject number beginning with 001 (eg, 001-001, 001-002, 001-003). Numbers must be assigned in chronological order.
5. Record subject's demographic information (sex, date of birth, age, ethnicity, and race).
6. Record subject's medical history including diabetes history.
7. Collect a detailed history of onychomycosis, including an estimated start date of infection, duration of current infection in the potential target great toenail, and all previous therapies used for onychomycosis treatment.
8. Review all prior medications (those used within 30 days prior to the Screening Visit) and previous antifungal medications used by the subject, including any recent over-the-counter topical treatments (those used within 60 days prior to the Screening Visit).
9. Review inclusion/exclusion criteria.
10. Examination of toenails for clinical presence of onychomycosis in at least 1 great toenail, within the definition of eligibility criteria. For subjects in the PK population, both great toenails and 4 other toenails must meet eligibility criteria.
11. Examination of all other toenails for presence or absence of onychomycosis on each toenail.
12. Examination of both feet for presence of symptomatic tinea pedis; reschedule completion of Screening after appropriate treatment and washout, as applicable.
13. Clip the toenails (before performing nail measurements). Remind subject and their parent/legal guardian not to clip toenails at home in between visits.
14. Perform the investigator's assessment of the great toenail(s) with a calculation of the percentage of toenail affected with disease, after clipping the unhealthy toenail. If the great toenail has been clipped proximal to the distal groove, the entire area to the distal groove should be included. The investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail.

- Subjects not included in the PK subset must have at least 1 great toenail with ≥ 20% involvement
- Subjects included in the PK subset must have both great toenails involved with ≥ 50% involvement in each great toenail.

15. Obtain specimens from the great toenail(s) for fungal culture and KOH examination. Both great toenails may be sampled if both are suspected of manifesting onychomycosis (at least 20% involvement).
16. Perform the KOH examination on site. If negative, screen-fail the subject and stop the Screening Visit. If positive, obtain additional samples from the same area of the toenail to send to the central mycology laboratory for confirmation of the KOH examination and fungal culture per instructions provided in the lab manual.
17. Perform a urine pregnancy test[1] for all FOCBP.[2] Exclude the subject if the pregnancy test result is positive.

    Urine pregnancy testing is mandatory for all FOCBP at the Screening Visit, Baseline Visit, and at all subsequent study visits. The decision may be made by the investigator to do additional urine pregnancy tests during the course of the study.

18. Collect blood and urine samples for routine safety laboratory analysis (hematology, serum chemistry, and urinalysis). Process and ship the samples to the central safety laboratory per instructions provided in the laboratory manual.
19. Schedule subject to return for the Baseline Visit (Visit 2, Day 1).

    If a subject fails screening, either at the Screening or Baseline visit (prior to enrollment to treatment), the subject may be rescreened at a later date. Subjects who are rescreened will be assigned a new screening number, must be re-consented, and undergo all screening procedures per protocol.

[1] Urine pregnancy tests must have a minimum sensitivity of 25 mIU of human chorionic gonadotropin per mL of urine. Urine pregnancy test kits will be provided by the sponsor.

[2] FOCBP include any female subjects who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal (defined as amenorrhea for > 12 consecutive months or women on hormone replacement therapy with documented plasma follicle-stimulating hormone levels > 35 mLU/mL). Even a female subject who is using an oral, implanted, injectable, or transdermal contraceptive hormone, an intrauterine device, a condom with spermicide, or a diaphragm with spermicide to prevent pregnancy, or is practicing abstinence, should be considered of childbearing potential.

11.1.2 Baseline Visit (Visit 2, Day 1)

If the Baseline Visit is more than 42 days after the Screening Visit, the subject must be reported as a screen failure and then may be rescreened (with a new subject number) at the investigator's discretion.

The following procedures will be conducted at this visit:

1. Record any AEs (query subjects and their parents/legal guardians, "Are there any changes in your health since the last visit?").
2. Confirm positive KOH and culture results from the central mycology laboratory.
    - All subjects (including those in PK subset) must have at least 1 great toenail with positive KOH (confirmed by central mycology lab) and positive dermatophyte culture for *T rubrum* or *T mentagrophytes*.
3. Review the safety laboratory test results.

    If any safety laboratory test results obtained at the Screening Visit, which will be received by the investigator prior to conducting the Baseline Visit, are abnormal and clinically significant as determined by the investigator, the investigator should discuss with the medical monitor whether it is in the subject's best interest to participate in the study.
4. Confirm the subject's medical history and prior medication uses.
5. Review all concomitant medications and new medications started since the last study visit.
6. Obtain vital sign measurements. Vital signs will be measured after the subject is seated for at least 5 minutes, and will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.
7. Measure height and weight.
8. Conduct an abbreviated physical examination (excludingurogenital/reproductive systems).
9. Perform a urine pregnancy test for all FOCBP. Exclude the subject if the pregnancy test result is positive.
10. Clip the toenails to the distal groove (before performing toenail measurements and close-up photography).
11. Conduct the investigator's assessment of the great toenail (s), with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
    - Subjects not included in the PK subset must have at least 1 great toenail with ◆ 20% involvement

- Subjects included in the PK subset must have both great toenails involved with ≥ 50% involvement in each great toenail.

12. Select target great toenail in each eligible subject for efficacy assessments. Where both great toenails are study-eligible (including percent involvement, KOH-positive, and culture-positive results), the toenail with the greater percent affected area at the Baseline Visit will be selected as the target great toenail prior to enrollment in the treatment period. In the instance where the percent affected area is the same for both study-eligible great toenails at the Baseline Visit, the investigator may choose either great toenail to be the target great toenail.
13. Inscribe a transverse notch in the great toenail at the proximal nail fold with a file or scalpel. This will be used as a marker at subsequent visits for determining new toenail growth.
14. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis. Subjects in the PK subset must have at least 4 toenails other than the great toenails with onychomycosis.
15. Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
16. Review inclusion/exclusion criteria. If the subject continues to meet all inclusion criteria and none of the exclusion criteria, enroll the subject in the treatment period.
17. Obtain 1 bottle of study drug and weigh the bottle. Record the assigned bottle number for the study drug in the subject's source document and on the appropriate eCRF. Dispense the bottle to the subject and their parent/legal guardian (complete the label and required records). For subjects in the PK subset, 2 bottles of study drug should be obtained. The bottles should be weighed separately and recorded as separate entries, as described above.
18. Instruct the subject and their parent/legal guardian on diary completion and dispense diary.
19. The subject or their parent/legal guardian will apply the first dose of study drug in the investigational center. Instruct the subject and their parent/legal guardian in the proper application technique for the study drug and provide the appropriate Subject Instruction Sheet with dosing instructions (ie, for non-PK or PK subjects), depending on whether the subject is enrolled in the PK subset. Record any AEs following the initial treatment application.
20. Record local skin reactions. Instruct the subject and their parent/legal guardian to report local skin reactions (if any) at each study visit.
21. Schedule the next study visit (Visit 3 [Week 4, Day 28]) in 28 days (± 5 days). Instruct the subject and their parent/legal guardian to return for each study visit at the same time of day as the Baseline Visit.

Note: (± 5 days) only applies to Non-PK subjects, PK subset only has a (± 1 day) visit window

- For subjects in the PK subset, Visit 3 (Week 4, Day 28) to Visit 3A (Week 4, Day 29) remind subjects not to apply study drug the night prior to their Visit 3 (Week 4, Day 28) visit.

11.1.3 Visit 3 (Week 4, Day 28 [± 5 days]), Visit 4 (Week 8 [± 5 days]), Visit 6 (Week 16 [± 5 days]), Visit 7 (Week 20 [± 5 days]), Visit 9 (Week 28 [± 5 days]), Visit 10 (Week 32 [± 5 days]), Visit 12 (Week 40 [± 5 days]), Visit 13 (Week 44 [± 5days])

Visits are to be scheduled in reference to Visit 2 (Baseline).

The following procedures will be conducted at this visit:

1. Record any AEs (query subjects and their parents/legal guardians, "Are there any changes in your health since the last visit?").
2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Clip the toenails.
5. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch). If the most recently applied notch has grown out or has been clipped off, inscribe a new notch adjacent to the proximal nail fold.
6. Collect the diary and study drug bottle from the subject and/or their parent/legal guardian. Weigh the used bottle of the study drug. Record the number of missed doses from the subject diary and review compliance with the subject.
7. Conduct a urine pregnancy test on FOCBP subjects (discontinue any subject from the study who has a positive test result)
8. Obtain 1 bottle of study drug and weigh the bottle, complete the label and drug log, and dispense the bottle to the subject and their parent/legal guardian. Review the dosing instructions with the subject. (Subjects in the PK subset will not be dispensed study drug this day).
9. Dispense diary. (Subjects in the PK subset will not be dispensed a diary this day.)
10. Schedule the next study visit. Instruct the subject and their parent/legal guardian to return for each study visit at the same time of day as the Baseline Visit.

For subjects in the PK subset <u>at Visit 3 only</u>:

- Collect a predose blood sample after all other study procedures are completed.
- Apply the study drug to all 10 toenails at the investigational center within 1 hour after collecting the predose blood sample.

- Collect postdose blood samples at approximately 2 hours (± 5 min), 4 hours (± 5 min), and 12 hours (± 15 min) after study drug application.
- Instruct the subject to return the following morning for their 24-hour blood sample (Visit 3A (Day 29). Subject will not dose on the evening of Day 28.

11.1.4 Visit 3A (Week 4, Day 29) – Additional Visit for Subjects in the PK Subset

The following procedures will be conducted at this visit:

1. Record any AEs (query subject "Are there any changes in your health?").
2. Record local skin reaction scores reported by the subject.
3. Review concomitant medications.
4. Collect a blood sample 24 hours (± 30 min) after study drug application at Visit 3.
5. Obtain 1 bottle of study drug and weigh the bottle, complete the label and drug log, and dispense the bottle to the subject and their parent/legal guardian. Review the new dosing instructions with the subject (application to only the target great toenail and to any other affected toenails) and provide a copy of new dosing instructions to the subject.
6. Dispense a new diary that includes the new dosing instructions.
7. Schedule the PK subset subject for the next study visit. Instruct the subject and their parent/legal guardian to return for each study visit at the same time of day as the Baseline Visit.

11.1.5 Visit 5 (Week 12 [± 5 days]), Visit 8 (Week 24 [± 5 days]), Visit 11 (Week36 [± 5 days])

Visits are to be scheduled in reference to Visit 2 (Baseline).

The following procedures will be conducted at these visits:

1. Record any AEs (query subject and their parent/legal guardian "Are there any changes in your health since the last visit?").
2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Conduct a urine pregnancy test on FOCBP subjects (discontinue any subject from the study who has a positive test result).
5. Clip the toenails.
6. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch). If the most recently applied notch has grown out or has been clipped off, inscribe a new notch adjacent to the proximal nail fold.

7. Conduct the investigator's assessment of the target great toenail, with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
8. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis.
9. Obtain specimens from the target great toenail for fungal culture and KOH examination and send to the mycology central lab per instructions provided in the laboratory manual.
10. Obtain vital sign measurements. Vital signs will be measured after the subject is seated for at least 5 minutes and will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.
11. At Visit 8/Week 24 only: Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
12. Collect the diary and study drug bottle from the subject and/or their parent/legal guardian. Weigh the used bottle of the study drug. Record the number of missed doses from the subject diary and review compliance with the subject and parent/legal guardian.
13. Obtain 1 bottle of study drug and weigh the bottle, complete the label and drug log, and dispense the bottle to the subject and parent/legal guardian.
14. Review the dosing instructions with the subject.
15. Dispense diary.
16. Schedule the subject for the Visit 6 (Week 16 [± 5 days]) study visit, and instruct the subject to return at the same time of day as the Baseline Visit. The Visit 7 (Week 20 [± 5 days]) and Visit 8 (Week 24 [± 5 days]) study visits will follow Visit 6. Instruct the subject and their parent/legal guardian to return for each study visit at the same time of day as the Baseline Visit.

11.1.6 Visit 14 (Week 48 [± 5 days]) / Early Termination Visit

The following procedures will be conducted at this visit:

1. Record any AEs (query subject and their parent/legal guardian "Are there any changes in your health since the last visit?").
2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Clip the toenails.

5. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch). If the most recently applied notch has grown out or has been clipped off, inscribe a new notch adjacent to the proximal nail fold.
6. Conduct the investigator's assessment of the target great toenail, with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
7. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis.
8. Obtain specimens from the target great toenail for fungal culture and KOH examination and send to the mycology central lab per instructions provided in the laboratory manual.
9. Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
10. Conduct an abbreviated physical examination (excluding urogenital/reproductive systems).
11. Measure height and weight
12. Obtain vital sign measurements. Vital signs will be measured after the subject is seated for at least 5 minutes, and include systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.
13. Collect the diary and study drug bottle from the subject and/or parent/legal guardian. Weigh the used bottle of the study drug. Record the number of missed doses from the subject diary and review compliance with the subject and parent/legal guardian.
14. Conduct a urine pregnancy test on FOCBP subjects (if positive test result, the subject should return for Visit 15 [Week 52]
15. Collect blood and urine samples for routine safety laboratory analysis (hematology, serum chemistry, and urinalysis). Process and ship the samples to the central safety laboratory per instructions provided in the laboratory manual.
16. If this is the Early Termination Visit, record the reason for subject discontinuation from the study and complete the Exit Study eCRF. All other subjects should be scheduled to return for the Visit 15 (Week 52) study visit. Instruct the subject to return at the same time of day as the Baseline Visit.

11.1.7 Visit 15 (Week 52 [± 5 days]) Post-Treatment Follow-up Visit / Study Exit

For all subjects, this visit should occur 4 weeks after the last treatment visit for each subject, whether the 48-week treatment period is completed per protocol at Week 48 or the subject discontinues study treatment early for any reason.

The following procedures will be conducted at this visit:

1. Record any AEs (query subject and their parent/legal guardian, "Are there any changes in your health since the last visit?").
2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Clip the toenails.
5. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch).
6. Conduct the investigator's assessment of the target great toenail, with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
7. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis.
8. Obtain specimens from the target great toenail for fungal culture and KOH examination and send to the mycology central lab per instructions provided in the laboratory manual.
9. Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
10. Conduct a urine pregnancy test on FOCBP subjects.
11. Exit the subject from the study.

11.1.8 Unscheduled Visits

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional exams should be fully documented in the source documents and on Unscheduled Visit eCRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit range, are not unscheduled visits. In these cases, the visit data will be collected and transcribed to the appropriate scheduled visit eCRF.

11.1.9 Missed Visits

If a subject misses any scheduled visit and cannot be seen prior to the start of the allowed visit range for the next scheduled follow-up visit, the visit is considered missed.

11.1.10 Subject Completion

A subject has completed the study when Visit 15 (Week 52) has been completed and the subject has been exited from the study. Subjects who require further follow-up for an AE following completion of the study will be followed according to Section 12.0.

11.2 Study Evaluations

11.2.1 Local Skin Reactions

Tolerability will be evaluated through assessment of local redness, swelling, burning, itching, and vesiculation in the selected treatment areas on the toes. Each sign or symptom is to be reviewed with the subjects and their parents/legal guardians after the first application of the study drug at the Baseline Visit and at each follow-up visit through Week 52. The subjects and their parents/legal guardians should assess each reaction based on the worst reaction experienced since the prior visit using the following scales:

Reaction	Score
Redness, Swelling	0 = None 1 = Mild 2 = Moderate 3 = Severe
Burning, Itching, and Vesiculation	Yes or No

Occurrence of vesiculation will always be reported as an AE. Any other sign or symptom will be reported as an AE only if it requires concomitant therapy or results in a temporary interruption or permanent discontinuation of the study drug due to discomfort.

11.2.2 Clinical Laboratory Tests

Blood and urine samples will be collected for routine safety laboratory tests (hematology, serum chemistry, and urinalysis) at the Screening and Week 48/Early Termination visit. Any subject with a screening laboratory abnormality that is determined by the investigator to be clinically significant must be approved for inclusion in the study by the medical monitor. All results will be reported, including abnormal results. Clinically significant changes in lab results from Screening, in the opinion of the investigator, should be reported as AEs. Clinically significant changes present at Week 48/Early Termination are to be followed to resolution or until clinically stable as determined by the investigator. If an AE should require laboratory testing, the results of the test must be obtained by the investigational center and filed in the subject's documentation.

Materials for sample collection will be provided to the investigational centers by the sponsor or central laboratory. Instructions for processing and shipping samples to the central laboratory are contained in the study laboratory manual.

For all FOCBP, urine pregnancy testing will be performed at the Screening and Baseline Visits, as well as at each subsequent study visit. FOCBP is defined as any female subject who has experienced menarche. The results at the Screening and Baseline Visits must be negative for a subject to enter the study. Materials for pregnancy testing will be provided to the investigational centers by the sponsor or central laboratory.

11.2.3 Vital Sign Measurements

Measurement of vital signs will be performed at the Baseline Visit, as well as at Weeks 12, 24, 36, and 48/Early Termination. After the subjects have been sitting for at least 5 minutes, systolic and diastolic blood pressures, pulse rates, respiration rates, and oral temperatures will be recorded.

11.2.4 Physical Examinations

An abbreviated physical examination will be performed at the Baseline Visit and at Week 48/Early Termination. Height and weight will be measured at the Baseline Visit and at the Week 48/Early Termination Visit.

11.2.5 Efficacy for Assessing Treatment Compliance and Safety

Efficacy assessments will be performed throughout the study. The efficacy analyses will be based on microscopic examination and mycological culture results for the target great toenail, the percent involvement of the target great toenail, the length of the unaffected part of the target great toenail, the growth of the target great toenail, and the number of affected nontarget toenails.

Investigators/evaluators will be trained by the sponsor to ensure consistency across investigational centers regarding toenail clipping, evaluations and measurements, as well as collection of sufficient material for KOH examinations and fungal cultures. Evaluators must be pre-approved by the sponsor and must have appropriate documented experience and training, or have a waiver obtained from the sponsor based on experience (or through additional training organized by the sponsor).

Every effort should be made to have the same sponsor-approved evaluator perform the target great toenail assessments and measurements for a particular subject at the Baseline Visit and each follow-up visit.

11.2.5.1 KOH Examination and Fungal Culturing

The KOH examination and fungal culturing of toenail scraping and subungual debris will be performed for study-eligible great toenail(s) at the Screening Visit and for the target great toenail only (as determined at the Baseline Visit) at Weeks 12, 24, 36, 48/Early Termination, and 52 (the 4-week post-treatment follow-up) study visits. At the Screening visit, KOH examination will be performed at the investigative site. If positive, additional specimens for KOH and fungal cultures are obtained from study-eligible great toenails at this visit and sent to the central mycology laboratory.

Fungal culturing will be performed by the central mycology laboratory. Toenail specimens will be taken by clipping the toenail to the point of attachment (removing unhealthy nail) and obtaining any crumbling subungual debris from under the distal edge of the target great toenail using a disposable curette. All target great toenail plate clippings and "distal" subungual debris should be discarded. Only the soft nail bed keratin beneath the clipped edge of the nail should be collected and used as a specimen for both the KOH examination and the fungal culture. Careful specimen collection in this manner will minimize toenail specimen contaminants and maximize dermatophytic pathogen isolation.

Materials for sample collection will be provided to the investigational centers by the sponsor or central mycology laboratory. Instructions for processing and shipping samples to the central laboratory are contained in the study laboratory manual.

11.2.5.2 Target Great Toenail Assessments

The percent of the affected toenail area and healthy (unaffected) toenail measurements for the target great toenail(s) will be evaluated by the investigator/evaluator at the Screening and Baseline Visits, and at Weeks 12, 24, 36, 48/Early Termination, and 52 (the 4-week post-treatment follow-up) study visits.

Percent of Affected Target Great Toenail Area

The affected area of the toenail will be estimated as the percent of toenail area (nail and nail bed) involved (the distal margin for determining area will be the distal groove after the toenail has been clipped).

Healthy (Unaffected) Target Great Toenail Measurement and Growth

The healthy (unaffected) toenail measurement will be defined as the distance (in mm) between the proximal nail fold and a transverse line on the healthy part of the toenail immediately proximal to the nail infection. At each evaluation, this distance will be measured from the proximal nail fold to the proximal onychomycotic border.

Toenail growth will be measured by inscribing a transverse notch in the nail of the target great toenail(s) adjacent to the proximal nail fold at the center of the nail at the Baseline Visit, and measuring nail growth from that point forward. At every subsequent visit, the distance (in mm) between the proximal nail fold and the notch will be measured and recorded. The notch should be enhanced as needed at subsequent visits to allow continued measurement of toenail growth over the course of the study. If the initially applied notch inscribed at the Baseline Visit has grown out or is clipped away, inscribe a new notch in the toenail adjacent to the proximal nail fold, and continue with measurements using the new notch.

11.2.5.3 Nontarget Toenail Assessment

An assessment of both feet will be made for assessing the presence or absence of onychomycosis of nontarget toenails at the Screening, Baseline, Weeks 12, 24, 36, 48/Early Termination, and 52 (the 4-week post-treatment follow-up) study visits. All nontarget toenails will be assessed for the presence or absence of onychomycosis. Subjects in the PK subset must present with onychomycosis on at least 4 toenails besides the great toenails.

11.2.6 Evaluation of Pharmacokinetics

The PK assessments will be performed on a subset of the study population who will receive treatment under maximal use conditions for 28 days. Plasma samples for determination of efinaconazole and metabolite levels will be collected at the following time points:

- Visit 3 (Day 28): Predose (after all Day 28 procedures are completed). Study drug must be applied within 1 hour after the predose sample is collected. Samples are then collected at 2 (± 5 min), and at 4 (± 5 min), and at 12 (± 15 min) hours postdose.
- Visit 3A (Day 29): 24 (± 30 min) hours after Day 28 study drug application.

Materials for sample collection will be provided to the investigational centers by the sponsor or central laboratory. Instructions for processing and shipping samples to the bioanalytical laboratory are contained in the study laboratory manual.

11.2.7 Photography

At all investigational centers, close-up photographs of the target great toenail(s) will be taken at the Baseline, Weeks 24, 48/Early Termination, and 52 (the 4-week post-treatment follow-up) study visits. One photograph will be taken after toenail clipping. After the first photograph has been taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. After the ink has dried, a second photograph will be taken. The collected photographs will be used for documentation purposes only and will

not be used for determinations of eligibility, efficacy, or any study-related activities. Before photographs are taken, the study subject and their parent(s)/legal guardian(s) must consent/assent to photography. If the photography consent/assent is declined, the subject may still participate in the study.

11.3 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the study drug. Thus, AEs include any unfavorable and unintended illness, sign, symptom, clinically significant laboratory test abnormality, or disease temporally associated with the use of a medicinal product that has appeared or worsened during the course of the clinical study, regardless of causal relationship to the study drug(s) under study. The collection of nonserious AEs and serious adverse events (SAEs) should begin following the subject's completion of the consent/assent process to participate in the study.

11.3.1.1 Definition of Serious Adverse Events

All AEs will be assessed as either serious or nonserious. An SAE or serious adverse reaction is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is immediately life threatening, (the term "life threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires in subject hospitalization or prolongation of existing hospitalization (hospitalization for elective surgery for a baseline condition is not considered an AE).
- Results in persistent or significant disability/incapacity (permanent or substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the above listed outcomes.

Important medical events that may not have resulted in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or

surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization is a criterion for assessment of seriousness. To qualify as serious under the criteria of "hospitalization," a hospital admission of at least a 24-hour period is required. If a subject is retained the emergency room greater than 24 hours, but not admitted for medical care, these cases should be evaluated individually, as criteria such as "medically significant" may also apply.

Hospitalization without a medical AE should not be considered either serious or an AE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality).
- Hospitalization for a purpose unrelated to the study (eg, "planned" or elective surgery scheduled prior to study participation) would not ordinarily need to be reported, unless a complication occurred which otherwise caused prolongation of this hospitalization.
- Protocol-specified admission or procedure (eg, cataract surgery required by a study protocol; or overnight stay for monitoring due to protocol required surgery, *with no associated SAE or complication necessitating prolonged stay*)
- Social admission (eg, social hospitalization for purposes of respite care)

Note: A spontaneous abortion will be considered an SAE, and must be reported to the sponsor within 24 hours of your awareness of the event.

11.3.1.2 Assessment of Severity

The severity assigned to an AE should be determined by the maximum severity of the AE. The categories described below should be used to estimate the severity of AEs:

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- Moderate: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.

- Severe: Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization or prolongation of current hospitalization possible; may be incapacitating or life threatening.

11.3.1.3 Assessment of Causality

The investigator should assess the relationship of the AE, if any, to the study drug as either "Related" or "Not Related".

- **Related:** There is at least a reasonable possibility that the AE/SAE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.
- **Not Related:** There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists.

The following should be taken into account when assessing AE/SAE causality:

- Positive temporal relationship to study drug, such as if the study drug was withdrawn and the SAE resolved or the event recurred after reintroduction.
- If there is a reasonable possibility that the AE is associated with an underlying or concomitant illness.
- Possible association with previous or concomitant therapy.
- No temporal relationship to the study drug and/or a more likely alternative etiology exists.
- If the AE is directly related to study procedures or there is a lack of efficacy.

11.3.1.4 Procedures for Reporting Adverse Events and Serious Adverse Events

Throughout the course of the study, efforts will be made by the Investigator to remain alert to possible AEs that are either systemic or ocular in nature. The period of observation for collection of AEs extends from the time the subject and parent/legal guardian gives informed consent/assent until the last study visit or discontinuation from the study. The first concern will be the safety of the subject, and appropriate medical intervention will be made.

The Investigator or designee will elicit reports (ie, via direct questioning, observation, clinical evaluation) of AEs from the subject at each study visit and record all AEs. The Investigator will document the dates of onset, progress, outcome, and resolution of such AEs. The Investigator will also provide an assessment of all AEs as to the severity, causal relationship to study drug, and causal relationship to study protocol.

It is the investigator's responsibility to document all AEs that occur during the study. The AEs should be documented as a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject and/or their parent/legal guardian at each study visit.

All AEs occurring after the subject and their parent/legal guardian signs the assent/informed consent through the last study visit must be reported, regardless of whether or not the AEs are considered drug-related. All AEs, whether in response to a query, observed by the study site personnel, or reported spontaneously by the subject and/or their parent/legal guardian, will be recorded.

At each visit during the study, the subject will be assessed for the occurrence of new and ongoing AEs. Cutaneous tolerability signs and symptoms that result in the subject's requiring a concomitant therapy or discontinuation from the study will be reported as an AE. The following data will be collected on all AEs and recorded on the appropriate eCRF:

- Event name (diagnosis preferred, if unknown, record the signs/symptoms).
- Onset date and end date.
- Maximum intensity (severity).
- Seriousness.
- Action taken regarding study drug.
- Corrective treatment, if given.
- Outcome.

In addition, the investigator's assessment of causality will be recorded.

Any SAE must be reported to the Sponsor, independent of the circumstance or suspected cause, within 24 hours from the time the event was reported to the Investigator. All SAEs experienced from the date of consent through at least 30 days after the last dose of study drug must be reported to the Sponsor regardless of the relationship to the study drug or the protocol. For events occurring beyond the minimum 30-day period after the last dose of study drug, or for any timeframe afterward deemed medically significant, only SAEs considered related to the study drug should be reported promptly to the Sponsor.

Within 24 hours of notification the Investigator will fax or email a completed Serious Adverse Event Report to the Sponsor:

Fax: [redacted]

SAE Inbox: [redacted]

Attn: Valeant Global Safety and Vigilance

Investigators should not wait to receive additional information to document the event before notifying the sponsor of an SAE. If only limited information is initially available, follow-up reports are required. If the Investigator becomes aware of any new information regarding a SAE (ie, resolution, change in condition, or new treatment), a new SAE Form must be completed and faxed/emailed to the Sponsor within 24 hours. The original SAE form is not to be altered. The report should be marked as a "follow-up report" and describe whether the event has resolved or continues and how the event was treated. Additional relevant information such as hospital records and autopsy reports should be provided to the sponsor as soon as they are available.

Should the investigator become aware of an SAE (regardless of its relationship to investigational product) that occurs within 30 days after stopping the study drug, the SAE must be reported in accordance with procedures specified in this protocol.

The investigator should take all appropriate measures to ensure the safety of the subjects, notably he/she should follow a subject with an SAE until the event has resolved or the condition has stabilized. This may imply that follow-up will continue after the subject has left the study, and that additional investigations may be requested by the sponsor.

11.3.1.5 Submitting an Expedited Safety Report to the IRB (Central or Local)

Any suspected unexpected serious adverse reaction (SUSAR) warrants expedited reporting. In addition, any unexpected SAE related to a subject's participation in the study (or conduct of study), regardless if the study drug was administered, will be evaluated by Global Safety and Vigilance to determine if expedited reporting is required. For example, an unexpected, serious and severe reaction which could be associated to the study procedures, and which could modify the study conduct requires expedited reporting.

Each expedited safety report will routinely include a brief cover memorandum, the completed MedWatch Form FDA 3500A or Council for International Organizations of Medical Sciences I Form, a clinical analysis of the event with any similar events that have occurred with the product, and any additional pertinent information recommended by the study Medical Monitor. Once the report is compiled by Bausch + Lomb Global Safety and Vigilance, the site Investigator must submit the expedited safety report to the local IRB/EC within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available. The site principal Investigator must retain a complete copy of each expedited safety report as it was submitted to the IRB. It is important that the principal Investigator review these expedited reports, as they contain safety information that may be relevant to each of the participating subjects.

11.3.2 Pregnancy

All female subjects of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of contraceptive failure is minimized. Abstinence is allowed as a birth control method.

Before enrolling a female subject of childbearing potential in this clinical study, the investigator must review the following information about study participation:

- Informed consent/assent requirements.
- Contraceptives in current use.

Following review of this information and appropriate counseling for the subject and their parent/legal guardian, the investigator or designee and the subject and parent/legal guardian must sign the assent/informed consent before study enrollment.

During the study, all female subjects of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to study enrollment, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study drug and must not be enrolled in the study. If pregnancy is suspected while the subject is receiving study treatment, the study drug must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued and the subject will be followed until the pregnancy comes to term. A Pregnancy Report form will be submitted to the sponsor, initially and at the end of the pregnancy, which includes the outcome of the pregnancy and any complications occurring during the pregnancy or the delivery.

12 Statistics

12.1 Assessment of Safety

12.1.1 Adverse Events

All AEs that occur during the study will be recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are those AEs with an onset on or after the date of first study drug application. All TEAEs will be summarized by the number of subjects reporting each TEAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the safety, PK, and non-PK populations. Each subject will be counted only once within a system

organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category.

All SAEs will be summarized by the number of subjects reporting each SAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the safety, PK, and non-PK populations.

All information pertaining to AEs noted during the study will be listed by subject and will include the verbatim term given by the investigator, the associated system organ class and preferred term, the start and stop (if stopped) dates, the seriousness, and the severity of the event. Additionally, any action taken with the study drug, any corrective treatment administered, the outcome, and the relationship to study drug as well as a list of subjects who prematurely discontinue from the study due to an AE will be provided.

12.1.2 Local Skin Reactions

Local skin reaction scores (redness, swelling, burning, itching, and vesiculation) at each visit will be summarized using frequency tables for the safety, PK, and non-PK populations. Additionally, redness and swelling severity scores will be summarized using descriptive statistics (mean, standard deviation [SD], median, and minimum, and maximum). Subjects with a severity score worse than baseline will also be summarized at each post-baseline visit. The worst score and the last score during the post-baseline period will also be summarized.

12.1.3 Clinical Laboratory Tests

Results of safety laboratory parameters will be summarized at each study visit using descriptive statistics or frequencies and percentages, as appropriate, for the safety, PK, and non-PK populations. Changes from baseline in safety laboratory values will be summarized by treatment group at Week 48 using descriptive statistics. In addition, changes from baseline in safety laboratory values will be summarized using shift tables according to normal ranges.

12.1.4 Vital Signs

Results of vital sign measurements will be summarized at Weeks 12, 24, 36, and 48 using descriptive statistics or frequencies and percentages, as appropriate, for the safety, PK, and non-PK populations. Changes from baseline in vital sign measurements will be summarized at these visits.

12.1.5 Concomitant Medications

All previous therapies and concomitant medications will be classified based on terminology from the World Health Organization Drug Dictionary. Previous therapies and concomitant medications data will be presented in data listings.

12.1.6 Efficacy for Assessing Treatment Compliance

This primary objective of this study is to assess the safety of the study drug. Descriptive efficacy statistics for the endpoints will assist in evaluating compliance with treatment for the purposes of safety assessment. The efficacy variables evaluated in this study include microscopic KOH examination and mycological culture outcomes of the target great toenail, percent involvement of the target great toenail, growth of the target great toenail, and assessments of the nontarget toenails. The efficacy endpoints include the following:

- Complete Cure, defined as 0% clinical involvement of the target toenail and negative KOH and fungal culture at Week 52
- Complete or Almost Complete Cure at Week 52, defined as :S 5% toenail involvement
- The Clinical Efficacy rate at Week 52, defined as an affected target great toenail area of < 10%
- The Mycologic Cure rate at Week 52, defined as a negative KOH examination and a negative fungal culture of the target great toenail sample

The Complete Cure rate, the Complete or Almost Complete Cure rate, the Clinical Efficacy rate, and the Mycologic Cure rate will be presented using descriptive statistics (sample size n, frequency counts, and percentages) for the safety, PK, and non-PK populations. In addition, the growth of the target great toenail at each study visit and the change from baseline in the number of affected nontarget toenails will be summarized descriptively.

A last observation carried forward (LOCF) imputation will be used to impute missing values for the efficacy variables at Week 52. No sensitivity analyses will be conducted.

12.2 Assessment of Pharmacokinetics

The PK objectives will be considered met when approximately 16 evaluable subjects are treated under maximal use conditions through day 28 of the PK evaluation.

No imputations will be made for missing data. Plasma concentrations that are reported as below the limit of quantitation (BLQ) in the data transfer file and will be set to zero for the summaries of concentrations as well as calculation of PK parameters. Missing values will be treated as if they were never drawn. Plasma concentrations and PK parameters will be summarized for the PK analysis set using descriptive statistics (n, mean, SD, standard error of the mean [SEM], coefficient of variation [CV], median, minimum, and maximum). Geometric means will also be used to summarize C_{max}, C_{min}, $AUC_{(0-t)}$ and $AUC_{(0-24h)}$.

Plasma concentrations of efinaconazole and metabolite (H3 and H4) at each scheduled sampling time point will be summarized using descriptive statistics. The individual plasma concentrations will be listed for each subject. Concentrations BLQ will be displayed as BLQ in the listings.

The mean plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will be presented graphically for Days 28 and 29 in both linear and logarithmic scales. Individual subject plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will also be created.

Plasma PK parameters for efinaconazole and metabolites (H3 and H4) will be calculated using noncompartmental analysis. The PK parameters will be calculated for each subject using actual sampling times. The maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) will be taken directly from the data.

The following PK parameters will be calculated from the individual plasma concentrations on Days 28 and 29 when possible:

- C_{max} (observed peak drug [efinaconazole and metabolites] concentration)
- T_{max} (time at which C_{max} occurs)
- C_{min} (observed minimum drug concentration)
- AUC_{0-t} (area under the concentration-time curve from time 0 up to the sampling time corresponding to the last quantifiable concentration)
- AUC_{0-24h} (area under the concentration-time curve from time 0 through 24 hours [corresponding to the dosing interval])

Additional PK parameters may be calculated as appropriate.

12.3 Subject Disposition

Subject disposition will be summarized for each analysis population.

12.4 Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized using descriptive statistics for each analysis population.

12.5 Protocol Deviations

All protocol deviations will be reported to the sponsor and recorded throughout the study. A tabulation of protocol deviations will be included in the final study report.

12.6 Compliance

Efficacy evaluations are being conducted to assess treatment compliance. Information regarding the evaluations and their analyses are presented in Section 12.1.6.

Study drug compliance will be calculated for each subject by taking into account whether a subject took all doses of study drug as instructed. Calculation of study drug compliance will be documented in the analysis plan.

12.7 Interim Analyses

No interim analyses are planned.

12.8 Additional Statistical Considerations

When approximately 40 evaluable subjects have been treated for 48 weeks meeting the primary safety objective (regardless if subjects in the PK subset are continuing), a data cut will be done and the study report will be written. Once all subjects in the PK subset completes the study, database lock will be performed and the study report amendment will be written.

All statistical processing will be performed using SAS® version 9.3 or higher unless otherwise stated. No hypothesis testing will be conducted in this study. A statistical analysis plan, describing all statistical analyses, will be provided as a separate document prior to data analysis is performed.

12.8.1 Analysis Populations

All subjects who receive at least 1 confirmed dose of study drug will be included in the safety population.

All subjects in the PK subset who receive at least 1 confirmed dose of study drug and have any PK data on Days 28 and 29 will be included in the PK population.

All safety population subjects who are not in the PK subset will be included in the Non-PK population.

12.8.2 Sample Size Determination

Approximately 60 subjects will be enrolled and receive treatment with study drug. Approximately 20 of the 60 subjects will be enrolled in the PK subset. These sample sizes were based on PK and clinical considerations; no formal sample size calculation was performed. The numbers of planned subjects are considered adequate for determining the safety profile and the PK parameters of efinaconazole in a pediatric population of subjects aged 6 to 16 years 11 months with mild to severe onychomycosis of the toenails.

12.8.3 Handling of Missing Data

No imputations will be made for missing safety or PK data. As indicated previously, the efficacy endpoints, which are used to assess treatment compliance, will have missing data imputed with LOCF for non-PK population analyses. Missing efficacy data will not be imputed for safety and PK population analyses.

12.8.4 Multicenter Issues

The study will be conducted at multiple investigational centers in the US, Central America, and the Caribbean with the intention of pooling the results for analysis.

12.8.5 Multiplicity Issues

Not applicable.

12.8.6 Windowing Rules

The timing of all study visits is relative to the Baseline (Day 1) visit. Visit 3 (Week 4) should occur within 5 days of Day 28 and Visit 3A (Week 4) should occur 1 day after Visit 3. The Week 8 and all subsequent visits should occur within 5 days of the targeted times.

13 Quality Control and Quality Assurance

This study will be conducted under the sponsorship of Valeant, in conformation with all appropriate local and federal regulations as well as ICH guidelines.

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, GCP guidelines, and applicable regulatory requirements. In addition, the sponsor will be responsible for securing agreement from all involved parties to ensure direct access to all study-related sites, source data/documents, eCRFs, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

Central laboratory services will be performed by a qualified, licensed facility that will be listed on the US Food and Drug Administration Form 1572. Copies of all normal values (as applicable), laboratory certifications, and the director's curriculum vitae will be provided to each investigational center and to the sponsor.

13.1 Study Monitoring

The conduct of the study will be closely monitored. Sponsor representatives must be permitted to visit all study site locations to assess the data, quality of study performance, and

study integrity in a manner consistent with applicable health authority regulations and the procedures described in this protocol.

Prior to the start of the study, the Sponsor or its designee(s) will review the protocol, eCRFs, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator/Sub/Co Investigator and relevant study site personnel.

Monitoring visits and telephone consultations will occur as necessary, or per the study monitoring plan, during the course of the investigation to verify the following:

- The rights and well-being of subjects are protected
- The conduct of the investigation is in compliance with the currently approved protocol/amendment, ICH GCPs, and IRB/EC requirements
- The integrity of the data is maintained, including adequate study documentation
- The facilities remain acceptable
- The Investigator and site personnel remain qualified and able to conduct the study
- Study drug accountability is documented properly

During the course of the study, if the Sponsor determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor will take action to secure or reinstate compliance. In addition, the Sponsor may terminate the Investigator's participation in the study if appropriate, or if the Investigator remains non-compliant despite the remedial actions of the Sponsor..

13.2 Audits and Inspections

Interim and end of study audits of raw data, study files, and the final report may be conducted by the sponsor's quality assurance department or its designee. A certificate attesting to the audit(s) will be issued as applicable. In addition, inspections or on-site audits may be carried out by local authorities. The investigators will allow the sponsor's representatives and any regulatory agency to examine all study records and logs, eCRFs, corresponding subject medical records, study drug dispensing records, study drug storage area, and any other documents considered source documentation. The investigators agree to assist the representative, if required.

13.3 Data Quality Assurance

All assessments performed will be accurately documented in the subject's source documents and eCRFs. The investigator or designee will enter the information required by the protocol

into the source documents and eCRFs provided by the sponsor or designee. Subjects will be identified in the eCRFs by their assigned subject number and initials only.

The investigators must read the protocol thoroughly and must follow the instructions exactly. Any deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate written protocol amendments made prior to effecting the agreed upon changes. Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB/IEC before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

14 Ethics and Administrative Issues

14.1 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, ICH guidelines, GCP guidelines, and in compliance with local and federal regulatory requirements. The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP.

14.2 Ethics Review

This protocol, proposed informed consent/assent form and other information to the subjects, and all appropriate amendments, will be properly reviewed, and approved by an IRB/IEC. A signed and dated notification of the IRB/IEC approval will be provided to the sponsor and investigator prior to study initiation. The name and occupation of the chair and members of the IRB/IEC will be supplied to the sponsor. The investigator will provide required progress reports and report all SAEs to the IRB/IEC as required.

14.3 Written Informed Consent

Written informed consent/assent, in accordance with local clinical investigation regulations, must be obtained prior to participation in the study. The investigator or designee will discuss the purpose of the study with each subject and their parent(s)/legal guardian(s) and will provide a description of the study drug (including any potential and possible side effects) and the study procedures. Information must be given both in oral and written form. The subject information provided will be in a language understandable to the subject and their parent(s)/legal guardian(s) and may not include any language that appears to waive any of the subject's legal rights or appears to release the investigator, the sponsor, or the institution from liability or negligence.

The investigator or designee will provide the prospective subject and the subject's parent(s) or legal guardian(s) sufficient time to consider whether to participate, minimizing the possibility of coercion or undue influence and will discuss any questions the subject and/or their parent(s)/legal guardian(s) may have. The investigator or designee will explain to the subject and their parent(s)/legal guardian(s) that participation in the study is voluntary and that withdrawal from the study is possible at any time without detriment to care. The consent must include acknowledgment that medical records and medical data derived from the study may be forwarded to the sponsor or to the responsible authorities or federal authorities.

No subject can enter the study or have any study-related procedures performed before his/her written informed consent/assent has been obtained. Subjects under the age of consent must sign an assent form and their parents/legal guardians must sign the informed consent form. Subjects over the age of consent must sign the informed consent form. Subjects and their parents/legal guardians will also provide written consent/assent to obtain photographs of the target great toenail. The original signed and dated informed consent and assent forms will be retained with the study records, and a copy of the signed forms will be given to the subject and their parent or legal guardian as applicable.

An informed consent/assent template will be supplied by the sponsor to the investigator. Any changes to the informed consent/assent form must be agreed to by the sponsor prior to submission to the IRB/IEC, and a copy of the approved version must be provided to the sponsor after IRB/IEC approval.

14.4 Subject Data Protection

Subject data will be protected by ensuring that no captured data contain subject names, addresses, telephone numbers, email addresses, or other direct personally identifying information. It is acknowledged that subject initials, demographics (including birthdates), medical histories, and prior concomitant medication uses, along with the name and address of the enrolling investigator may allow for personal identification of study participants. Other than where necessary to meet regulatory requirements, all data collected in this study will be presented in tabulated (ie, aggregate) form and listings containing information that could be used to identify an individual subject will not be included in any public disclosures of the study data or the study results.

14.5 Data Monitoring Committee

Not applicable.

14.6 Financial Disclosure

Financial disclosures will be obtained from all investigators in order to document any potential conflicts of interest.

14.7 Essential Documents

Investigator must maintain essential documents during the conduct of the study and retain these documents after the completion of the study in accordance with the Sponsor's record retention instructions. The Investigator agrees to adhere to the document retention procedures when signing the protocol Investigator Statement of Approval.

Essential documents include, but are not limited to, the following:

- IRB approvals for the study protocol, all amendments, ICF(s), and advertisements
- IRB annual study review
- IRB correspondence and reports (eg, SAE reports, protocol deviations, and safety updates)
- Regulatory documents (eg, financial disclosure and delegation of authority forms)
- All source documents
- CRFs
- Subject's signed ICF
- FDA Form 1572
- Accountability records for the study drug
- Correspondence from and to sponsor
- Any other documents relevant to the conduct of the study

In the event that the Investigator withdraws from the study (eg, retirement or relocation), study records will be transferred to a mutually agreed upon designee (eg, another Investigator or site IRB/EC). The Investigator will provide notice of such transfer in writing to the sponsor

14.8 Investigator Obligations

The investigators must read the protocol thoroughly, complete and sign the protocol signature page, and must follow the instructions exactly. Whenever possible, any planned deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate documentation of sponsor approval prior to effecting the agreed upon

changes. Any deviations should be reported to the sponsor and reported to the IRB/IEC according to the requirements of the IRB/IEC.

14.9 Changes to the Protocol

Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without prior written approval from the sponsor.

14.10 Confidentiality/Publication of the Study

All the data furnished to the investigator and his/her staff and all data obtained through this protocol will be regarded as confidential and proprietary in nature and will not be disclosed to any third party, except for the US Food and Drug Administration or other regulatory body, without written consent from the sponsor.

The results of the study may be published or presented by the Investigator(s) after the review by, and in consultation and agreement with the Sponsor, and such that confidential or proprietary information is not disclosed. Prior to submission for publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Sponsor or its designee for review and comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to the Sponsor products and activities receive fair, accurate, and reasonable presentation.

14.11 Study Termination

The sponsor reserves the right to discontinue the study overall or at a particular study site at any time for reasons including but not limited to:

- Emergence of effects that do not justify the benefit/risk relationship to the study population as a whole.
- Failure to comply with the protocol, GCP, or any other violation disturbing the appropriate conduct of the study.
- Failure to meet enrollment goals overall or at a particular study site.

If a study is terminated, the Sponsor will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects and their parents/legal guardians within a reasonable timeframe agreed upon by the Sponsor. All study materials must be collected and all eCRFs completed to the greatest extent possible

15 Data Handling and Record Keeping

15.1 Inspection of Records

Investigators must maintain detailed records on all study subjects who are enrolled in the study or who undergo screening. Data will be recorded in the subject's source documents and in applicable study logs provided by the sponsor. Source documents include subject's medical records, hospital charts, clinic charts, and the investigator's subject study files, as well as the results of diagnostic tests (eg, laboratory tests). All medical information obtained at each study visit must be recorded in the subject's source documentation in real time as it is collected and then entered onto the eCRF by site personnel.

Subject-completed forms such as diaries and questionnaires are also considered source data. Only subjects are to record information in subject diaries and questionnaires. In no instance, should an Investigator or study site personnel record any data or make changes to subject completed forms. The Investigator or designee should review subject-completed forms during study visits. If an entry is found to be illegible or a mistake is found (eg, an incorrect year was recorded), the subject should be instructed to edit the entry by drawing a single line through the original entry, entering the new information, dating, and writing subject's year of birth to acknowledge.

Upon study completion or at any other time specified by the sponsor or designee, the appropriate study documents must be submitted to the sponsor.

Telephone conversations and electronic mail with the subject, the sponsor, or the sponsor's designee concerning the study must be recorded or kept on file. All source documents must be made available to the sponsor and the sponsor's designated monitor upon request.

15.2 Case Report Forms

Subject data required by this protocol are to be recorded on eCRFs. Subject data recorded on eCRFs during the study will be documented in a coded fashion. The subject will only be identified by the subject number and by their year of birth if also required. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

The Investigator and study site personnel will be responsible for completing the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

The study monitor will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. The eCRFs will be submitted to Bausch + Lomb or its designee(s) for quality assurance review, and statistical analysis.

A copy of the eCRFs will be retained by the Investigator at the conclusion of the study, who must ensure that it is stored in a secure place

15.3 Retention of Records

The investigator should properly store and maintain all study records in accordance with sponsor directives. All records relating to the conduct of this study are to be retained by the investigator until notified by the sponsor in writing that the records may be destroyed.

16 References

1. Elewski BE. Onychomycosis: pathogenesis, diagnosis, and management. Clin Microbiol Rev. 1998;11(3):415-29.
2. Levy L. Epidemiology of onychomycosis in special-risk populations. J Am Podiatr Med Assoc. 1997;87(12):546-50.
3. Zaias N, Tosti A, Rebell G, Morelli R, Bardazzi F, Bieley H, et al. Autosomal dominant pattern of distal subungual onychomycosis caused by Trichophyton rubrum. J Am Acad Dermatol. 1996;34(2 Pt 1):302-4.
4. Trepanier EF, Amsden GW. Current issues in onychomycosis. Ann Pharmacother. 1998;32(2):204-14.
5. Gupta AK, Tu LQ. Therapies for onychomycosis: a review. Dermatol Clin. 2006;24(3):375 9.
6. Jublia (efinaconazole) topical solution, 10%. [US Prescribing Information]. Valeant Pharmaceuticals North America, LLC; 2014.

Clinical Study Protocol

Efinaconazole 10% Topical Solution

Protocol V01-108A-401

A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails

Development phase of study:	4
Study design:	Multicenter, open label, single-arm, safety and pharmacokinetics study
Date:	May 10, 2016
Amendment 1 Date:	December 05, 2016
Sponsor:	Dow Pharmaceutical Sciences, a wholly owned subsidiary of Valeant Pharmaceuticals International 1330 Redwood Way, Suite C Petaluma, CA 94954

CONFIDENTIAL

Nothing herein is to be disclosed without prior approval of the sponsor.

VALEANT
Research & Development

Protocol Review and Approvals

A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pbarmacokinetics ofEfinaconazole 10% Topical Solution in Subjects with Mild to Severe Onycbomycosis of the Toenails

Reviewed and approved:

[redacted]

[redacted]

12/9/11
Date

[redacted]

12/6/16
Date

[redacted]

06/2016
Date

[redacted]

DEC-6-2016
Date

Personnel Responsible for Conducting the Study

A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails

Sponsor
Dow Pharmaceuticals Sciences, a wholly owned subsidiary of
Valeant Pharmaceuticals International
1330 Redwood Way, Suite C
Petaluma, CA 94954

Contact for Reporting Serious Adverse Events
MedTrials Safety
Fax: [redacted]
Email : [redacted]

Return of Used and Unused Study Drug
Clinical Trial Materials
Supply Chain, Area 56
1400 North Goodman Street
Rochester, NY 14609

Contract Research Organization/Medical Monitor
MedTrials, Inc. CRO

[redacted]
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]

Principal Investigator Protocol Agreement Page

I agree:

- To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IEC) for the study protocol, written informed consent, consent form updates, subject-recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study.
- Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study.
- To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies).
- That I am thoroughly familiar with the appropriate use of the investigational products(s), as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current Investigator Brochure or equivalent document and approved product label (if applicable).
- To provide sufficient time and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions.

_____

Principal Investigator (print name)

_____ _____

Principal Investigator (signature) Date

2 Synopsis

Name of Sponsor/Company: **Dow Pharmaceuticals Sciences, a wholly owned subsidiary of Valeant Pharmaceuticals International**
Name of investigational product: Efinaconazole 10% Topical Solution
Name of active ingredient: Efinaconazole
Title of study: A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails
Number of clinical centers: Approximately 20-25 investigational centers in the United States, and the Caribbean
Objectives: The primary objectives of this study are to evaluate: 1) safety of once daily topically administered efinaconazole 10% for 48 weeks in pediatric subjects (6-16 years 11 months of age) with at least mild onychomycosis of the toenails, and 2) pharmacokinetics PK (4 weeks) of once daily topically administered efinaconazole 10% in pediatric subjects (12-16 years 11 months of age) with moderate to severe onychomycosis of the toenails.
Methodology: This is an open label, single-arm study designed to evaluate the safety and PK of a once daily topical application of efinaconazole in the treatment of pediatric subjects with mild to severe onychomycosis of the toenails. The study will include subjects 6 to 16 years of age, inclusive, but PK assessments will only be performed on subjects 12 to 16 years of age, inclusive (referred to throughout the protocol as the PK subset). All subjects must have onychomycosis of at least 1 great toenail; subjects in the PK subset must have onychomycosis of both great toenails and at least 4 other toenails. Efforts will be made to enroll subjects into the PK subset such that the subjects are evenly distributed across the required age range. For subjects not participating in the PK subset, the study will consist of 14 scheduled visits, including Screening (up to Day -42), Baseline (Day 1), 12 treatment visits (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). Subjects included in the PK subset will attend the scheduled visits up to Week 4 and an additional study visit at Day 29 for collection of the final PK blood sample. The PK assessments will be performed under maximal use conditions. Once PK assessments are complete at Day 29, the PK subset of subjects will continue treatment through week 48 with additional visits at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). At the Screening Visit, subjects and/or their parents/legal guardians will sign an informed consent/assent form and a photography consent/assent form, provide their medical histories, report their previous and concomitant medications, and be evaluated against the inclusion/exclusion criteria. Females of childbearing potential (FOCBP) will have urine pregnancy tests performed. During this visit, subjects will undergo an examination of their feet to visually ascertain the presence of onychomycosis in at least 1 great toenail for subjects not included in the PK assessments, and on both great toenails and at least 4 other toenails for subjects included in the PK assessments. Additionally, the percent involvement of the affected great

toenail(s) will be recorded. Specimen will be obtained from the great toenail(s) to ship to the mycology lab. Both toenails may be sampled if both are suspected of manifesting onychomycosis (at least 20% involvement). Blood and urine specimens will be collected for serum chemistry, hematology, and urinalysis evaluations. At relevant post-Screening Visits, the target great toenail will be trimmed back to the distal groove before the clinical evaluations are performed and before photographs are taken.

At the Baseline Visit (which should be scheduled after KOH and fungal culture results have been obtained from the mycology lab), subjects and/or their parents/legal guardians will update their medical histories and concomitant medication uses, and the inclusion/exclusion criteria will be confirmed. Subjects will undergo abbreviated physical examinations, clinical laboratory evaluations, assessments of vital signs (sitting blood pressure, respiration, pulse, and temperature), and measurements of height and weight. All FOCBP will have urine pregnancy tests performed. For the purposes of efficacy assessments, 1 target great toenail will be selected from the study-eligible great toenail(s), including subjects in the PK subset for whom both great toenails must be involved. Where both great toenails are study-eligible, the toenail with the greater percent of affected area will be selected for mycologic data and for inclusion in the efficacy analysis. In the instance where the percent of affected area is the same for both study-eligible great toenails, the investigator may select either great toenail as the target toenail. The target great toenail will be identified and recorded for each subject, photographs of the target great toenail will be obtained, and a transverse notch will be inscribed in the target great toenail adjacent to the proximal toenail fold (as a marker for measuring toenail growth at subsequent visits). Assessments of all other nontarget toenails, including the other involved toenails of subjects in the PK subset, will also be conducted to assess the presence or absence of onychomycosis on each toenail. This assessment will continue throughout the study visits through week 52.

After confirming eligibility at the Baseline Visit, subjects will be enrolled in the treatment period. Subjects or their parents/legal guardians will apply the first dose of study drug to the qualified toenails at the investigational center under the supervision of designated study personnel. Any local skin reactions that occur at the study drug application site, along with any adverse events (AEs), will be recorded. Subjects or their parents/legal guardians will receive weighed study drug bottles and given verbal and written instructions for treatment application. Specifically, subjects who are not included in the PK subset will be instructed to apply the study drug to the affected toenails once daily at bedtime for 48 weeks. Subjects who are included in the PK subset will be instructed to apply the study drug to all 10 toenails once daily at bedtime for 4 weeks. Following the PK blood collections on Days 28 and 29, these subjects will be instructed to continue treatment with study drug to only the affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). All subjects or their parents/legal guardians will also receive diaries, withinstructions to complete a record of all applications and to note any missed applications of the study drug.

Subjects in the PK subset will not apply study drug the night prior to the Week 4 (Day 28) visit. Following the Day 28 study procedures, subjects in the PK subset will undergo timed blood collections to assess plasma concentrations of efinaconazole and metabolites (H3 and H4). Assessments will require collection of approximately 4 mL of whole blood at each time point (approximately 20 mL total). Within 1 hour after the predose blood sample is drawn, the subjects/parents/legal guardians will apply study drug to all 10 toenails at the investigational center. Subsequent blood collections will occur 2, 4, and 12 hours postdose on Day 28. The subjects will go home after Day 28, but will not apply study drug on the night of the Day 28 visit. PK subjects will return to the investigational center the following day (Day 29) for collection of a 24-hour postdose blood sample. PK subjects will continue treatment with study drug to only the target great toenail and the other affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52).

Safety will be assessed by reviewing the occurrence of AEs and local skin reactions, assessing vital sign measurements and abbreviated physical examination findings, and noting any additions or changes in concomitant medication uses. Blood samples will be collected at Screening and Week 48 for routine safety laboratory evaluations (serum chemistry, hematology, and urinalysis); urine pregnancy tests will be obtained for all FOCBP at each study visit. Efficacy assessments will be performed throughout the study. The efficacy analyses will be based on microscopic examination and mycological culture results for the target great toenail, the percent involvement of the target great toenail, the length of the unaffected part of the target great toenail, the growth of the target great toenail, and the number of affected nontarget toenails.

Note that growth of the target great toenail will be measured by inscribing a transverse notch, at the center of the toenail, in the toenail adjacent to the proximal toenail fold at Baseline and measuring toenail growth from that point forward. At every subsequent visit, the distance between the proximal toenail fold and the notch will be measured and recorded. A new notch will be inscribed in the toenail adjacent to the proximal toenail fold if the initially applied notch grows out during the course of the study.

A post-treatment follow-up visit will occur 4 weeks after the last treatment visit for each subject (ie, at Week 52). Subjects who discontinue from the study prior to Week 48 will complete the Week 48 study procedures.

Number of subjects planned:

Approximately 60 subjects total

Approximately 20 subjects in the PK subset

Diagnosis and criteria for inclusion:

1. Male or female subjects of any race, 6 to 16 years of age (inclusive) at Screening.
    - **PK Subset:** Male or female subjects of any race, 12 to 16years of age (inclusive) at Screening.
2. Verbal and written informed consent/assent obtained from the subject and/or their parent or legal guardian.
3. Good general health, as assessed by the investigator, based on the subject's medical history, physical examination, and safety laboratory tests.
4. At least 1 great toenail (the "target great toenail") with clinically diagnosed distal lateral subungual onychomycosis involving at least 20% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. There is no specific upper limit for percent involvement. Up to 6 toenails may have onychomycosis.
    - **PK Subset:** Both great toenails with clinically diagnosed distal lateral subungual onychomycosis involving at least 50% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. There is no specific upper limit for percent involvement. Subjects must also have at least 4 toenails other than the great toenails with onychomycosis.
5. Target great toenail for all subjects, and both great toenails for subjects in the PK subset, must have evidence of toenail growth, per subject's report that monthly clipping is needed.
6. Within 42 days prior to the Baseline (Day 1) Visit, have a positive KOH examination (results will be provided by the central mycology lab) of the target great toenail for all subjects,
7. Within 42 days prior to the Baseline (Day 1) Visit, have a positive dermatophyte culture for *Trichophyton rubrum* or *Trichophyton mentagrophytes* (at the central mycology laboratory) from the target great toenail in all subjects
    - **PK Subset:** Prior to the Baseline Visit, the great toenail designated for efficacy assessments as the target great toenail must have both a positive KOH examination (results will be provided by the central mycology lab) and a positive fungal culture.
8. All FOCBP must have a negative urine pregnancy test at the Screening and Baseline Visits and must agree to use an effective method of contraception throughout the study. Effective contraception is defined as use of an intrauterine device, condom with spermicide, diaphragm with spermicide, abstinence (subject is not sexually active), or stable use of a hormonal contraceptive (oral, implant, injection, or transdermal patch) for at least 3 months prior to the Baseline Visit.
9. Subjects and their parents/legal guardians are willing to comply with study instructions and return to the investigational center for all required visits (a visit schedule with the length of each visit will be provided to ensure that the subject can meet the requirements and have adequate transportation).

10. Subject and their parents/legal guardians agree that the subject will avoid the use of toenail polish, cosmetic toenail products, and pedicures during the study period.

Exclusion criteria:

1. Females who are pregnant, nursing an infant, or planning a pregnancy during the study period.
2. History of immunosuppression and/or clinical signs indicative of possible immunosuppression, as determined by the investigator, or known human immunodeficiency virus infection.
3. History of diabetes that is uncontrolled as determined by the investigator (diabetes that is controlled by diet or medication does not exclude a subject).
4. Presence of any toenail infection other than or in addition to dermatophytes, such as *Scytalidium* as determined by the investigator (candidal onychomycosis infection, concurrent with a positive dermatophyte culture, is acceptable).
5. Presence of any of the following: dermatophytoma, fungal "spikes" within 3 mm of the proximal toenail fold on the target great toenail, infection extending to the matrix, or only lateral toenail disease in the target great toenail.
6. Presence of severe moccasin tinea pedis at the Screening or Baseline Visits, as determined by the investigator. (If the subject has interdigital tinea pedis that requires treatment, the subject must agree to use only an investigator-approved topical antifungal therapy).
7. Presence of any disease/condition that might cause toenail abnormalities or may interfere with the evaluation of the study drug as determined by the investigator (eg, open sores or ulceration on the toes of affected toenails, psoriasis, immune dysfunction, collagen-vascular diseases, lichen planus, peripheral vascular disease, or traumatic onychodystrophy due to chronic physical stimuli).
8. Any previous surgery on the target great toenail.
9. Presence of onychomycosis of the fingernail.
10. History of immunodeficiency as determined by the investigator.
11. Presence of 1-hand, 2-foot syndrome, or fingernail dermatophytosis.
12. Target great toenail (including toenail plate and any subungual debris) thicker than 3 mm at the Screening and Baseline Visits.
13. Presence of onychodystrophy that could interfere with clinical assessments as determined by the investigator.
14. History of hypersensitivity or allergic reactions to azole derivatives or any of the study drug constituents.
15. Presence of any underlying disease that, in the opinion of the investigator, could present a safety concern for the subject by participating in the study.
16. Subject has received treatment for any type of cancer in the previous 6 months, except for nonmelanoma skin cancer (eg, basal cell carcinoma or nonmetastatic squamous cell carcinoma) that was treated successfully.
17. Presence of any dermatological condition on the feet that could interfere with clinical evaluations as determined by the investigator.
18. Presence of any underlying disease or dermatological condition other than onychomycosis that requires the use of interfering topical or systemic therapy and would make evaluations inconclusive as determined by the investigator, or subject requires treatment with a topical product on the toenails other than the study drug during the study.
19. Subjects using the following topical preparations within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following topical preparations during the study:
    - Toenail polish or cosmetic toenail products: 1 day
    - Other topical prescription or over-the-counter medications to the toenails (with the exception of bland emollients): 2 weeks

- Topical prescription or over-the-counter antifungal therapy for the toenails, including devices to treat onychomycosis: 4 weeks

20. Subjects using the following systemic medications within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following systemic medications during the study:
    - Systemic antifungal therapy: 4 weeks
    - Systemic immunosuppressive agents: 6 months
21. Subject has previously been nonresponsive to systemic antifungal therapy for onychomycosis.
22. Subject is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
23. Use of any investigational drug or device within 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit, or concurrent participation in another clinical study with an investigational drug or device.

Investigational product, dosage and mode of administration:

Investigational Drug: Efinaconazole 10% Solution (efinaconazole)

Dosing for Subjects NOT Included in the PK Subset: Subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) (if any) once daily at bedtime. Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be given instructions regarding how to apply the study drug, ie, by completely covering the target great toenail, including the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate. The study drug will be applied to each of the other infected toenails in a similar manner.

Dosing for Subjects Included in the PK Subset:

Days1 to 28 - Subjects and their parents/legal guardians will be instructed to apply study drug to all 10 toenails, once daily at bedtime for 4 weeks. During this period, all PK subjects will be instructed to apply the study drug by completely covering each toenail and 0.5 cm of adjacent skin, including the toenail folds, toenail bed, hyponychium, undersurface of the toenail plate. The subjects will not apply study drug the night prior to the Week 4 (Day 28) visit, nor will they apply study drug on the night of the Week 4/Day 28 Visit. Within 1 hour after the predose blood sample is drawn on Day 28, subjects and/or their parents/legal guardians will apply study drug to all 10 toenails in the manner described above at the investigational center.

Days 29 to Week 48:

After completion of the PK portion of the study, subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) once daily at bedtime. Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be given instructions regarding how to apply the study drug, ie, by completely covering the target great toenail, including the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate (if onychomycosis is present). The study drug will be applied to each of the other infected toenails in a similar manner.

Mode of Administration:

Topical application: the subjects will apply the study drug to their toenail(s), the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate. The subjects and their parents/legal guardians will be instructed to wait for the toenails to air-dry thoroughly before touching with clothing.

Duration of treatment:

48 weeks

Reference therapy, dosage and mode of administration:

Not applicable

Criteria for evaluation:

Safety:

Adverse events will be collected as spontaneous reports by the subjects and as observations by the investigators. The collection of AEs should begin following the subject's completion of the consent/assent process to participate in the study.

Local skin reactions (redness, swelling, burning, itching, and vesiculation) will be reviewed with the subject starting at the Baseline Visit (after study drug application at the investigational center) and continuing through the last study visit. The presence or absence of burning, itching, and vesiculation will be reported simply as "yes" or "no". The worst instances of redness and swelling observed since the previous study visit will be reported using a 4-point scale (where 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe).

Blood and urine samples will be collected for routine clinical laboratory tests (hematology, serum chemistry, and urinalysis) within the 42 day Screening visit window and at Week 48. Any clinically significant abnormalities in safety laboratory test results that are present at the last treatment visit (Week 48/Early Termination) will be followed to resolution (ie, return to normal values or to the baseline state) or until clinically stable as determined by the investigator.

Vital sign measurements (sitting blood pressure, respiration, pulse, and temperature) will be obtained at Baseline and Weeks 12, 24, 36, and 48. An abbreviated physical examination will be performed at Baseline and Week 48; as part of the examination, height and weight will be measured at Baseline and Week 48.

Urine pregnancy tests will be performed for all FOCBP at the Screening Visit and at each subsequent study visit. If a subject becomes pregnant during the treatment period, the study drug will be discontinued immediately, the subject will be discontinued from the study, and the investigator will notify the sponsor. The pregnancy will be followed to term with the outcome reported to the sponsor.

Efficacy will be assessed to evaluate compliance with treatment as part of the safety assessment. The efficacy variables evaluated in this study include microscopic KOH examination and mycological culture outcomes of the target great toenail, percent involvement of the target great toenail, growth of the target great toenail, and assessments of the nontarget toenails.

Pharmacokinetics: Concentrations of efinaconazole and metabolites (H3 and H4), along with other relevant PK parameters, will be assessed based on blood samples collected at Days 28 and 29. The specific collection time points are predose on Day 28 and 2, 4, 12, and 24 hours postdose.

Photography:

Close-up photographs of the subject's target great toenail will be used for documentation purposes only and will not be used for determinations of eligibility or any study-related activities.

Statistical Methods:

Safety:

All subjects who receive at least 1 confirmed dose of study drug will be included in the safety analysis set. No imputations will be made for missing safety data. The primary safety objective will be considered met when approximately 40 evaluable subjects have been treated for 48 weeks.

All AEs occurring during the study will be recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are those AEs with an onset on or after the date of first study drug application. All TEAEs will be summarized by the number of subjects reporting each TEAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the Safety, PK and Non-PK populations. Each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category.

Serious adverse events (SAEs) will be summarized by the number of subjects reporting each SAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the Safety, PK and Non-PK populations.

Local skin reaction scores (redness, swelling, burning, itching, and vesiculation) at each study visit will be summarized using frequency tables for the Safety, PK and Non-PK populations. Additionally, redness and swelling severity scores will be summarized using descriptive statistics (mean, standard deviation [SD], median, and minimum and maximum). Subjects with a severity score worse than baseline will also be summarized at each postbaseline study visit. The worst score and the last score during the post-baseline period will also be summarized.

Results of safety laboratory parameters and vital sign measurements will be summarized at each study visit using descriptive statistics or frequencies and percentages, as appropriate, for the Safety, PK and Non-PK populations. Changes from baseline in safety laboratory values will be summarized by treatment group at Week 48 using descriptive statistics. In addition, changes from baseline in safety laboratory values will be summarized using shift tables according to normal ranges.

This study's primary object is to assess the safety of the study drug. Descriptive efficacy statistics for the endpoints will assist in evaluating compliance with treatment for the purposes of safety assessment.

The efficacy endpoints include the following:

- Complete Cure, defined as 0% clinical involvement of the target toenail and negative KOH and fungal culture at Week 52
- Complete or Almost Complete Cure at Week 52, defined as :: 5% toenail involvement
- Clinical Efficacy rate at Week 52, defined as an affected target great toenail area of < 10%
- Mycologic Cure rate at Week 52, defined as a negative KOH examination and a negative fungal culture of the target great toenail sample

The Complete Cure rate, the Complete or Almost Complete Cure rate, the Clinical Efficacy rate, and the Mycologic Cure rate will be presented using descriptive statistics (sample size n, frequency counts and percentages) for the Safety, PK and Non-PK populations. In addition, the growth of the target great toenail at each study visit and the change from baseline in the number of affected nontarget toenails will be descriptively summarized.

A last observation carried forward (LOCF) imputation will be used to impute missing values for the efficacy variables at Week 52. No sensitivity analyses will be conducted.

Any subjects remaining (i.e., have not been treated for 48 weeks) will be followed until completion. The final report will be amended with data on these subjects.

Pharmacokinetics:

All subjects in the PK subset who receive at least 1 confirmed dose of study drug and have any PK data on Days 28 and 29 will be included in the PK analysis set. Blood samples will be tested for plasma concentrations of efinaconazole and metabolites (H3 and H4). No imputations will be made for missing data.

Plasma concentrations that are reported as below the limit of quantitation (BLQ) in the data transfer file will be set to zero for the summaries of concentrations as well as calculation of PK parameters. Missing values will be treated as if they were never drawn. Plasma concentrations of efinaconazole and metabolite (H3 and H4) and PK parameters will be summarized using descriptive statistics (n, mean, SD, standard error of the mean [SEM], coefficient of variation [CV], median, minimum, and maximum). Geometric means will also be used to summarize C_{max}, C_{min}, $AUC_{(0-t)}$ and $AUC_{(0-24h)}$.

The mean plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will be presented graphically for Days 28 and 29 in both linear and logarithmic scales. Individual subject plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will also be created.

Plasma PK parameters for efinaconazole and metabolites (H3 and H4) will be calculated using noncompartmental analysis. The PK parameters will be calculated for each subject using actual sampling times. The maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) will be taken directly from the data.

The following PK parameters will be calculated from the individual plasma concentrations on Days 28 and 29 when possible:

- C_{max} (observed peak drug [efinaconazole and metabolites] concentration)
- T_{max} (time at which C_{max} occurs)
- C_{min} (observed minimum drug concentration)
- AUC_{0-t} (area under the concentration-time curve from time 0 up to the samplingtime corresponding to the last quantifiable concentration)
- AUC_{0-24h} (area under the concentration-time curve from time 0 through 24hours [corresponding to the dosing interval])

Additional PK parameters may be calculated as appropriate.

The PK objectives will be considered met when approximately 16 evaluable subjects are treated under maximal use conditions through day 28 of the PK evaluation.

Sample size calculations:

Approximately 60 subjects will be enrolled and receive treatment with study drug. Approximately 20 of the subjects will be enrolled in the PK subset. These sample sizes were based on PK and clinical considerations; no formal sample size calculation was performed. The numbers of planned subjects are considered adequate for determining the safety profile and the PK parameters of efinaconazole in a pediatric population of subjects aged 6 to 16 years 11 months with mild to severe onychomycosis of the toenails.

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4 List of Abbreviations and Definitions of Terms

Abbreviation or Specialist Term	Definition or Explanation
AE	Adverse event
AUC_{0-24h}	Area under the concentration-time curve from time 0 through 24 hours (corresponding to the dosing interval)
AUC_{0-t}	Area under the concentration-time curve from time 0 up to the sampling time corresponding to the last quantifiable concentration
C_{max}	Observed peak drug concentration
C_{min}	Observed minimum drug concentration
eCRF	Electronic case report form
Efinaconazole	Efinaconazole 10% Solution
FOCBP	Females of childbearing potential
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KOH	Potassium hydroxide
LOQ	Limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
T_{max}	Time at which the observed peak drug concentration occurs
US	United States

5 Introduction

Onychomycosis is a chronic and recurring fungal infection of the fingernails or toenails that accounts for about half of all nail disorders. Onychomycosis is usually caused by dermatophytes, either *Trichophyton rubrum* (71%) or *Trichophyton mentagrophytes* (20%). The prevalence of onychomycosis in the United States (US) may be as large as 13%, with the infection observed predominantly in elderly patients (60%) [1, 2]. Onychomycosis of the toenail can result in permanent toenail deformity and has a significant impact on quality of life due to concerns with the appearance of the toenails and interference with wearing shoes, walking, and participating in various sports activities [3, 4].

Cure rates for topical treatments have been significantly lower than currently available systemic medications [5], presumably because they bind strongly to keratin and do not adequately penetrate the nail unit. However, while effective, oral therapy is limited by safety concerns due to systemic exposure. For example, both oral itraconazole and oral terbinafine have the potential to cause drug-drug interactions and hepatotoxicity. Efinaconazole 10% Solution (efinaconazole) has a low affinity for keratin binding and has a higher binding reversibility than that of other reference drugs. Therefore, efinaconazole appears to be a promising antifungal compound for the topical treatment of onychomycosis.

Efinaconazole is a novel triazole antifungal agent that is active in vitro against a wide range of pathogenic fungi and is expected to be effective in the treatment of mild to moderate onychomycosis.

Efinaconazole has been shown to be efficacious in vitro against a panel of fungal species that invade human skin, hair, and nails including dermatophytes Trichophyton, Microsporum, Epidermophyton, and the yeast, Malassezia species, responsible for tinea unguium (onychomycosis), tinea corporis, tinea pedis, tinea capitis, and pityriasis versicolor. Efinaconazole has been shown to be fungicidal against *Candida albicans* and other Candida species responsible for the major yeast (nondermatophyte) form of onychomycosis and cutaneous candidiasis. In vitro studies against dermatophytes showed that efinaconazole was more potent than clotrimazole, but less potent than butenafine.

Efinaconazole has successfully treated experimentally induced dermal candidiasis, tinea corporis, tinea pedis, and tinea unguium in vivo in guinea pig models. It has generally out performed reference drugs in these models, and in particular out performed the marketed drugs for tinea unguium: ciclopirox olamine (approved for the topical treatment of onychomycosis in the US), amorolfine (available outside the US as a topical nail lacquer), and terbinafine (available in the US in oral form).

The safety and efficacy of once daily use of efinaconazole for the treatment of onychomycosis of the toenail were assessed in two 52-week prospective, multicenter, randomized, double-blind clinical studies. These studies were conducted in subjects 18 to 70 years of age with 20% to 50% clinical involvement of the target great toenail, without dermatophytomas or lunula (matrix) involvement (n = 870 in Study 1 and n = 781 in Study 2) [6]. These studies evaluated 48-weeks of treatment with efinaconazole relative to vehicle solution. At Week 52 (4-weeks after completion of therapy), efinaconazole was superior to vehicle solution in both studies and thus demonstrated efficacy in the treatment of onychomycosis. The most common adverse reactions (ie, reactions with incidences > 1%) reported in the studies were ingrown toenails, application site dermatitis, application site vesicles, and application site pain.

Efinaconazole was approved by the US Food and Drug Administration in June 2014 for the topical treatment of onychomycosis of the toenail(s) due to *T rubrum* and *T mentagrophytes* (Julia® [efinaconazole] topical solution, 10% [6]). The approved drug is intended for topical application to affected toenails once daily for 48 weeks. During application, the toenail, toenail folds, toenail bed, hyponychium, and undersurface of the toenail plate are to be completely covered.

The current clinical study is designed to evaluate the safety and pharmacokinetics (PK) of once daily topical application of efinaconazole in the treatment of pediatric subjects with mild to severe onychomycosis of the toenails. Application and use of the study drug is consistent with the approved package insert. The evaluations included in the current study are consistent with the evaluations conducted in the development of the approved drug.

6 Study Objectives and Purpose

The primary objectives of this study are to evaluate: 1) safety of once daily topically administered efinaconazole 10% for 48 weeks in pediatric subjects (6-16 years, 11 months of age) with at least mild onychomycosis of the toenails, and 2) pharmacokinetics PK (4 weeks) of once daily topically administered efinaconazole 10% in pediatric subjects (12-16 years, 11 months of age) with moderate to severe onychomycosis of the toenails.

7 Investigational Plan

7.1 Investigators and Study Administrative Structure

Approximately 20-25 investigational centers are planned to participate in this study. Each clinical investigator will be required to provide a copy of his/her curriculum vitae and medical license, complete a financial disclosure statement, and generate a list of study personnel who will be involved in the study, with a summary of their roles and qualifications.

The Sponsor has designated a Contract Research Organization to assume responsibility for activities related to the conduct of the study. The Sponsor also has designated central laboratories to analyze biological samples related to clinical safety, pharmacokinetics, and mycology. A listing of the organizations involved in the conduct of the study is provided under Personnel Section in the front of the protocol. A complete description of the Sponsor's and delegates' study-related roles/responsibilities, including key personnel, is contained within the Sponsor's study project plan.

7.2 Summary of Study Design

This is an open label, single-arm study designed to evaluate the safety and PK of a once daily topical application of efinaconazole in the treatment of pediatric subjects with mild to severe onychomycosis of the toenails. The study will include a total of 60 subjects, 40 of whom will be 6 to 16 years of age, inclusive, and PK assessments will be performed on approximately 20 subjects 12 to 16 years of age, inclusive (referred to throughout the protocol as the PK subset). All subjects must have onychomycosis of at least 1 great toenail; subjects in the PK subset must have onychomycosis of both great toenails and at least 4 other toenails. Efforts will be made to enroll subjects into the PK subset such that the subjects are evenly distributed across the required age range.

For subjects not participating in the PK subset, the study will consist of 14 scheduled visits, including Screening (up to Day -42), Baseline (Day 1), 12 treatment visits (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). Subjects included in the PK subset will attend the scheduled visits up to Week 4 (Day 28) and an additional study visit at Day 29 for collection of the final PK blood sample. The PK assessments will be performed under maximal use conditions. Once PK assessments are complete at Day 29, the PK subset of subjects will continue treatment through week 48 with visits at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48, and a 4-week post-treatment follow-up visit (Week 52).

At the Screening Visit, subjects and their parents/legal guardians will sign an informed consent/assent form and a photography consent/assent form, provide their medical histories, report their previous and concomitant medications, and be evaluated against the inclusion/exclusion criteria. Females of childbearing potential (FOCBP) will have urine pregnancy tests performed. During this visit, subjects will undergo an examination of their feet to visually ascertain the presence of onychomycosis in at least 1 great toenail for subjects not included in the PK assessments, and on both great toenails and at least 4 other toenails for subjects included in the PK assessments. Additionally, the percent involvement of the affected great toenail(s) will be recorded. Specimen will be obtained from the great toenail(s) to ship to the mycology lab. Both toenails may be sampled if both are suspected of

manifesting onychomycosis (at least 20% involvement). Blood and urine specimens will be collected for serum chemistry, hematology, and urinalysis evaluations. At relevant post-Screening Visits, the target great toenail will be trimmed back to the distal groove before the clinical evaluations are performed and before photographs are taken.

If a subject fails screening, either at the Screening or Baseline visit (prior to enrollment to treatment), the subject may be rescreened at a later date. Subjects who are rescreened, will be assigned a new screening number, must be re-consented, and undergo all screening procedures per protocol.

At the Baseline Visit (which should be scheduled after KOH and fungal culture results have been obtained from the mycology lab), subjects and/or their parents/legal guardians will update their medical histories and concomitant medication uses, and the inclusion/exclusion criteria will be confirmed. Subjects will undergo abbreviated physical examinations, clinical laboratory evaluations, assessments of vital signs (sitting blood pressure, respiration, pulse, and temperature), and measurements of height and weight. All FOCBP will have urine pregnancy tests performed. For the purposes of efficacy assessments, 1 target great toenail will be selected from the study-eligible great toenail(s), including subjects in the PK subset for whom both great toenails must be involved. Where both great toenails are study-eligible, the toenail with the greater percent of affected area will be selected for mycologic data and for inclusion in the efficacy analysis. In the instance where the percent of affected area is the same for both study-eligible great toenails, the investigator may select either great toenail as the target toenail. The target great toenail will be identified and recorded for each subject, photographs of the target great toenail will be obtained, and a transverse notch will be inscribed in the target great toenail adjacent to the proximal toenail fold (as a marker for measuring toenail growth at subsequent visits). Assessments of all other nontarget toenails, including the other involved toenails of subjects in the PK subset, will also be conducted to assess the presence or absence of onychomycosis on each toenail. This assessment will continue throughout the study visits through week 52.

After confirming eligibility at the Baseline Visit (Day 1), subjects will be enrolled in the treatment period. Subjects or their parents/legal guardians will apply the first dose of study drug to the qualified toenails at the investigational center under the supervision of designated study personnel. Any local skin reactions that occur at the study drug application site, along with any adverse events (AEs), will be recorded. Subjects and their parents/legal guardians will receive weighed study drug bottles and given verbal and written instructions for treatment application. Specifically, subjects who are not included in the PK subset will be instructed to apply the study drug to the affected toenails once daily at bedtime for 48 weeks.

Subjects who are included in the PK subset will be instructed to apply the study drug to all 10 toenails once daily at bedtime for 4 weeks. Following the PK blood collections on Days 28 and 29, these subjects will be instructed to continue treatment with study drug to only the affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). All subjects or their parents/legal guardians will also receive diaries, with instructions to complete a record of all applications and to note any missed applications of the study drug.

Subjects in the PK subset will not apply study drug the night prior to the Week 4 (Day 28) visit. Following the Day 28 study procedures, subjects in the PK subset will undergo timed blood collections to assess plasma concentrations of efinaconazole and metabolites (H3 and H4). Assessments will require collection of approximately 4 mL of whole blood at each time point (approximately 20 mL total). Within 1 hour after the predose blood sample is drawn, the subjects/parents/legal guardians will apply study drug to all 10 toenails at the investigational center. Subsequent blood collections will occur 2, 4, and 12 hours postdose on Day 28. The subjects will go home after Day 28, but will not apply study drug on the night of the Day 28 visit. PK subjects will return to the investigational center the following day (Day 29) for collection of a 24-hour postdose blood sample. PK subjects will continue treatment with study drug to only the target great toenail and the other affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52).

Safety will be assessed by reviewing the occurrence of AEs and local skin reactions, assessing vital sign measurements and abbreviated physical examination findings, and noting any additions or changes in concomitant medication uses. Blood samples will be collected at Screening and Week 48 for routine safety laboratory evaluations (serum chemistry, hematology, and urinalysis); urine pregnancy tests will be obtained for all FOCBP at each study visit. Efficacy assessments will be performed throughout the study. Efficacy analyses will be based on microscopic examination and mycological culture results for the target great toenail, the percent involvement of the target great toenail, the length of the unaffected part of the target great toenail, the growth of the target great toenail, and the number of affected nontarget toenails.

A post-treatment follow-up visit will occur 4 weeks after the last treatment visit for each subject who continues through Week 48 (ie, at Week 52). Subjects who discontinue from the study prior to Week 48 will return to complete the Week 48 study procedures.

The study design and schedule of assessments is presented in Table 1.

Table 1: Study Design and Schedule of Assessments

		Treatment Period														Post-Treatment
Visit	1-SCR	2-BL	3	3A [a]	4	5	6	7	8	9	10	11	12	13	14 [b]	15
Week	Up to Day -42	Day 1	4 (Day 28)	4 (Day 29)	8	12	16	20	24	28	32	36	40	44	48	52
PROCEDURES																
Obtain Informed Consent/Assent and Photography Consent/Assent	X															
Review Medical History	X	X [c]														
Review Previous Therapies	X	X [c]														
Review Inclusion/Exclusion Criteria	X	X [c]														
Conduct Urine Pregnancy Test (all females of childbearing potential) [d]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Clip Toenails [e]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Notch Target Great Toenail [f]		X														
Measure Target Great Toenail Growth (from the PNF to the notch) [f]			X		X	X	X	X	X	X	X	X	X	X	X	X
Conduct Target Great Toenail Assessments [g]	X	X				X			X			X			X	X
Conduct Nontarget Toenail Assessments [h]	X	X				X			X			X			X	X
Obtain Photography		X							X						X	X
Perform KOH Examination [i]	X					X			X			X			X	X
Sample for Fungal Culture [i]	X					X			X			X			X	X
Conduct Abbreviated Physical Exam [j]		X													X	
Obtain Vital Signs [k]		X				X			X			X			X	

		Treatment Period														Post-Treatment
Visit	1-SCR	2-BL	3	3A [a]	4	5	6	7	8	9	10	11	12	13	14 [b]	15
Week	Up to Day -42	Day 1	4 (Day 28)	4 (Day 29)	8	12	16	20	24	28	32	36	40	44	48	52
PROCEDURES																
Collect Blood and Urine Samples for CBC/Diff, Chemistry, and Urinalysis	X [p]														X [l]	
Enroll Qualified Subjects		X														
Review Dosing Instructions		X	X		X	X	X	X	X	X	X	X	X	X		
Apply First Dose in Clinic		X														
Weigh/Dispense Study Drug		X	X [n]		X	X	X	X	X	X	X	X	X	X		
Apply Study Drug		X [q]	◄	———	———	———	———	———	———	———	———	———	———	———	►	
Collect/Weigh Study Drug			X		X	X	X	X	X	X	X	X	X	X	X	
Review Compliance			X		X	X	X	X	X	X	X	X	X	X	X	
Dispense Diary		X	X [o]		X	X	X	X	X	X	X	X	X	X		
Collect/Review Diary			X		X	X	X	X	X	X	X	X	X	X	X	
PK Blood Sample Collection [m]			X [m]	X [m]												
Review Local Skin Reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exit Study																X

Abbreviations: BL = Baseline Visit; CBC/Diff = complete blood count/differential; KOH = potassium hydroxide; PK = pharmacokinetic; PNF = proximal toenail fold; SCR = Screening Visit

Note: Post-baseline visits are to be scheduled in reference to Visit 2 (Baseline Visit) and within a window of ± 5 days.

[a] Visit 3A (Day 29) is only to be conducted for subjects in the PK subset.

[b] All Week 48 procedures are to be completed for subjects who discontinue from the study during the treatment period (ie, Early Termination).

[c] Confirmation of evaluations conducted at the Screening Visit.

[d] Urine pregnancy tests are required to have a minimum sensitivity of 25 mIU of human chorionic gonadotropin per mL of urine.
[e] Toenails are clipped prior to conducting the assessments.
[f] The transverse notch inscribed at the Baseline Visit is enhanced, as needed, at subsequent visits to allow continued measurement of toenail growth over the course of the study. In cases where the initial notch grows out or is clipped away, a new notch is inscribed in the toenail adjacent to the proximal toenail fold and measurements of toenail growth (ie, proximal toenail fold to notch) will continue using the new notch.
[g] Assessments include calculation of the percent involvement of the toenail affected by onychomycosis and measurement of the distance from the proximal toenail fold to the proximal onychomycotic border.
[h] Assessment of nontarget nails for presence or absence of onychomycosis.
[i] At the Screening visit, KOH specimens for KOH and fungal cultures will be shipped to the mycology lab. At all subsequently indicated study visits, specimens for KOH examinations and fungal cultures are obtained from the target great toenail.
[j] The abbreviated physical examination at the Baseline Visit and Week 48 includes height and weight,
[k] Vital sign measurements at each visit include temperature, pulse, respirations, and sitting blood pressure.
[l] Any clinically significant laboratory abnormality present at Week 48 (or Early Termination) is to be followed to resolution or until clinically stable as determined by the investigator.
[m] A subset of enrolled subjects will be assigned to PK evaluations. At the Week 4/Day 28 Visit, subjects in the PK subset will undergo timed blood sampling on Days 28 to 29 as follows:
n Study drug should be weighed and dispense at Visit 3A for PK subjects
o Diary should be dispensed with study drug at Visit 3A for PK subjects.
[p] Collection of Screening safety labs may be postponed until after positive Screening mycology results are received, only if the subject/parent are willing to return to the research site for safety lab collection prior to the end of the 42-day screening window. Screening safety lab results must be received within the 42-day screening visit window.
[q] The subject or their parent/legal guardian will apply the first dose of study drug in the investigational center, with guidance from study staff.

Visit	3					3A
Day (Week)	28 (4)					29 (4)
PROCEDURES	Predose	~1 h Following Pre-dose Sample	2 h (± 5 min)	4 h (± 5 min)	12 h (± 15 min)	24 h (± 30 min)
PK Subset - Collect Blood for Plasma Concentrations	X [p]		X	X	X	X

Visit	3					3A
Day (Week)	28 (4)					29 (4)
PK Subset - Study Drug Application		X [q]				

[p] The predose blood sample is to be collected after all Day 28/Week 4 study procedures are completed.

[q] Study drug application on Day 28/Week 4 will occur at the investigational center within 1 hour after collecting the predose blood sample. This will be the last application of study drug to all 10 toenails for subjects in the PK subset. Post Day 28, subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s). Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s).

8 Selection and Withdrawal of Subjects

8.1 Subject Inclusion Criteria

Subjects meeting all of the following criteria will be eligible for study entry:

1. Male or female subjects of any race, 6 to 16 years of age (inclusive) at Screening.
   - **PK Subset**: Male or female subjects of any race, 12 to 16 years of age (inclusive) at Screening.
2. Verbal and written informed consent/assent obtained from the subject and/or their parent or legal guardian.
3. Good general health, as assessed by the investigator, based on the subject's medical history, physical examination, and safety laboratory tests.
4. At least 1 great toenail (the "target great toenail") with clinically diagnosed distal lateral subungual onychomycosis involving at least 20% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. There is no specific upper limit for percent involvement. Up to 6 toenails may have onychomycosis in subjects not participating in the PK subset.
   - **PK Subset**: Both great toenails with clinically diagnosed distal lateral subungual onychomycosis involving at least 50% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. There is no specific upper limit for percent involvement. Subjects must also have at least 4 toenails other than the great toenails with onychomycosis.
5. Target great toenail for all subjects, and both great toenails for subjects in the PK subset, must have evidence of toenail growth, per subject's report that monthly clipping is needed.
6. Within 42 days prior to the Baseline (Day 1) Visit, have a positive KOH examination (results will be provided by the central the mycology lab) of the target great toenail for all subjects
7. Within 42 days prior to the Baseline (Day 1) Visit, have a positive dermatophyte culture for *T rubrum* or *T mentagrophytes* (at the central mycology laboratory) from the target great toenail in all subjects
   - **PK Subset**: Prior to the Baseline Visit, the great toenail designated for efficacy assessments as the target great toenail must have both a positive KOH examination (results will be provided by the central mycology lab) and a positive fungal culture.

8. All FOCBP must have a negative urine pregnancy test at the Screening and Baseline Visits and must agree to use an effective method of contraception throughout the study. Effective contraception is defined as use of an intrauterine device, condom with spermicide, diaphragm with spermicide, abstinence (subject is not sexually active), or stable use of a hormonal contraceptive (oral, implant, injection, or transdermal patch) for at least 3 months prior to the Baseline Visit.
9. Subjects and their parents/legal guardians are willing to comply with study instructions and return to the investigational center for all required visits (a visit schedule with the length of each visit will be provided to ensure that the subject can meet the requirements and have adequate transportation).
10. Subjects and parents/legal guardians agree that the subject will avoid the use of toenail polish, cosmetic toenail products, and pedicures during the study period.

8.2 Subject Exclusion Criteria

Subjects meeting any one of the following criteria will be excluded from the study:

1. Females who are pregnant, nursing an infant, or planning a pregnancy during the study period.
2. History of immunosuppression and/or clinical signs indicative of possible immunosuppression, as determined by the investigator, or known human immunodeficiency virus infection.
3. History of diabetes that is uncontrolled as determined by the investigator (diabetes that is controlled by diet or medication does not exclude a subject).
4. Presence of any toenail infection other than or in addition to dermatophytes, such as *Scytalidium* as determined by the investigator (candidal onychomycosis infection, concurrent with a positive dermatophyte culture, is acceptable).
5. Presence of any of the following: dermatophytoma, fungal "spikes" within 3 mm of the proximal toenail fold on the target great toenail, infection extending to the matrix, or only lateral toenail disease in the target great toenail.
6. Presence of severe moccasin tinea pedis at the Screening or Baseline Visits, as determined by the investigator. If the subject has interdigital tinea pedis that requires treatment, the subject must agree to use only an investigator-approved topical antifungal therapy.
7. Presence of any disease/condition that might cause toenail abnormalities or may interfere with the evaluation of the study drug as determined by the investigator (eg, open sores or ulceration on the toes of affected toenails, psoriasis, immune dysfunction, collagen-vascular diseases, lichen planus, peripheral vascular disease, or traumatic onychodystrophy due to chronic physical stimuli).
8. Any previous surgery on the target great toenail.

9. Presence of onychomycosis of the fingernail.
10. History of immunodeficiency as determined by the investigator.
11. Presence of 1-hand, 2-foot syndrome, or fingernail dermatophytosis.
12. Target great toenail (including toenail plate and any subungual debris) thicker than 3 mm at the Screening and Baseline Visits.
13. Presence of onychodystrophy that could interfere with clinical assessments as determined by the investigator.
14. History of hypersensitivity or allergic reactions to azole derivatives or any of the study drug constituents.
15. Presence of any underlying disease that, in the opinion of the investigator, could present a safety concern for the subject by participating in the study.
16. Subject has received treatment for any type of cancer in the previous 6 months, except for nonmelanoma skin cancer (eg, basal cell carcinoma or nonmetastatic squamous cell carcinoma) that was treated successfully.
17. Presence of any dermatological condition on the feet that could interfere with clinical evaluations as determined by the investigator.
18. Presence of any underlying disease or dermatological condition other than onychomycosis that requires the use of interfering topical or systemic therapy and would make evaluations inconclusive as determined by the investigator, or subject requires treatment with a topical product on the toenails other than the study drug during the study.
19. Subjects using the following topical preparations within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following topical preparations during the study:

- Toenail polish or cosmetic toenail products: 1 day
- Other topical prescription or over-the-counter medications to the toenails (with the exception of bland emollients): 2 weeks
- Topical prescription or over-the-counter antifungal therapy for the toenails, including devices to treat onychomycosis: 4 weeks

20. Subjects using the following systemic medications within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following systemic medications during the study:

- Systemic antifungal therapy: 4 weeks
- Systemic immunosuppressive agents: 6 months

21. Subject has previously been nonresponsive to systemic antifungal therapy for onychomycosis.
22. Subject is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
23. Use of any investigational drug or device within 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit, or concurrent participation in another clinical study with an investigational drug or device.

8.3 Subject Withdrawal Criteria

When possible, subjects who discontinue from the study prior to completing the 48-week treatment period should return to the investigational center to perform the assessments scheduled for Week 48. If appropriate, discontinued subjects may be placed on other conventional therapy upon request or whenever clinically necessary, as determined by the Investigator. The End of Study source documents and all relevant data should be entered into the electronic case report form (eCRF) system at the time the subject discontinues from the study.

Reasons for subject withdrawal may include, but are not limited to, the following:

- Onychomycosis progression, as determined by the investigator, which requires treatment with a prohibited therapy
- Either at the investigator's discretion for safety reasons (eg, severe adverse reactions or unauthorized concomitant therapy), or at the subject's request for personal reasons
- When the requirements of the protocol are not followed
- When a concomitant therapy likely to interfere with the results of the study is reported or required by the subject (the investigator will report all such information on the source documents/eCRFs and decide, in accordance with the Sponsor, whether the subject is to be withdrawn)
- When a subject is lost to follow-up; the investigator (or designee) will try twice to reach the subject by telephone, and will send a follow-up letter by certified mail before considering the subject as lost to follow-up; these actions will be documented in the source documents and recorded on the End of Study eCRF, with a copy of the follow-up letter maintained in the investigator's file
- If a subject becomes pregnant during the treatment period, the study drug will be discontinued immediately, the subject will be discontinued from the study, and the investigator will notify the sponsor. The pregnancy will be followed to term with the outcome reported to the sponsor.

9 Treatments Planned

9.1 Methods of Assigning Subjects to Treatment Groups

This is a single-arm, open label study. After confirming eligibility at the Baseline Visit, subjects will be enrolled in the treatment period and will receive efinaconazole in accordance with the protocol (Section 10).

9.2 Randomization and Blinding

Randomization and blinding do not apply.

PK assessments will be performed on a subset of the study population. Efforts will be made to enroll subjects into the PK subset such that they are evenly distributed across the required age range.

9.3 Treatment Compliance

Subjects and their parents/legal guardians will be dispensed an initial bottle of study drug at Baseline (Day 1). Subjects and their parents/legal guardians will be instructed on the importance of returning the subject's study drug bottle(s) at the next study visit. If a subject does not return his/her study drug bottle, he/she will be instructed to return it at his/her next study visit. A new study drug bottle will be dispensed to the subjects at each post baseline study visit through Week 44. Subjects in the PK subset will be dispensed 2 bottles of study drug at Baseline (Day 1), and will be dispensed one bottle of study drug at each subsequent study visit through Week 44. All used and unused study drug bottles will be collected at Week 48.

The investigational center staff will weigh and record each bottle of study drug before dispensing to the subject and their parent/legal guardian and following return by the subject. Bottle weights will be recorded in the individual study drug log and in the appropriate eCRF.

At each post baseline study visit, subjects and/or their parents/legal guardians will be asked to report any missed doses of study drug, and provide the date and an explanation for each missed dose. A subject who has deviated from the once daily dosing regimen will be counseled in the presence of their parent/legal guardian. The dates of any missed doses of study drug will be recorded in the subject's source document and appropriate eCRF.

9.4 Treatment Administration

Subjects and their parents/legal guardians will receive both verbal and written instructions on the application of the study drug. The subject and/or their parent/legal guardian will apply the first dose of study drug at the investigational center during the Baseline Visit. All of the

remaining study drug doses will be applied by the subject at home. The subjects and their parents/legal guardians will be instructed to wait for the toenails to air-dry thoroughly before touching with clothing.

Dosing for Subjects NOT Included in the PK Subset: Subjects and their parents/legal guardians will be instructed to apply their assigned study drug to the target great toenail and all other affected toenail(s) (if any) once daily at bedtime. Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be instructed to apply the study drug by completely covering the target great toenail, including the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate. The study drug will be applied to each of the other infected toenails in a similar manner.

Dosing for Subjects Included in the PK Subset:

Days 1 to 28 - Subjects and their parents/legal guardians will be instructed to apply study drug to all 10 toenails, once daily at bedtime. During this period, all PK subjects will be instructed to apply the study drug by completely covering each toenail and 0.5 cm of adjacent skin, including the toenail folds, toenail bed, hyponychium, undersurface of the toenail plate. The subjects will not apply study drug the night prior to the Week 4 (Day 28) visit, nor will they apply study drug on the night of the Week 4/Day 28 Visit. Within 1 hour after the predose blood sample is drawn on Day 28, subjects will apply study drug to all 10 toenails in the manner described above at the investigational center.

Days 29 to Week 48:

After completion of the PK portion of the study, subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) once daily at bedtime. Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be given instructions regarding

how to apply the study drug, ie, by completely covering the target great toenail, including the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate (if onychomycosis is present). The study drug will be applied to each of the other infected toenails in a similar manner.

9.5 Concomitant Medications

Concomitant medications/therapies refer to all medications/therapies used by the subject during the study. During the course of the study, if appropriate, every attempt should be made to keep the dosing and regimen of concomitant medications/therapies constant, and any change to a medication/therapy during the study must be recorded. Information on concomitant medications/therapies (including indication, dosing, and start and stop dates) will be recorded in the source document and on the appropriate eCRF. All concomitant medications/therapies (including foot care products) used during the study will be recorded under Concomitant Medications.

All prior medications (those used within 30 days prior to the Screening Visit) and previous antifungal medications used by the subject, including any recent over-the-counter topical treatments (those used within 60 days prior to the Screening Visit) will be recorded under Prior and Concomitant Medications in the eCRF (eg, aspirin, acetaminophen, birth control pills, vitamins, herbal products, homeopathic preparations).

During the study, all foot care products used by the subject will be recorded under Prior and Concomitant Medications.

9.5.1 Allowed Medications/Therapies

Concomitant medications (prescription or over-the-counter) that are considered necessary for the subject's welfare and do not interfere with study assessments and evaluations will be allowed during the study at the investigator's discretion.

If, during the study, a subject requires topical antifungal therapy for tinea pedis, the investigator is to document the problem and the investigator-approved treatment on the AE and concomitant therapy eCRFs, respectively, and to ensure that the subject avoids application of the concomitant therapy to the toenails or adjacent surrounding skin surface.

9.5.2 Prohibited Medications/Therapies

No topical treatments/products will be allowed on the toes or feet other than the study drug during the study, except for investigator-approved treatments. The subject may use any topical antifungal therapy the Investigator approves for use. Use of the following topical treatments is prohibited within the indicated time prior to the Baseline Visit:

Toenail polish or cosmetic toenail products	1 day
Other topical prescription or over-the-counter medications to the toenails (with the exception of bland emollients)	2 weeks
Topical prescription or over-the-counter antifungal therapy for the toenails, including devices used to treat onychomycosis	4 weeks

Use of the following systemic medications is prohibited within the indicated time prior to the Baseline Visit and for the duration of the study:

Systemic antifungal therapy	4 weeks
Systemic immunosuppressive agents	6 months

In addition, use of any investigational drug or device within 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit, or concurrent participation in another clinical study with an investigational drug or device during the study period is not allowed.

If a specific medication/therapy has the potential to interfere with the treatment effect of the study drug or interpretation of the study results, the investigator should contact the medical monitor prior to use (if possible).

Any subject using a prohibited therapy during the course of the study that could interfere with the treatment effect of the study drug or interpretation of the study results (including, but not limited to, those listed above) may be withdrawn from the study at the discretion of the investigator and/or sponsor. However, the investigator should not withdraw a subject without first confirming it with the sponsor.

9.6 Protocol Deviations and Violations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the sponsor and the institutional review board (IRB) or independent ethics committee (IEC) and agreed to by the investigator. Deviations usually have an impact on individual subjects or a small group of subjects and do not involve inclusion/exclusion or primary endpoint criteria.

A protocol violation occurs when there is nonadherence to the protocol that results in a significant, additional risk to the subject, when the subject or investigator has failed to adhere to significant protocol requirements (inclusion/exclusion criteria) and the subject was enrolled without prior sponsor approval, or when there is nonadherence to US Food and Drug Administration regulations and/or International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline.

The investigator or designee must record and explain in the subjects' source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the sponsor for agreement, to the IRB/IEC for review and approval, and to the regulatory authorities, if required.

10 Study Drug Materials and Management

The study drug will be provided to the investigational centers by the sponsor and will be dispensed to the subject and their parent/legal guardian by the pharmacy or an appropriately qualified member of the study staff assigned by the investigator.

All laboratory kits containing materials necessary to collect blood and urine for routine clinical laboratory tests, urine pregnancy tests, fungal cultures, and PK analyses will be supplied to the investigational centers by the designated central laboratories.

10.1 Study Drug

A description of the study drug is included in Table 2.

Table 2. Study Drug Identification

	Investigational Product
Drug Name	Efinaconazole 10% solution for topical administration
Name of Active Ingredient	Efinaconazole
Manufacturer	Valeant Pharmaceuticals
Chemical Name	(2R,3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol
Chemical Formula/Molecular Weight	$C_{18}H_{22}F_2N_4O$ / 348.39 amu
Therapeutic Category	Antifungal
Appearance	Clear to yellow solution
Inactive Ingredients	Alcohol, anhydrous citric acid, butylated hydroxytoluene, C12-15 alkyl lactate, cyclomethicone, diisopropyl adipate, disodium edetate, and purified water.

10.1.1 Packaging and Labeling

Efinaconazole will be provided to the investigational centers in 10 mL bottles containing 8 mL of study drug per bottle. Individual bottles will be supplied to the investigational center. The subjects and their parents/legal guardians will be dispensed 1 bottle at the Baseline Visit and 1 bottle at each subsequent study visit through Week 44. Subjects in the

PK subset will be dispensed 2 bottles of study drug at the Baseline Visit, and will be dispensed one bottle of study drug at each subsequent study visit through Week 44.

The label on each bottle of study drug will identify the product as "Efinaconazole". The label on the study drug bottles will contain the following information:

- Protocol number
- Kit number
- Product identification (Efinaconazole 10% Solution)
- Subject number_____
- Subject initials_____
- Date dispensed _____
- A statement indicating the volume of the contents as 8 mL
- Instructions to keep bottle tightly closed and store in an upright position at room temperature (20°C to 25°C [68°F to 77°F]), with excursions permitted between 15°C and 30°C (59°F and 86°F)
- Lot number/expiration date
- Sponsor name and address
- A statement indicating, "Caution: New Drug - Limited by Federal Law to Investigational Use"
- A statement indicating that the drug should be kept out of reach of children

Additional information may be included on the bottle label as necessary.

10.1.2 Storage, Handling, and Disposal of Study Drug

Study drug should be stored in a secure area at the investigational center according to local regulations, in an upright position at controlled room temperature (20°C to 25°C [68°F to 77°F]), with excursions permitted between 15°C and 30°C (59°F and 86°F).

Subjects and their parents/legal guardians will be instructed to keep their study drug bottle at room temperature, out of the reach of children, not to share the study drug with anyone else, and to use it only on the affected toenails as directed by the investigator. Subjects and their parents/legal guardians will be asked to notify the investigational center immediately if a study drug bottle is damaged or lost.

All used and unused study drug supplies will be returned to the sponsor for destruction.

10.1.3 Study Drug Preparation

Not applicable; subjects and/or their parents/legal guardians will apply the study drug directly from the study drug bottles.

10.2 Study Drug Accountability

The Investigator or designee will be responsible for keeping current and accurate records of the amount of study drug received and dispensed, and its disposition. The study drug must be stored under the appropriate conditions in a secure area and is to be dispensed only to subjects enrolled in the study, in accordance with the conditions specified in this protocol. During the course of the study, the Investigator or designee must maintain an inventory of all study drug dispensed to or returned by the subject, including subject identifiers.

A study drug accountability log will be completed by the investigator or designee to document the receipt, dispensation, and return of study drug bottles.

All supplies sent to the Investigators will be accounted for and, in no case, used in any unauthorized situation. Bottles will be weighed (with the cap on) before dispensing to and upon return by the subjects, and weights will be recorded on the pharmacy log and appropriate CRF. All used and unused supplies will be returned to sponsor/designee for destruction at the conclusion of the study.

11 Study Procedures and Evaluations

11.1 Schedule of Evaluations and Procedures

All subject information and data obtained during the study visit procedures must be recorded in the source documents, applicable study logs, and eCRFs.

11.1.1 Screening Visit (Visit 1, Up to Day -42)

After signing the informed consent/assent, subjects will undergo the screening procedures to confirm eligibility to participate in the study.

The following procedures will be conducted at this visit:

1. Review and explain the nature of the study. Provide a visit schedule with the length of each visit to ensure that the subject can meet the requirements and has adequate transportation.
2. Obtain verbal and written informed consent/assent from the subject and the subject's parent(s) or legal guardian(s) prior to performing any study-related procedures. Provide signed copies of the consent and assent forms to the subject/parent(s) or legal guardian(s).

3. Obtain photography consent/assent from subject and/or the subject's parent(s) or legal guardian(s).
4. Assign a 6-digit study number, which includes the 3-digit investigational center number plus a unique 3-digit subject number beginning with 001 (eg, 001-001, 001-002, 001-003). Numbers must be assigned in chronological order.
5. Record subject's demographic information (sex, date of birth, age, ethnicity, and race).
6. Record subject's medical history including diabetes history.
7. Collect a detailed history of onychomycosis, including an estimated start date of infection, duration of current infection in the potential target great toenail, and all previous therapies used for onychomycosis treatment.
8. Review all prior medications (those used within 30 days prior to the Screening Visit) and previous antifungal medications used by the subject, including any recent over-the-counter topical treatments (those used within 60 days prior to the Screening Visit).
9. Review inclusion/exclusion criteria.
10. Examination of toenails for clinical presence of onychomycosis in at least 1 great toenail, within the definition of eligibility criteria. For subjects in the PK population, both great toenails and 4 other toenails must meet eligibility criteria
11. Examination of all other toenails for presence or absence of onychomycosis on each toenail.
12. Examination of both feet for presence of symptomatic tinea pedis; treat as appropriate using investigator approved topical antifungal therapy
13. Clip the toenails (before performing nail measurements). Remind subject and their parent/legal guardian not to clip toenails at home in between visits.
14. Perform the investigator's assessment of the great toenail(s) with a calculation of the percentage of toenail affected with disease, after clipping the unhealthy toenail. If the great toenail has been clipped proximal to the distal groove, the entire area to the distal groove should be included. The investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail (this is optional at this visit since photography is not done at this visit; outlining should be done if beneficial to performing assessments).
    - Subjects not included in the PK subset must have at least 1 great toenail with 2 20% involvement
    - Subjects included in the PK subset must have both great toenails involved with 2 50% involvement in each great toenail.

15. Obtain specimen from the great toenail(s) to ship to the mycology lab. Both great toenails may be sampled if both are suspected of manifesting onychomycosis (at least 20% involvement).
16. Perform a urine pregnancy test[1] for all FOCBP.[2] Exclude the subject if the pregnancy test result is positive.

    Urine pregnancy testing is mandatory for all FOCBP at the Screening Visit, Baseline Visit, and at all subsequent study visits. The decision may be made by the investigator to do additional urine pregnancy tests during the course of the study.

17. Collect blood and urine samples for routine safety laboratory analysis (hematology, serum chemistry, and urinalysis). Process and ship the samples tothe central safety laboratory per instructions provided in the laboratory manual.

    Note: Collection of Screening safety labs may be postponed until after positive Screening mycology results are received, only if the subject/parent are willing to return to the research site for safety lab collection prior to the end of the 42-day screening window. Screening safety lab results must be received within the 42-day screening visit window.

18. Schedule subject to return for the Baseline Visit (Visit 2, Day 1).

    If a subject fails screening, either at the Screening or Baseline visit (prior to enrollment to treatment), the subject may be rescreened at a later date. Subjects who are rescreened will be assigned a new screening number, must be re-consented, and undergo all screening procedures per protocol.

11.1.2 Baseline Visit (Visit 2, Day 1)

If the Baseline Visit is more than 42 days after the Screening Visit, the subject must be reported as a screen failure and then may be rescreened (with a new subject number) at the investigator's discretion.

[1] Urine pregnancy tests must have a minimum sensitivity of 25 mIU of human chorionic gonadotropin per mL of urine. Urine pregnancy test kits will be provided by the sponsor.

[2] FOCBP include any female subjects who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal (defined as amenorrhea for > 12 consecutive months or women on hormone replacement therapy with documented plasma follicle-stimulating hormone levels > 35 mLU/mL). Even a female subject who is using an oral, implanted, injectable, or transdermal contraceptive hormone, an intrauterine device, a condom with spermicide, or a diaphragm with spermicide to prevent pregnancy, or is practicing abstinence, should be considered of childbearing potential.

The following procedures will be conducted at this visit:

1. Record any AEs (query subjects and their parents/legal guardians, "Are there any changes in your health since the last visit?").
2. Confirm positive KOH and culture results from the central mycology laboratory.
    - All subjects (including those in PK subset) must have at least 1 great toenail with positive KOH (performed at central mycology lab) and positive dermatophyte culture for *T rubrum* or *T mentagrophytes*.
3. Review the safety laboratory test results.

    If any safety laboratory test results obtained at the Screening Visit, are abnormal and clinically significant as determined by the investigator, the investigator should discuss with the medical monitor whether it is in the subject's best interest to participate in the study.
4. Confirm the subject's medical history and prior medication uses.
5. Review all concomitant medications and new medications started since the last study visit.
6. Obtain vital sign measurements. Vital signs will be measured after the subject is seated for at least 5 minutes, and will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.
7. Measure height and weight.
8. Conduct an abbreviated physical examination (excluding urogenital/reproductive systems).
9. Perform a urine pregnancy test for all FOCBP. Exclude the subject if the pregnancy test result is positive.
10. Clip the toenails to the distal groove (before performing toenail measurements and close-up photography).
11. Conduct the investigator's assessment of the great toenail (s), with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
    - Subjects not included in the PK subset must have at least 1 great toenail with 2 20% involvement
    - Subjects included in the PK subset must have both great toenails involved with 2 50% involvement in each great toenail.
12. Select target great toenail in each eligible subject for efficacy assessments. Where both great toenails are study-eligible (including percent involvement, KOH-positive, and culture-positive results), the toenail with the greater percent affected area at the Baseline Visit will be selected as the target great toenail prior to

enrollment in the treatment period. In the instance where the percent affected area is the same for both study-eligible great toenails at the Baseline Visit, the investigator may choose either great toenail to be the target great toenail.

13. Inscribe a transverse notch in the great toenail at the proximal nail fold with a file or scalpel. This will be used as a marker at subsequent visits for determining new toenail growth.
14. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis. Subjects in the PK subset must have at least 4 toenails other than the great toenails with onychomycosis.
15. Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
16. Review inclusion/exclusion criteria. If the subject continues to meet all inclusion criteria and none of the exclusion criteria, enroll the subject in the treatment period.
17. Obtain 1 bottle of study drug and weigh the bottle. Record the assigned bottle number for the study drug in the subject's source document and on the appropriate eCRF. Dispense the bottle to the subject and their parent/legal guardian (complete the label and required records). For subjects in the PK subset, 2 bottles of study drug should be obtained. The bottles should be weighed separately and recorded as separate entries, as described above.
18. Instruct the subject and their parent/legal guardian on diary completion and dispense diary.
19. The subject or their parent/legal guardian will apply the first dose of study drug in the investigational center. Instruct the subject and their parent/legal guardian in the proper application technique for the study drug and provide the appropriate Subject Instruction Sheet with dosing instructions (ie, for non-PK or PK subjects), depending on whether the subject is enrolled in the PK subset. Record any AEs following the initial treatment application.
20. Record local skin reactions. Instruct the subject and their parent/legal guardian to report local skin reactions (if any) at each study visit.
21. Schedule the next study visit (Visit 3 [Week 4, Day 28]) in 28 days (± 5 days).

Note: (± 5 days) only applies to Non-PK subjects, PK subset only has a (± 1 day) visit window

- For subjects in the PK subset, Visit 3 (Week 4, Day 28) to Visit 3A (Week 4, Day 29) remind subjects not to apply study drug the night prior to their Visit 3 (Week 4, Day 28) visit.

11.1.3 Visit 3 (Week 4, Day 28 [± 5 days]), Visit 4 (Week 8 [± 5 days]), Visit 6 (Week 16 [± 5 days]), Visit 7 (Week 20 [± 5 days]), Visit 9 (Week 28 [± 5 days]), Visit 10 (Week 32 [± 5 days]), Visit 12 (Week 40 [± 5 days]), Visit 13 (Week 44 [± 5 days])

Visits are to be scheduled in reference to Visit 2 (Baseline).

The following procedures will be conducted at this visit:

1. Record any AEs (query subjects and their parents/legal guardians, "Are there any changes in your health since the last visit?").
2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Clip the toenails.
5. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch). If the most recently applied notch has grown out or has been clipped off, inscribe a new notch adjacent to the proximal nail fold.
6. Collect the diary and study drug bottle from the subject and/or their parent/legal guardian. Weigh the used bottle of the study drug. Record the number of missed doses from the subject diary and review compliance with the subject.
7. Conduct a urine pregnancy test on FOCBP subjects (discontinue any subject from the study who has a positive test result)
8. Obtain 1 bottle of study drug and weigh the bottle, complete the label and drug log, and dispense the bottle to the subject and their parent/legal guardian. Review the dosing instructions with the subject. (Subjects in the PK subset will not be dispensed study drug this day).
9. Dispense diary. (Subjects in the PK subset will not be dispensed a diary this day.)
10. Schedule the next study visit.

For subjects in the PK subset <u>at Visit 3 only</u>:

- Collect a predose blood sample after all other study procedures are completed.
- Apply the study drug to all 10 toenails at the investigational center within 1 hour after collecting the predose blood sample.
- Collect postdose blood samples at approximately 2 hours (± 5 min), 4 hours (± 5 min), and 12 hours (± 15 min) after study drug application.
- Instruct the subject to return the following morning for their 24-hour blood sample (Visit 3A (Day 29). Subject will not dose on the evening of Day 28.

11.1.4 Visit 3A (Week 4, Day 29) - Additional Visit for Subjects in the PK Subset

The following procedures will be conducted at this visit:

1. Record any AEs (query subject "Are there any changes in your health?").
2. Record local skin reaction scores reported by the subject.
3. Review concomitant medications.
4. Collect a blood sample 24 hours (± 30 min) after study drug application at Visit 3.
5. Obtain 1 bottle of study drug and weigh the bottle, complete the label and drug log, and dispense the bottle to the subject and their parent/legal guardian. Review the new dosing instructions with the subject (application to only the target great toenail and to any other affected toenails) and provide a copy of new dosing instructions to the subject.
6. Dispense a new diary that includes the new dosing instructions.

11.1.5 Schedule the PK subset subject for the next study visit. Visit 5 (Week 12 [± 5 days]), Visit 8 (Week 24 [± 5 days]), Visit 11 (Week 36 [± 5 days])

Visits are to be scheduled in reference to Visit 2 (Baseline).

The following procedures will be conducted at these visits:

1. Record any AEs (query subject and their parent/legal guardian "Are there any changes in your health since the last visit?").
2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Conduct a urine pregnancy test on FOCBP subjects (discontinue any subject from the study who has a positive test result).
5. Clip the toenails.
6. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch). If the most recently applied notch has grown out or has been clipped off, inscribe a new notch adjacent to the proximal nail fold.
7. Conduct the investigator's assessment of the target great toenail, with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
8. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis.

9. Obtain specimens from the target great toenail for fungal culture and KOH examination and send to the mycology central lab per instructions provided in the laboratory manual.
10. Obtain vital sign measurements. Vital signs will be measured after the subject is seated for at least 5 minutes and will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.
11. At Visit 8/Week 24 only: Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
12. Collect the diary and study drug bottle from the subject and/or their parent/legal guardian. Weigh the used bottle of the study drug. Record the number of missed doses from the subject diary and review compliance with the subject and parent/legal guardian.
13. Obtain 1 bottle of study drug and weigh the bottle, complete the label and drug log, and dispense the bottle to the subject and parent/legal guardian.
14. Review the dosing instructions with the subject.
15. Dispense diary.
16. Schedule the subject for the Visit 6 (Week 16 [± 5 days]) study visit, and instruct the subject to return at the same time of day as the Baseline Visit. The Visit 7 (Week 20 [± 5 days]) and Visit 8 (Week 24 [± 5 days]) study visits will follow Visit 6.

11.1.6 Visit 14 (Week 48 [± 5 days]) / Early Termination Visit

The following procedures will be conducted at this visit:

1. Record any AEs (query subject and their parent/legal guardian "Are there any changes in your health since the last visit?").
2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Clip the toenails.
5. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch). If the most recently applied notch has grown out or has been clipped off, inscribe a new notch adjacent to the proximal nail fold.

6. Conduct the investigator's assessment of the target great toenail, with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
7. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis.
8. Obtain specimens from the target great toenail for fungal culture and KOH examination and send to the mycology central lab per instructions provided in the laboratory manual.
9. Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
10. Conduct an abbreviated physical examination (excluding urogenital/reproductive systems).
11. Measure height and weight
12. Obtain vital sign measurements. Vital signs will be measured after the subject is seated for at least 5 minutes, and include systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.
13. Collect the diary and study drug bottle from the subject and/or parent/legal guardian. Weigh the used bottle of the study drug. Record the number of missed doses from the subject diary and review compliance with the subject and parent/legal guardian.
14. Conduct a urine pregnancy test on FOCBP subjects (if positive test result, the subject should return for Visit 15 [Week 52]
15. Collect blood and urine samples for routine safety laboratory analysis (hematology, serum chemistry, and urinalysis). Process and ship the samples to the central safety laboratory per instructions provided in the laboratory manual.
16. If this is the Early Termination Visit, record the reason for subject discontinuation from the study and complete the Week 48 eCRF. All other subjects should be scheduled to return for the Visit 15 (Week 52) study visit.

11.1.7 Visit 15 (Week 52 [± 5 days]) Post-Treatment Follow-up Visit / Study Exit

For all subjects who continue through the Week 48 visit, this visit should occur 4 weeks after the last treatment visit.

The following procedures will be conducted at this visit:

1. Record any AEs (query subject and their parent/legal guardian, "Are there any changes in your health since the last visit?").

2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Clip the toenails.
5. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch).
6. Conduct the investigator's assessment of the target great toenail, with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
7. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis.
8. Obtain specimens from the target great toenail for fungal culture and KOH examination and send to the mycology central lab per instructions provided in the laboratory manual.
9. Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
10. Conduct a urine pregnancy test on FOCBP subjects.
11. Exit the subject from the study.

11.1.8 Unscheduled Visits

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional exams should be fully documented in the source documents and on Unscheduled Visit eCRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit range, are not unscheduled visits. In these cases, the visit data will be collected and transcribed to the appropriate scheduled visit eCRF.

11.1.9 Missed Visits

If a subject misses any scheduled visit and cannot be seen prior to the start of the allowed visit range for the next scheduled follow-up visit, the visit is considered missed.

11.1.10 Subject Completion

A subject has completed the study when Visit 15 (Week 52) has been completed and the subject has been exited from the study. Subjects who require further follow-up for an AE following completion of the study will be followed according to Section 12.0.

11.2 Study Evaluations

11.2.1 Local Skin Reactions

Tolerability will be evaluated through assessment of local redness, swelling, burning, itching, and vesiculation in the selected treatment areas on the toes. Each sign or symptom is to be reviewed with the subjects and their parents/legal guardians after the first application of the study drug at the Baseline Visit and at each follow-up visit through Week 52. The subjects and their parents/legal guardians should assess each reaction based on the worst reaction experienced since the prior visit using the following scales:

Reaction	Score
Redness, Swelling	0 = None 1 = Mild 2 = Moderate 3 = Severe
Burning, Itching, and Vesiculation	Yes or No

Occurrence of vesiculation will always be reported as an AE. Any other sign or symptom will be reported as an AE only if it requires concomitant therapy or results in a temporary interruption or permanent discontinuation of the study drug due to discomfort.

11.2.2 Clinical Laboratory Tests

Blood and urine samples will be collected for routine safety laboratory tests (hematology, serum chemistry, and urinalysis) at the Screening and Week 48/Early Termination visit. Any subject with a screening laboratory abnormality that is determined by the investigator to be clinically significant must be approved for inclusion in the study by the medical monitor. All results will be reported, including abnormal results. Clinically significant changes in lab results from Screening, in the opinion of the investigator, should be reported as AEs. Clinically significant changes present at Week 48/Early Termination are to be followed to resolution or until clinically stable as determined by the investigator. If an AE should require laboratory testing, the results of the test must be obtained by the investigational center and filed in the subject's documentation.

Materials for sample collection will be provided to the investigational centers by the sponsor or central laboratory. Instructions for processing and shipping samples to the central laboratory are contained in the study laboratory manual.

For all FOCBP, urine pregnancy testing will be performed at the Screening and Baseline Visits, as well as at each subsequent study visit. FOCBP is defined as any female subject who has experienced menarche. The results at the Screening and Baseline Visits must be negative

for a subject to enter the study. Materials for pregnancy testing will be provided to the investigational centers by the sponsor or central laboratory.

11.2.3 Vital Sign Measurements

Measurement of vital signs will be performed at the Baseline Visit, as well as at Weeks 12, 24, 36, and 48/Early Termination. After the subjects have been sitting for at least 5 minutes, systolic and diastolic blood pressures, pulse rates, respiration rates, and oral temperatures will be recorded.

11.2.4 Physical Examinations

An abbreviated physical examination will be performed at the Baseline Visit and at Week 48/Early Termination. Height and weight will be measured at the Baseline Visit and at the Week 48/Early Termination Visit.

11.2.5 Efficacy for Assessing Treatment Compliance and Safety

Efficacy assessments will be performed throughout the study. The efficacy analyses will be based on microscopic examination and mycological culture results for the target great toenail, the percent involvement of the target great toenail, the length of the unaffected part of the target great toenail, the growth of the target great toenail, and the number of affected nontarget toenails.

Investigators/evaluators will be trained by the sponsor to ensure consistency across investigational centers regarding toenail clipping, evaluations and measurements, as well as collection of sufficient material for KOH examinations and fungal cultures. Evaluators must be pre-approved by the sponsor and must have appropriate documented experience and training, or have a waiver obtained from the sponsor based on experience (or through additional training organized by the sponsor).

Every effort should be made to have the same sponsor-approved evaluator perform the target great toenail assessments and measurements for a particular subject at the Baseline Visit and each follow-up visit.

11.2.5.1 KOH Examination and Fungal Culturing

The KOH examination and fungal culturing of toenail scraping and subungual debris will be performed for study-eligible great toenail(s) at the Screening Visit and for the target great toenail only (as determined at the Baseline Visit) at Weeks 12, 24, 36, 48/Early Termination, and 52 (the 4-week post-treatment follow-up) study visits. At the Screening visit, specimens for KOH and fungal cultures are obtained from study-eligible great toenails at this visit and sent to the central mycology laboratory for testing.

Toenail specimens will be taken by clipping the toenail to the point of attachment (removing unhealthy nail) and obtaining any crumbling subungual debris from under the distal edge of the target great toenail using a disposable curette. All target great toenail plate clippings and "distal" subungual debris should be discarded. Only the soft nail bed keratin beneath the clipped edge of the nail should be collected and used as a specimen for both the KOH examination and the fungal culture. Careful specimen collection in this manner will minimize toenail specimen contaminants and maximize dermatophytic pathogen isolation.

Materials for sample collection will be provided to the investigational centers by the sponsor or central mycology laboratory. Instructions for processing and shipping samples to the central laboratory are contained in the study laboratory manual.

11.2.5.2 Target Great Toenail Assessments

The percent of the affected toenail area and healthy (unaffected) toenail measurements for the target great toenail will be evaluated by the investigator/evaluator at the Screening and Baseline Visits, and at Weeks 12, 24, 36, 48/Early Termination, and 52 (the 4-week post-treatment follow-up) study visits.

Percent of Affected Target Great Toenail Area

The affected area of the toenail will be estimated as the percent of toenail area (nail and nail bed) involved (the distal margin for determining area will be the distal groove after the toenail has been clipped).

Healthy (Unaffected) Target Great Toenail Measurement and Growth

The healthy (unaffected) toenail measurement will be defined as the distance (in mm) between the proximal nail fold and a transverse line on the healthy part of the toenail immediately proximal to the nail infection. At each evaluation, this distance will be measured from the proximal nail fold to the proximal onychomycotic border.

Toenail growth will be measured by inscribing a transverse notch in the nail of the target great toenail adjacent to the proximal nail fold at the center of the nail at the Baseline Visit, and measuring nail growth from that point forward. At every subsequent visit, the distance (in mm) between the proximal nail fold and the notch will be measured and recorded. The notch should be enhanced as needed at subsequent visits to allow continued measurement of toenail growth over the course of the study. If the initially applied notch inscribed at the Baseline Visit has grown out or is clipped away, inscribe a new notch in the toenail adjacent to the proximal nail fold, and continue with measurements using the new notch.

11.2.5.3 Nontarget Toenail Assessment

An assessment of both feet will be made for assessing the presence or absence of onychomycosis of nontarget toenails at the Screening, Baseline, Weeks 12, 24, 36, 48/Early Termination, and 52 (the 4-week post-treatment follow-up) study visits. All nontarget toenails will be assessed for the presence or absence of onychomycosis. Subjects in the PK subset must present with onychomycosis on at least 4 toenails besides the great toenails.

11.2.6 Evaluation of Pharmacokinetics

The PK assessments will be performed on a subset of the study population who will receive treatment under maximal use conditions for 28 days. Plasma samples for determination of efinaconazole and metabolite levels will be collected at the following time points:

- Visit 3 (Day 28): Predose (after all Day 28 procedures are completed). Study drug must be applied within 1 hour after the predose sample is collected. Samples are then collected at 2 (± 5 min), and at 4 (± 5 min), and at 12 (± 15 min) hours postdose.
- Visit 3A (Day 29): 24 (± 30 min) hours after Day 28 study drug application.

Materials for sample collection will be provided to the investigational centers by the sponsor or central laboratory. Instructions for processing and shipping samples to the bioanalytical laboratory are contained in the study laboratory manual.

11.2.7 Photography

At all investigational centers, close-up photographs of the target great toenail will be taken at the Baseline, Weeks 24, 48/Early Termination, and 52 (the 4-week post-treatment follow-up) study visits. One photograph will be taken after toenail clipping. After the first photograph has been taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. After the ink has dried, a second photograph will be taken. The collected photographs will be used for documentation purposes only and will not be used for determinations of eligibility, efficacy, or any study-related activities. Before photographs are taken, the study subject and their parent(s)/legal guardian(s) must consent/assent to photography. If the photography consent/assent is declined, the subject may still participate in the study.

11.3 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the study drug. Thus, AEs include any unfavorable and unintended illness, sign,

symptom, clinically significant laboratory test abnormality, or disease temporally associated with the use of a medicinal product that has appeared or worsened during the course of the clinical study, regardless of causal relationship to the study drug(s) under study. The collection of nonserious AEs and serious adverse events (SAEs) should begin following the subject's completion of the consent/assent process to participate in the study.

11.3.1.1 Definition of Serious Adverse Events

All AEs will be assessed as either serious or nonserious. An SAE or serious adverse reaction is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is immediately life threatening, (the term "life threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires in subject hospitalization or prolongation of existing hospitalization (hospitalization for elective surgery for a baseline condition is not considered an AE).
- Results in persistent or significant disability/incapacity (permanent or substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the above listed outcomes.

Important medical events that may not have resulted in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization is a criterion for assessment of seriousness. To qualify as serious under the criteria of "hospitalization," a hospital admission of at least a 24-hour period is required. If a subject is retained the emergency room greater than 24 hours, but not admitted for medical

care, these cases should be evaluated individually, as criteria such as "medically significant" may also apply.

Hospitalization without a medical AE should not be considered either serious or an AE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality).
- Hospitalization for a purpose unrelated to the study (eg, "planned" or elective surgery scheduled prior to study participation) would not ordinarily need to be reported, unless a complication occurred which otherwise caused prolongation of this hospitalization.
- Protocol-specified admission or procedure (eg, cataract surgery required by a study protocol; or overnight stay for monitoring due to protocol required surgery, *with no associated SAE or complication necessitating prolonged stay*)
- Social admission (eg, social hospitalization for purposes of respite care)

Note: A spontaneous abortion will be considered an SAE, and must be reported to the sponsor within 24 hours of your awareness of the event.

11.3.1.2 Assessment of Severity

The severity assigned to an AE should be determined by the maximum severity of the AE. The categories described below should be used to estimate the severity of AEs:

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- Moderate: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.
- Severe: Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization or prolongation of current hospitalization possible; may be incapacitating or life threatening.

11.3.1.3 Assessment of Causality

The investigator should assess the relationship of the AE, if any, to the study drug as either "Related" or "Not Related".

- **Related:** There is at least a reasonable possibility that the AE/SAE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.

- **Not Related:** There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists.

The following should be taken into account when assessing AE/SAE causality:

- Positive temporal relationship to study drug, such as if the study drug was withdrawn and the SAE resolved or the event recurred after re introduction.
- If there is a reasonable possibility that the AE is associated with an underlying or concomitant illness.
- Possible association with previous or concomitant therapy.
- No temporal relationship to the study drug and/or a more likely alternative etiology exists.
- If the AE is directly related to study procedures or there is a lack of efficacy.

11.3.1.4 Procedures for Reporting Adverse Events and Serious Adverse Events

The period of observation for collection of AEs extends from the time the subject and parent/legal guardian gives informed consent/assent until the last study visit or discontinuation from the study. The first concern will be the safety of the subject, and appropriate medical intervention will be made.

The Investigator or designee will elicit reports (ie, via direct questioning, observation, clinical evaluation) of AEs from the subject at each study visit and record all AEs. The Investigator will document the dates of onset, progress, outcome, and resolution of such AEs. The Investigator will also provide an assessment of all AEs as to the severity, causal relationship to study drug, and causal relationship to study protocol.

It is the investigator's responsibility to document all AEs that occur during the study. The AEs should be documented as a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject and/or their parent/legal guardian at each study visit.

All AEs occurring after the subject and their parent/legal guardian signs the assent/informed consent through the last study visit must be reported, regardless of whether or not the AEs are considered drug-related. All AEs, whether in response to a query, observed by the study site personnel, or reported spontaneously by the subject and/or their parent/legal guardian, will be recorded.

At each visit during the study, the subject will be assessed for the occurrence of new and ongoing AEs. Cutaneous tolerability signs and symptoms that result in the subject's requiring a concomitant therapy or discontinuation from the study will be reported as an AE. The following data will be collected on all AEs and recorded on the appropriate eCRF:

- Event name (diagnosis preferred, if unknown, record the signs/symptoms).
- Onset date and end date.
- Maximum intensity (severity).
- Seriousness.
- Action taken regarding study drug.
- Corrective treatment, if given.
- Outcome.

In addition, the investigator's assessment of causality will be recorded.

Any SAE must be reported to the Sponsor, independent of the circumstance or suspected cause, within 24 hours from the time the event was reported to the Investigator. All SAEs experienced from the date of consent through at least 30 days after the last dose of study drug must be reported to the Sponsor regardless of the relationship to the study drug or the protocol. For events occurring beyond the minimum 30-day period after the last dose of study drug, or for any timeframe afterward deemed medically significant, only SAEs considered related to the study drug should be reported promptly to the Sponsor.

Within 24 hours of notification the Investigator will fax or email a completed Serious Adverse Event Report to the Sponsor:

MedTrials Safety:
Fax: [redacted]
**Please follow up with an email notification to [redacted] to confirm the faxed submission.

Investigators should not wait to receive additional information to document the event before notifying the sponsor of an SAE. If only limited information is initially available, follow-up reports are required. If the Investigator becomes aware of any new information regarding a SAE (ie, resolution, change in condition, or new treatment), a new SAE Form must be completed and faxed/emailed to the Sponsor within 24 hours. The original SAE form is not to be altered. The report should be marked as a "follow-up report" and describe whether the event has resolved or continues and how the event was treated. Additional relevant

information such as hospital records and autopsy reports should be provided to the sponsor as soon as they are available.

Should the investigator become aware of an SAE (regardless of its relationship to investigational product) that occurs within 30 days after stopping the study drug, the SAE must be reported in accordance with procedures specified in this protocol.

The investigator should take all appropriate measures to ensure the safety of the subjects, notably he/she should follow a subject with an SAE until the event has resolved or the condition has stabilized. This may imply that follow-up will continue after the subject has left the study, and that additional investigations may be requested by the sponsor.

11.3.1.5 Submitting an Expedited Safety Report to the IRB (Central or Local)

Any suspected unexpected serious adverse reaction (SUSAR) warrants expedited reporting. In addition, any unexpected SAE related to a subject's participation in the study (or conduct of study), regardless if the study drug was administered, will be evaluated by Global Pharmacovigilance and Risk Management (GPRM) to determine if expedited reporting is required. For example, an unexpected, serious and severe reaction which could be associated to the study procedures, and which could modify the study conduct requires expedited reporting. Each expedited safety report will routinely include a brief cover memorandum, the completed MedWatch Form FDA 3500A or Council for International Organizations of Medical Sciences I Form, a clinical analysis of the event with any similar events that have occurred with the product, and any additional pertinent information recommended by the study Medical Monitor. Once the report is compiled by GPRM, the site Investigator must submit the expedited safety report to the local IRB/EC within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available. The site principal Investigator must retain a complete copy of each expedited safety report as it was submitted to the IRB. It is important that the principal Investigator review these expedited reports, as they contain safety information that may be relevant to each of the participating subjects.

11.3.2 Pregnancy

All female subjects of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of contraceptive failure is minimized. Abstinence is allowed as a birth control method.

Before enrolling a female subject of childbearing potential in this clinical study, the investigator must review the following information about study participation:

- Informed consent/assent requirements.

- Contraceptives in current use.

Following review of this information and appropriate counseling for the subject and their parent/legal guardian, the investigator or designee and the subject and parent/legal guardian must sign the assent/informed consent before study enrollment.

During the study, all female subjects of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to study enrollment, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study drug and must not be enrolled in the study. If pregnancy is suspected while the subject is receiving study treatment, the study drug must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued and the subject will be followed until the pregnancy comes to term. A Pregnancy Report form will be submitted to the sponsor, initially and at the end of the pregnancy, which includes the outcome of the pregnancy and any complications occurring during the pregnancy or the delivery.

12 Statistics

12.1 Assessment of Safety

12.1.1 Adverse Events

All AEs that occur during the study will be recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are those AEs with an onset on or after the date of first study drug application. All TEAEs will be summarized by the number of subjects reporting each TEAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the safety, PK, and non-PK populations. Each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category.

All SAEs will be summarized by the number of subjects reporting each SAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the safety, PK, and non-PK populations.

All information pertaining to AEs noted during the study will be listed by subject and will include the verbatim term given by the investigator, the associated system organ class and

preferred term, the start and stop (if stopped) dates, the seriousness, and the severity of the event. Additionally, any action taken with the study drug, any corrective treatment administered, the outcome, and the relationship to study drug as well as a list of subjects who prematurely discontinue from the study due to an AE will be provided.

12.1.2 Local Skin Reactions

Local skin reaction scores (redness, swelling, burning, itching, and vesiculation) at each visit will be summarized using frequency tables for the safety, PK, and non-PK populations. Additionally, redness and swelling severity scores will be summarized using descriptive statistics (mean, standard deviation [SD], median, and minimum, and maximum). Subjects with a severity score worse than baseline will also be summarized at each post-baseline visit. The worst score and the last score during the post-baseline period will also be summarized.

12.1.3 Clinical Laboratory Tests

Results of safety laboratory parameters will be summarized at each study visit using descriptive statistics or frequencies and percentages, as appropriate, for the safety, PK, and non-PK populations. Changes from baseline in safety laboratory values will be summarized by treatment group at Week 48 using descriptive statistics. In addition, changes from baseline in safety laboratory values will be summarized using shift tables according to normal ranges.

12.1.4 Vital Signs

Results of vital sign measurements will be summarized at Weeks 12, 24, 36, and 48 using descriptive statistics or frequencies and percentages, as appropriate, for the safety, PK, and non-PK populations. Changes from baseline in vital sign measurements will be summarized at these visits.

12.1.5 Concomitant Medications

All previous therapies and concomitant medications will be classified based on terminology from the World Health Organization Drug Dictionary. Previous therapies and concomitant medications data will be presented in data listings.

12.1.6 Efficacy for Assessing Treatment Compliance

This primary objective of this study is to assess the safety of the study drug. Descriptive efficacy statistics for the endpoints will assist in evaluating compliance with treatment for the purposes of safety assessment. The efficacy variables evaluated in this study include microscopic KOH examination and mycological culture outcomes of the target great toenail, percent involvement of the target great toenail, growth of the target great toenail, and assessments of the nontarget toenails. The efficacy endpoints include the following:

- Complete Cure, defined as 0% clinical involvement of the target toenail and negative KOH and fungal culture at Week 52
- Complete or Almost Complete Cure at Week 52, defined as :: 5% toenail involvement
- The Clinical Efficacy rate at Week 52, defined as an affected target great toenail area of < 10%
- The Mycologic Cure rate at Week 52, defined as a negative KOH examination and a negative fungal culture of the target great toenail sample

The Complete Cure rate, the Complete or Almost Complete Cure rate, the Clinical Efficacy rate, and the Mycologic Cure rate will be presented using descriptive statistics (sample size n, frequency counts, and percentages) for the safety, PK, and non-PK populations. In addition, the growth of the target great toenail at each study visit and the change from baseline in the number of affected nontarget toenails will be summarized descriptively.

A last observation carried forward (LOCF) imputation will be used to impute missing values for the efficacy variables at Week 52. No sensitivity analyses will be conducted.

12.2 Assessment of Pharmacokinetics

The PK objectives will be considered met when approximately 16 evaluable subjects are treated under maximal use conditions through day 28 of the PK evaluation.

No imputations will be made for missing data. Plasma concentrations that are reported as below the limit of quantitation (BLQ) in the data transfer file and will be set to zero for the summaries of concentrations as well as calculation of PK parameters. Missing values will be treated as if they were never drawn. Plasma concentrations and PK parameters will be summarized for the PK analysis set using descriptive statistics (n, mean, SD, standard error of the mean [SEM], coefficient of variation [CV], median, minimum, and maximum). Geometric means will also be used to summarize C_{max}, C_{min}, $AUC_{(0-t)}$ and $AUC_{(0-24h)}$.

Plasma concentrations of efinaconazole and metabolite (H3 and H4) at each scheduled sampling time point will be summarized using descriptive statistics. The individual plasma concentrations will be listed for each subject. Concentrations BLQ will be displayed as BLQ in the listings.

The mean plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will be presented graphically for Days 28 and 29 in both linear and logarithmic scales.

Individual subject plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will also be created.

Plasma PK parameters for efinaconazole and metabolites (H3 and H4) will be calculated using noncompartmental analysis. The PK parameters will be calculated for each subject using actual sampling times. The maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) will be taken directly from the data.

The following PK parameters will be calculated from the individual plasma concentrations on Days 28 and 29 when possible:

- C_{max} (observed peak drug [efinaconazole and metabolites] concentration)
- T_{max} (time at which C_{max} occurs)
- C_{min} (observed minimum drug concentration)
- AUC_{0-t} (area under the concentration-time curve from time 0 up to the sampling time corresponding to the last quantifiable concentration)
- AUC_{0-24h} (area under the concentration-time curve from time 0 through 24 hours [corresponding to the dosing interval])

Additional PK parameters may be calculated as appropriate.

12.3 Subject Disposition

Subject disposition will be summarized for each analysis population.

12.4 Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized using descriptive statistics for each analysis population.

12.5 Protocol Deviations

All protocol deviations will be reported to the sponsor and recorded throughout the study. A tabulation of protocol deviations will be included in the final study report.

12.6 Compliance

Efficacy evaluations are being conducted to assess treatment compliance. Information regarding the evaluations and their analyses are presented in Section 12.1.6.

Study drug compliance will be calculated for each subject by taking into account whether a subject took all doses of study drug as instructed. Calculation of study drug compliance will be documented in the analysis plan.

12.7 Interim Analyses

No interim analyses are planned.

12.8 Additional Statistical Considerations

When approximately 40 evaluable subjects have been treated for 48 weeks meeting the primary safety objective (regardless if subjects in the PK subset are continuing), a data cut will be done and the study report will be written. Once all subjects in the PK subset completes the study, database lock will be performed and the study report amendment will be written.

All statistical processing will be performed using SAS® version 9.3 or higher unless otherwise stated. No hypothesis testing will be conducted in this study. A statistical analysis plan, describing all statistical analyses, will be provided as a separate document prior to data analysis is performed.

12.8.1 Analysis Populations

All subjects who receive at least 1 confirmed dose of study drug will be included in the safety population.

All subjects in the PK subset who receive at least 1 confirmed dose of study drug and have any PK data on Days 28 and 29 will be included in the PK population.

All safety population subjects who are not in the PK subset will be included in the Non-PK population.

12.8.2 Sample Size Determination

Approximately 60 subjects will be enrolled and receive treatment with study drug. Approximately 20 of the 60 subjects will be enrolled in the PK subset. These sample sizes were based on PK and clinical considerations; no formal sample size calculation was performed. The numbers of planned subjects are considered adequate for determining the safety profile and the PK parameters of efinaconazole in a pediatric population of subjects aged 6 to 16 years 11 months with mild to severe onychomycosis of the toenails.

12.8.3 Handling of Missing Data

No imputations will be made for missing safety or PK data. As indicated previously, the efficacy endpoints, which are used to assess treatment compliance, will have missing data

imputed with LOCF for non-PK population analyses. Missing efficacy data will not be imputed for safety and PK population analyses.

12.8.4 Multicenter Issues

The study will be conducted at multiple investigational centers in the US and the Caribbean with the intention of pooling the results for analysis.

12.8.5 Multiplicity Issues

Not applicable.

12.8.6 Windowing Rules

The timing of all study visits is relative to the Baseline (Day 1) visit. Visit 3 (Week 4) should occur within 5 days of Day 28, (except for the PK-subset; Visit 3 should occur within 1 day of Day 28) and Visit 3A (Week 4) should occur 1 day after Visit 3. The Week 8 and all subsequent visits should occur within 5 days of the targeted times.

13 Quality Control and Quality Assurance

This study will be conducted under the sponsorship of Valeant, in conformation with all appropriate local and federal regulations as well as ICH guidelines.

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, GCP guidelines, and applicable regulatory requirements. In addition, the sponsor will be responsible for securing agreement from all involved parties to ensure direct access to all study-related sites, source data/documents, eCRFs, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

Central laboratory services will be performed by a qualified, licensed facility that will be listed on the US Food and Drug Administration Form 1572. Copies of all normal values (as applicable), laboratory certifications, and the director's curriculum vitae will be provided to each investigational center and to the sponsor.

13.1 Study Monitoring

The conduct of the study will be closely monitored. Sponsor representatives must be permitted to visit all study site locations to assess the data, quality of study performance, and study integrity in a manner consistent with applicable health authority regulations and the procedures described in this protocol.

Prior to the start of the study, the Sponsor or its designee(s) will review the protocol, eCRFs, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator/Sub/Co Investigator and relevant study site personnel.

Monitoring visits and telephone consultations will occur as necessary, or per the study monitoring plan, during the course of the investigation to verify the following:

- The rights and well-being of subjects are protected
- The conduct of the investigation is in compliance with the currently approved protocol/amendment, ICH GCPs, and IRB/EC requirements
- The integrity of the data is maintained, including adequate study documentation
- The facilities remain acceptable
- The Investigator and site personnel remain qualified and able to conduct the study
- Study drug accountability is documented properly

During the course of the study, if the Sponsor determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor will take action to secure or reinstate compliance. In addition, the Sponsor may terminate the Investigator's participation in the study if appropriate, or if the Investigator remains non-compliant despite the remedial actions of the Sponsor..

13.2 Audits and Inspections

Interim and end of study audits of raw data, study files, and the final report may be conducted by the sponsor's quality assurance department or its designee. A certificate attesting to the audit(s) will be issued as applicable. In addition, inspections or on-site audits may be carried out by local authorities. The investigators will allow the sponsor's representatives and any regulatory agency to examine all study records and logs, eCRFs, corresponding subject medical records, study drug dispensing records, study drug storage area, and any other documents considered source documentation. The investigators agree to assist the representative, if required.

13.3 Data Quality Assurance

All assessments performed will be accurately documented in the subject's source documents and eCRFs. The investigator or designee will enter the information required by the protocol into the source documents and eCRFs provided by the sponsor or designee. Subjects will be identified in the eCRFs by their assigned subject number and initials only.

The investigators must read the protocol thoroughly and must follow the instructions exactly. Any deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate written protocol amendments made prior to effecting the agreed upon changes. Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB/IEC before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

14 Ethics and Administrative Issues

14.1 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, ICH guidelines, GCP guidelines, and in compliance with local and federal regulatory requirements. The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP.

14.2 Ethics Review

This protocol, proposed informed consent/assent form and other information to the subjects, and all appropriate amendments, will be properly reviewed, and approved by an IRB/IEC. A signed and dated notification of the IRB/IEC approval will be provided to the sponsor and investigator prior to study initiation. The name and occupation of the chair and members of the IRB/IEC will be supplied to the sponsor. The investigator will provide required progress reports and report all SAEs to the IRB/IEC as required.

14.3 Written Informed Consent

Written informed consent/assent, in accordance with local clinical investigation regulations, must be obtained prior to participation in the study. The investigator or designee will discuss the purpose of the study with each subject and their parent(s)/legal guardian(s) and will provide a description of the study drug (including any potential and possible side effects) and the study procedures. Information must be given both in oral and written form. The subject information provided will be in a language understandable to the subject and their parent(s)/legal guardian(s) and may not include any language that appears to waive any of the subject's legal rights or appears to release the investigator, the sponsor, or the institution from liability or negligence.

The investigator or designee will provide the prospective subject and the subject's parent(s) or legal guardian(s) sufficient time to consider whether to participate, minimizing the

possibility of coercion or undue influence and will discuss any questions the subject and/or their parent(s)/legal guardian(s) may have. The investigator or designee will explain to the subject and their parent(s)/legal guardian(s) that participation in the study is voluntary and that withdrawal from the study is possible at any time without detriment to care. The consent must include acknowledgment that medical records and medical data derived from the study may be forwarded to the sponsor or to the responsible authorities or federal authorities.

No subject can enter the study or have any study-related procedures performed before his/her written informed consent/assent has been obtained. Subjects under the age of consent must sign an assent form and their parents/legal guardians must sign the informed consent form. Subjects over the age of consent must sign the informed consent form. Subjects and their parents/legal guardians will also provide written consent/assent to obtain photographs of the target great toenail. The original signed and dated informed consent and assent forms will be retained with the study records, and a copy of the signed forms will be given to the subject and their parent or legal guardian as applicable.

An informed consent/assent template will be supplied by the sponsor to the investigator. Any changes to the informed consent/assent form must be agreed to by the sponsor prior to submission to the IRB/IEC, and a copy of the approved version must be provided to the sponsor after IRB/IEC approval.

14.4 Subject Data Protection

Subject data will be protected by ensuring that no captured data contain subject names, addresses, telephone numbers, email addresses, or other direct personally identifying information. It is acknowledged that subject initials, demographics (including birthdates), medical histories, and prior concomitant medication uses, along with the name and address of the enrolling investigator may allow for personal identification of study participants. Other than where necessary to meet regulatory requirements, all data collected in this study will be presented in tabulated (ie, aggregate) form and listings containing information that could be used to identify an individual subject will not be included in any public disclosures of the study data or the study results.

14.5 Data Monitoring Committee

Not applicable.

14.6 Financial Disclosure

Financial disclosures will be obtained from all investigators in order to document any potential conflicts of interest.

14.7 Essential Documents

Investigator must maintain essential documents during the conduct of the study and retain these documents after the completion of the study in accordance with the Sponsor's record retention instructions. The Investigator agrees to adhere to the document retention procedures when signing the protocol Investigator Statement of Approval.

Essential documents include, but are not limited to, the following:

- IRB approvals for the study protocol, all amendments, ICF(s), and advertisements
- IRB annual study review
- IRB correspondence and reports (eg, SAE reports, protocol deviations, and safety updates)
- Regulatory documents (eg, financial disclosure and delegation of authority forms)
- All source documents
- CRFs
- Subject's signed ICF
- FDA Form 1572
- Accountability records for the study drug
- Correspondence from and to sponsor
- Any other documents relevant to the conduct of the study

In the event that the Investigator withdraws from the study (eg, retirement or relocation), study records will be transferred to a mutually agreed upon designee (eg, another Investigator or site IRB/EC). The Investigator will provide notice of such transfer in writing to the sponsor

14.8 Investigator Obligations

The investigators must read the protocol thoroughly, complete and sign the protocol signature page, and must follow the instructions exactly. Whenever possible, any planned deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate documentation of sponsor approval prior to effecting the agreed upon changes. Any deviations should be reported to the sponsor and reported to the IRB/IEC according to the requirements of the IRB/IEC.

14.9 Changes to the Protocol

Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without prior written approval from the sponsor.

14.10 Confidentiality/Publication of the Study

All the data furnished to the investigator and his/her staff and all data obtained through this protocol will be regarded as confidential and proprietary in nature and will not be disclosed to any third party, except for the US Food and Drug Administration or other regulatory body, without written consent from the sponsor.

The results of the study may be published or presented by the Investigator(s) after the review by, and in consultation and agreement with the Sponsor, and such that confidential or proprietary information is not disclosed. Prior to submission for publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Sponsor or its designee for review and comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to the Sponsor products and activities receive fair, accurate, and reasonable presentation.

14.11 Study Termination

The sponsor reserves the right to discontinue the study overall or at a particular study site at any time for reasons including but not limited to:

- Emergence of effects that do not justify the benefit/risk relationship to the study population as a whole.
- Failure to comply with the protocol, GCP, or any other violation disturbing the appropriate conduct of the study.
- Failure to meet enrollment goals overall or at a particular study site.

If a study is terminated, the Sponsor will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects and their parents/legal guardians within a reasonable timeframe agreed upon by the Sponsor. All study materials must be collected and all eCRFs completed to the greatest extent possible

15 Data Handling and Record Keeping

15.1 Inspection of Records

Investigators must maintain detailed records on all study subjects who are enrolled in the study or who undergo screening. Data will be recorded in the subject's source documents and in applicable study logs provided by the sponsor. Source documents include subject's medical records, hospital charts, clinic charts, and the investigator's subject study files, as well as the results of diagnostic tests (eg, laboratory tests). All medical information obtained at each study visit must be recorded in the subject's source documentation in real time as it is collected and then entered onto the eCRF by site personnel.

Subject-completed forms such as diaries and questionnaires are also considered source data. Only subjects are to record information in subject diaries and questionnaires. In no instance, should an Investigator or study site personnel record any data or make changes to subject completed forms. The Investigator or designee should review subject-completed forms during study visits. If an entry is found to be illegible or a mistake is found (eg, an incorrect year was recorded), the subject should be instructed to edit the entry by drawing a single line through the original entry, entering the new information, dating, and writing subject's year of birth to acknowledge.

Upon study completion or at any other time specified by the sponsor or designee, the appropriate study documents must be submitted to the sponsor.

Telephone conversations and electronic mail with the subject, the sponsor, or the sponsor's designee concerning the study must be recorded or kept on file. All source documents must be made available to the sponsor and the sponsor's designated monitor upon request.

15.2 Case Report Forms

Subject data required by this protocol are to be recorded on eCRFs. Subject data recorded on eCRFs during the study will be documented in a coded fashion. The subject will only be identified by the subject number and by their year of birth if also required. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

The Investigator and study site personnel will be responsible for completing the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

The study monitor will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. The eCRFs will be submitted to Valeant or its designee(s) for quality assurance review, and statistical analysis.

A copy of the eCRFs will be retained by the Investigator at the conclusion of the study, who must ensure that it is stored in a secure place

15.3 Retention of Records

The investigator should properly store and maintain all study records in accordance with sponsor directives. All records relating to the conduct of this study are to be retained by the investigator until notified by the sponsor in writing that the records may be destroyed.

16 References

1. Elewski BE. Onychomycosis: pathogenesis, diagnosis, and management. Clin Microbiol Rev. 1998;11(3):415-29.
2. Levy L. Epidemiology of onychomycosis in special-risk populations. J Am Podiatr Med Assoc. 1997;87(12):546-50.
3. Zaias N, Tosti A, Rebell G, Morelli R, Bardazzi F, Bieley H, et al. Autosomal dominant pattern of distal subungual onychomycosis caused by Trichophyton rubrum. J Am Acad Dermatol. 1996;34(2 Pt 1):302-4.
4. Trepanier EF, Amsden GW. Current issues in onychomycosis. Ann Pharmacother. 1998;32(2):204-14.
5. Gupta AK, Tu LQ. Therapies for onychomycosis: a review. Dermatol Clin. 2006;24(3):375 9.
6. Jublia (efinaconazole) topical solution, 10%. [US Prescribing Information]. Valeant Pharmaceuticals North America, LLC; 2014.

Clinical Study Protocol

Efinaconazole 10% Topical Solution

Protocol V01-10SA-401

A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails

Development phase of study:	4
Study design:	Multicenter, open label, single-arm, safety and pharmacokinetics study
Date:	May 10, 2016
Amendment 1 Date:	December 05, 2016
Amendment 2 Date:	August 18, 2017
Sponsor:	Dow Pharmaceutical Sciences, a wholly owned subsidiary of Valeant Pharmaceuticals International 1330 Redwood Way, Suite C Petaluma, CA 94954

CONFIDENTIAL

Nothing herein is to be disclosed without prior approval of the sponsor.

VALEANT
Research & Development

Protocol Review and Approvals

A Multiccnter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazolc 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails

Reviewed and approved:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

SEPT 2017

28-Aug-17
Date

6 Aug 2017
Date

Y AUG 2017
Date

Personnel Responsible for Conducting the Study

A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails

Sponsor
Dow Pharmaceuticals Sciences, a wholly owned subsidiary of
Valeant Pharmaceuticals International
1330 Redwood Way, Suite C
Petaluma, CA 94954

Contact for Reporting Serious Adverse Events
MedTrials Safety
Fax: [redacted]
Email : [redacted]

Return of Used and Unused Study Drug
Clinical Trial Materials
Supply Chain, Area 56
1400 North Goodman Street
Rochester, NY 14609

Contract Research Organization/Medical Monitor
MedTrials, Inc. CRO

[redacted]
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]

Principal Investigator Protocol Agreement Page

I agree:

- To assume responsibility for the proper conduct of this clinical study at this site and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IEC) for the study protocol, written informed consent, consent form updates, subject-recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study.
- Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study.
- To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies).
- That I am thoroughly familiar with the appropriate use of the investigational products(s), as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current Investigator Brochure or equivalent document and approved product label (if applicable).
- To provide sufficient time and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions.

_____

Principal Investigator (print name)

_____ _____

Principal Investigator (signature) Date

2 Synopsis

Name of Sponsor/Company: **Dow Pharmaceuticals Sciences, a wholly owned subsidiary of Valeant Pharmaceuticals International**
Name of investigational product: Efinaconazole 10% Topical Solution
Name of active ingredient: Efinaconazole
Title of study: A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails
Number of clinical centers: Approximately 20-25 investigational centers in the United States, and the Caribbean
Objectives: The primary objectives of this study are to evaluate: 1) safety of once daily topically administered efinaconazole 10% for 48 weeks in pediatric subjects (6-16 years 11 months of age) with at least mild onychomycosis of the toenails, and 2) pharmacokinetics PK (4 weeks) of once daily topically administered efinaconazole 10% in pediatric subjects (12-16 years 11 months of age) with moderate to severe onychomycosis of the toenails.
Methodology: This is an open label, single-arm study designed to evaluate the safety and PK of a once daily topical application of efinaconazole in the treatment of pediatric subjects with mild to severe onychomycosis of the toenails. The study will include subjects 6 to 16 years of age, inclusive, but PK assessments will only be performed on subjects 12 to 16 years of age, inclusive (referred to throughout the protocol as the PK subset). All subjects must have onychomycosis of at least 1 great toenail; subjects in the PK subset must have onychomycosis of both great toenails and at least 4 other toenails. Efforts will be made to enroll subjects into the PK subset such that the subjects are evenly distributed across the required age range. For subjects not participating in the PK subset, the study will consist of 14 scheduled visits, including Screening (up to Day -42), Baseline (Day 1), 12 treatment visits (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). Subjects included in the PK subset **MUST** decide at time of consent whether to participate in the 4-Week trial, attend the scheduled visits up to Week 4 (Day 29) for collection of the final PK and exit the study **OR** participate in the 52-Week trial, with the same scheduled visits as in the 4-Week trial followed by continued treatment through week 48 with additional visits at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). The PK assessments will be performed under maximal use conditions . At the Screening Visit, subjects and/or their parents/legal guardians will sign an informed consent/assent form and a photography consent/assent form, provide their medical histories, report their previous and concomitant medications, and be evaluated against the inclusion/exclusion criteria. Females of childbearing potential (FOCBP) will have urine pregnancy tests performed. During this visit, subjects will undergo an examination of their feet to visually ascertain the presence of onychomycosis in at least 1 great toenail for subjects not included in the PK assessments, and on both great toenails and at least 4 other toenails for subjects included in the PK assessments. Additionally, the percent involvement of the affected great

toenail(s) will be recorded. Specimen will be obtained from the great toenail(s) to ship to the mycology lab. Both toenails may be sampled if both are suspected of manifesting onychomycosis (at least 20% involvement). Blood and urine specimens will be collected for serum chemistry, hematology, and urinalysis evaluations. At relevant post-Screening Visits, the target great toenail will be trimmed back to the distal groove before the clinical evaluations are performed and before photographs are taken.

At the Baseline Visit (which should be scheduled after KOH and fungal culture results have been obtained from the mycology lab), subjects and/or their parents/legal guardians will update their medical histories and concomitant medication uses, and the inclusion/exclusion criteria will be confirmed. Subjects will undergo abbreviated physical examinations, clinical laboratory evaluations, assessments of vital signs (sitting blood pressure, respiration, pulse, and temperature), and measurements of height and weight. All FOCBP will have urine pregnancy tests performed. For the purposes of efficacy assessments, 1 target great toenail will be selected from the study-eligible great toenail(s), including subjects in the PK subset for whom both great toenails must be involved. Where both great toenails are study-eligible, the toenail with the greater percent of affected area will be selected for mycologic data and for inclusion in the efficacy analysis. In the instance where the percent of affected area is the same for both study-eligible great toenails, the investigator may select either great toenail as the target toenail. The target great toenail will be identified and recorded for each subject, photographs of the target great toenail will be obtained, and a transverse notch will be inscribed in the target great toenail adjacent to the proximal toenail fold (as a marker for measuring toenail growth at subsequent visits). Assessments of all other nontarget toenails, including the other involved toenails of subjects in the PK subset, will also be conducted to assess the presence or absence of onychomycosis on each toenail. This assessment would continue throughout the study visits through week 52.

After confirming eligibility at the Baseline Visit, subjects will be enrolled in the treatment period. Subjects or their parents/legal guardians will apply the first dose of study drug to the qualified toenails at the investigational center under the supervision of designated study personnel. Any local skin reactions that occur at the study drug application site, along with any adverse events (AEs), will be recorded. Subjects or their parents/legal guardians will receive weighed study drug bottles and given verbal and written instructions for treatment application. Specifically, subjects who are not included in the PK subset will be instructed to apply the study drug to the affected toenails once daily at bedtime for 48 weeks.

Subjects who are included in the PK subset will be instructed to apply the study drug to all 10 toenails once daily at bedtime for 4 weeks. Following the PK subjects participating in the 52-Week trial, ffFollowing the PK blood collections on Days 28 and 29, PK subjects that consented to the 52-Week trial will continue treatment with study drug to **only** the affected toenails .

All subjects or their parents/legal guardians will also receive diaries, with instructions to complete a record of all applications and to note any missed applications of the study drug.

Subjects in the PK subset will not apply study drug the night prior to the Week 4 (Day 28) visit. Following the Day 28 study procedures, subjects in the PK subset will undergo timed blood collections to assess plasma concentrations of efinaconazole and metabolites (H3 and H4). Assessments will require collection of approximately 4 mL of whole blood at each time point (approximately 20 mL total). Within 1 hour after the predose blood sample is drawn, the subjects/parents/legal guardians will apply study drug to all 10 toenails at the investigational center. Subsequent blood collections will occur 2, 4, and 12 hours postdose on Day 28.

The subjects will go home after Day 28, but will not apply study drug on the night of the Day 28 visit. All PK subjects in the 4-Week trial will return to the investigational center the following day (Day 29) for collection of a 24-hour post dose blood sample and exit the study. PK subjects that consented to the 52-Week trial will continue treatment with study drug to only the target great toenail and the other affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52).

Safety will be assessed by reviewing the occurrence of AEs and local skin reactions, assessing vital sign measurements and abbreviated physical examination findings, and noting any additions or changes in concomitant medication uses. Blood samples will be collected at Screening, Week 4(Day 28) and Week 48 for routine safety laboratory evaluations (serum chemistry, hematology, and urinalysis); urine pregnancy tests will be obtained for all FOCBP at each study visit. Efficacy assessments will be performed throughout the study. The efficacy analyses will be based on microscopic examination and mycological culture results for the target great toenail, the percent involvement of the target great toenail, the length of the unaffected

part of the target great toenail, the growth of the target great toenail, and the number of affected nontarget toenails.

Note that growth of the target great toenail will be measured by inscribing a transverse notch, at the center of the toenail, in the toenail adjacent to the proximal toenail fold at Baseline and measuring toenail growth from that point forward. At every subsequent visit, the distance between the proximal toenail fold and the notch will be measured and recorded. A new notch will be inscribed in the toenail adjacent to the proximal toenail fold if the initially applied notch grows out during the course of the study.

A post-treatment follow-up visit will occur 4 weeks after the last treatment visit for each subject (ie, at Week 52). Subjects who discontinue from the study prior to Week 48 will complete the Week 48 study procedures.

Number of subjects planned:

Approximately 60 subjects total

Approximately 20 subjects in the PK subset

Diagnosis and criteria for inclusion:

1. Male or female subjects of any race, 6 to 16 years of age (inclusive) at Screening.
    - **PK Subset:** Male or female subjects of any race, 12 to 16 years of age (inclusive) at Screening.
2. Verbal and written informed consent/assent obtained from the subject and/or their parent or legal guardian.
3. Good general health, as assessed by the investigator, based on the subject's medical history, physical examination, and safety laboratory tests.
4. At least 1 great toenail (the "target great toenail") with clinically diagnosed distal lateral subungual onychomycosis involving at least 20% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. There is no specific upper limit for percent involvement. Up to 6 toenails may have onychomycosis.
    - **PK Subset:** Both great toenails with clinically diagnosed distal lateral subungual onychomycosis involving at least 50% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. There is no specific upper limit for percent involvement. Subjects must also have at least 4 toenails other than the great toenails with onychomycosis.
5. Target great toenail for all subjects, and both great toenails for subjects in the PK subset, must have evidence of toenail growth, per subject's report that monthly clipping is needed.
6. Within 42 days prior to the Baseline (Day 1) Visit, have a positive KOH examination (results will be provided by the central mycology lab) of the target great toenail for all subjects,
7. Within 42 days prior to the Baseline (Day 1) Visit, have a positive dermatophyte culture for *Trichophyton rubrum* or *Trichophyton mentagrophytes* (at the central mycology laboratory) from the target great toenail in all subjects
    - **PK Subset:** Prior to the Baseline Visit, the great toenail designated for efficacy assessments as the target great toenail must have both a positive KOH examination (results will be provided by the central mycology lab) and a positive fungal culture.
8. All FOCBP must have a negative urine pregnancy test at the Screening and Baseline Visits and must agree to use an effective method of contraception throughout the study. Effective contraception is defined as use of an intrauterine device, condom with spermicide, diaphragm with spermicide, abstinence (subject is not sexually active), or stable use of a hormonal contraceptive (oral, implant, injection, or transdermal patch) for at least 3 months prior to the Baseline Visit.
9. Subjects and their parents/legal guardians are willing to comply with study instructions and return to the investigational center for all required visits (a visit schedule with the length of each visit will be

provided to ensure that the subject can meet the requirements and have adequate transportation).

10. Subject and their parents/legal guardians agree that the subject will avoid the use of toenail polish, cosmetic toenail products, and pedicures during the study period.

Exclusion criteria:

1. Females who are pregnant, nursing an infant, or planning a pregnancy during the study period.
2. History of immunosuppression and/or clinical signs indicative of possible immunosuppression, as determined by the investigator, or known human immunodeficiency virus infection.
3. History of diabetes that is uncontrolled as determined by the investigator (diabetes that is controlled by diet or medication does not exclude a subject).
4. Presence of any toenail infection other than or in addition to dermatophytes, such as *Scytalidium* as determined by the investigator (candidal onychomycosis infection, concurrent with a positive dermatophyte culture, is acceptable).
5. Presence of any of the following: dermatophytoma, fungal "spikes" within 3 mm of the proximal toenail fold on the target great toenail, infection extending to the matrix, or only lateral toenail disease in the target great toenail.
6. Presence of severe moccasin tinea pedis at the Screening or Baseline Visits, as determined by the investigator. (If the subject has interdigital tinea pedis that requires treatment, the subject must agree to use only an investigator-approved topical antifungal therapy).
7. Presence of any disease/condition that might cause toenail abnormalities or may interfere with the evaluation of the study drug as determined by the investigator (eg, open sores or ulceration on the toes of affected toenails, psoriasis, immune dysfunction, collagen-vascular diseases, lichen planus, peripheral vascular disease, or traumatic onychodystrophy due to chronic physical stimuli).
8. Any previous surgery on the target great toenail.
9. Presence of onychomycosis of the fingernail.
10. History of immunodeficiency as determined by the investigator.
11. Presence of 1-hand, 2-foot syndrome, or fingernail dermatophytosis.
12. Target great toenail (including toenail plate and any subungual debris) thicker than 3 mm at the Screening and Baseline Visits.
13. Presence of onychodystrophy that could interfere with clinical assessments as determined by the investigator.
14. History of hypersensitivity or allergic reactions to azole derivatives or any of the study drug constituents.
15. Presence of any underlying disease that, in the opinion of the investigator, could present a safety concern for the subject by participating in the study.
16. Subject has received treatment for any type of cancer in the previous 6 months, except for nonmelanoma skin cancer (eg, basal cell carcinoma or nonmetastatic squamous cell carcinoma) that was treated successfully.
17. Presence of any dermatological condition on the feet that could interfere with clinical evaluations as determined by the investigator.
18. Presence of any underlying disease or dermatological condition other than onychomycosis that requires the use of interfering topical or systemic therapy and would make evaluations inconclusive as determined by the investigator, or subject requires treatment with a topical product on the toenails other than the study drug during the study.
19. Subjects using the following topical preparations within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following topical preparations during the study:
    - Toenail polish or cosmetic toenail products: 1 day
    - Other topical prescription or over-the-counter medications to the toenails (with the

exception of bland emollients): 2 weeks

- Topical prescription or over-the-counter antifungal therapy for the toenails, including devices to treat onychomycosis: 4 weeks

20. Subjects using the following systemic medications within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following systemic medications during the study:
    - Systemic antifungal therapy: 4 weeks
    - Systemic immunosuppressive agents: 6 months
21. Subject has previously been nonresponsive to systemic antifungal therapy for onychomycosis.
22. Subject is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
23. Use of any investigational drug or device within 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit, or concurrent participation in another clinical study with an investigational drug or device.

Investigational product, dosage and mode of administration:

Investigational Drug: Efinaconazole 10% Solution (efinaconazole)

Dosing for Subjects NOT Included in the PK Subset: Subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) (if any) once daily at bedtime. Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be given instructions regarding how to apply the study drug, ie, by completely covering the target great toenail, including the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate. The study drug will be applied to each of the other infected toenails in a similar manner.

Dosing for Subjects Included in the PK Subset:

Days 1 to 2S - Subjects and their parents/legal guardians will be instructed to apply study drug to all 10 toenails, once daily at bedtime for 4 weeks. During this period, all PK subjects will be instructed to apply the study drug by completely covering each toenail and 0.5 cm of adjacent skin, including the toenail folds, toenail bed, hyponychium, undersurface of the toenail plate. The subjects will not apply study drug the night prior to the Week 4 (Day 28) visit, nor will they apply study drug on the night of the Week 4/Day 28 Visit. Within 1 hour after the predose blood sample is drawn on Day 28, subjects and/or their parents/legal guardians will apply study drug to all 10 toenails in the manner described above at the investigational center.

Days 29 to Week 4S (only PK subjects consented to the 52-Week Trial):

After completion of the PK portion of the study, if the subject consented to the 52-Week trial, subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) once daily at bedtime for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be given instructions regarding how to apply the study drug, ie, by completely covering the target great toenail, including the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate (if onychomycosis is present). The study drug will be applied to each of the other infected toenails in a similar manner.

Mode of Administration:

Topical application: the subjects will apply the study drug to their toenail(s), the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate. The subjects and their parents/legal guardians will be instructed to wait for the toenails to air-dry thoroughly before touching with clothing.

Duration of treatment:

48 weeks

Reference therapy, dosage and mode of administration:

Not applicable

Criteria for evaluation:

Safety:

Adverse events will be collected as spontaneous reports by the subjects and as observations by the investigators. The collection of AEs should begin following the subject's completion of the consent/assent process to participate in the study.

Local skin reactions (redness, swelling, burning, itching, and vesiculation) will be reviewed with the subject starting at the Baseline Visit (after study drug application at the investigational center) and continuing through the last study visit. The presence or absence of burning, itching, and vesiculation will be reported simply as "yes" or "no". The worst instances of redness and swelling observed since the previous study visit will be reported using a 4-point scale (where 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe).

Blood and urine samples will be collected for routine clinical laboratory tests (hematology, serum chemistry, and urinalysis) within the 42 day Screening visit window. These samples will be collected again at Week 48, or at Day 28 for PK subjects who consented to only the 4-Week trial. Any clinically significant abnormalities in safety laboratory test results that are present at the last treatment visit (Day 28/Week 48/Early Termination) will be followed to resolution (ie, return to normal values or to the baseline state) or until clinically stable as determined by the investigator.

Vital sign measurements (sitting blood pressure, respiration, pulse, and temperature) will be obtained at Baseline and weeks 12, 24, 36, and 48 or at Day 28 for PK subjects who consented to only the 4-Week trial. An abbreviated physical examination will be performed at Baseline and Week 48, and at Day 28 for PK subjects who consented to only the 4-Week trial; as part of the examination, height and weight will be measured at Baseline and Week 48.

Urine pregnancy tests will be performed for all FOCBP at the Screening Visit and at each subsequent study visit. If a subject becomes pregnant during the treatment period, the study drug will be discontinued immediately, the subject will be discontinued from the study, and the investigator will notify the sponsor. The pregnancy will be followed to term with the outcome reported to the sponsor.

Efficacy will be assessed to evaluate compliance with treatment as part of the safety assessment. The efficacy variables evaluated in this study include microscopic KOH examination and mycological culture outcomes of the target great toenail, percent involvement of the target great toenail, growth of the target great toenail, and assessments of the nontarget toenails.

Pharmacokinetics: Concentrations of efinaconazole and metabolites (H3 and H4), along with other relevant PK parameters, will be assessed based on blood samples collected at Days 28 and 29. The specific collection time points are predose on Day 28 and 2, 4, 12, and 24 hours postdose.

Photography:

Close-up photographs of the subject's target great toenail will be used for documentation purposes only and will not be used for determinations of eligibility or any study-related activities.

Statistical Methods:

Safety:

All subjects who receive at least 1 confirmed dose of study drug will be included in the safety analysis set. No imputations will be made for missing safety data. The primary safety objective will be considered met when approximately 40 evaluable subjects have been treated for 48 weeks.

All AEs occurring during the study will be recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are those AEs with an onset on or after the date of first study drug application. All TEAEs will be summarized by the number of subjects reporting each TEAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the Safety, PK and Non-PK populations. Each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category.

Serious adverse events (SAEs) will be summarized by the number of subjects reporting each SAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the Safety, PK and Non-PK populations.

Local skin reaction scores (redness, swelling, burning, itching, and vesiculation) at each study visit will be summarized using frequency tables for the Safety, PK and Non-PK populations. Additionally, redness and swelling severity scores will be summarized using descriptive statistics (mean, standard deviation [SD], median, and minimum and maximum). Subjects with a severity score worse than baseline will also be summarized at each postbaseline study visit. The worst score and the last score during the post-baseline period will also be summarized.

Results of safety laboratory parameters and vital sign measurements will be summarized at each study visit using descriptive statistics or frequencies and percentages, as appropriate, for the Safety, PK and Non-PK populations. Changes from baseline in safety laboratory values will be summarized by treatment group at Week 48 using descriptive statistics. In addition, changes from baseline in safety laboratory values will be summarized using shift tables according to normal ranges.

This study's primary object is to assess the safety of the study drug. Descriptive efficacy statistics for the endpoints will assist in evaluating compliance with treatment for the purposes of safety assessment.

The efficacy endpoints include the following:

- Complete Cure, defined as 0% clinical involvement of the target toenail and negative KOH and fungal culture at Week 52
- Complete or Almost Complete Cure at Week 52, defined as :: 5% toenail involvement
- Clinical Efficacy rate at Week 52, defined as an affected target great toenail area of < 10%
- Mycologic Cure rate at Week 52, defined as a negative KOH examination and a negative fungal culture of the target great toenail sample

The Complete Cure rate, the Complete or Almost Complete Cure rate, the Clinical Efficacy rate, and the Mycologic Cure rate will be presented using descriptive statistics (sample size n, frequency counts and percentages) for the Safety, PK and Non-PK populations. In addition, the growth of the target great toenail at each study visit and the change from baseline in the number of affected nontarget toenails will be descriptively summarized.

A last observation carried forward (LOCF) imputation will be used to impute missing values for the efficacy variables at Week 52. No sensitivity analyses will be conducted.

Any subjects remaining (i.e., have not been treated for 48 weeks) will be followed until completion. The final report will be amended with data on these subjects.

Pharmacokinetics:

All subjects in the PK subset who receive at least 1 confirmed dose of study drug and have any PK data on Days 28 and 29 will be included in the PK analysis set. Blood samples will be tested for plasma concentrations of efinaconazole and metabolites (H3 and H4). No imputations will be made for missing data. Plasma concentrations that are reported as below the limit of quantitation (BLQ) in the data transfer file will

be set to zero for the summaries of concentrations as well as calculation of PK parameters. Missing values will be treated as if they were never drawn. Plasma concentrations of efinaconazole and metabolite (H3 and H4) and PK parameters will be summarized using descriptive statistics (n, mean, SD, standard error of the mean [SEM], coefficient of variation [CV], median, minimum, and maximum). Geometric means will also be used to summarize C_{max}, C_{min}, $AUC_{(0-t)}$ and $AUC_{(0-24h)}$.

The mean plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will be presented graphically for Days 28 and 29 in both linear and logarithmic scales. Individual subject plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will also be created.

Plasma PK parameters for efinaconazole and metabolites (H3 and H4) will be calculated using noncompartmental analysis. The PK parameters will be calculated for each subject using actual sampling times. The maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) will be taken directly from the data.

The following PK parameters will be calculated from the individual plasma concentrations on Days 28 and 29 when possible:

- C_{max} (observed peak drug [efinaconazole and metabolites] concentration)
- T_{max} (time at which C_{max} occurs)
- C_{min} (observed minimum drug concentration)
- AUC_{0-t} (area under the concentration-time curve from time 0 up to the samplingtime corresponding to the last quantifiable concentration)
- AUC_{0-24h} (area under the concentration-time curve from time 0 through 24hours [corresponding to the dosing interval])

Additional PK parameters may be calculated as appropriate.

The PK objectives will be considered met when approximately 16 evaluable subjects are treated under maximal use conditions through day 28 of the PK evaluation.

Sample size calculations:

Approximately 60 subjects will be enrolled and receive treatment with study drug. Approximately 20 of the subjects will be enrolled in the PK subset. These sample sizes were based on PK and clinical considerations; no formal sample size calculation was performed. The numbers of planned subjects are considered adequate for determining the safety profile and the PK parameters of efinaconazole in a pediatric population of subjects aged 6 to 16 years 11 months with mild to severe onychomycosis of the toenails.

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4 List of Abbreviations and Definitions of Terms

Abbreviation or Specialist Term	Definition or Explanation
AE	Adverse event
AUC_{0-24h}	Area under the concentration-time curve from time 0 through 24 hours (corresponding to the dosing interval)
AUC_{0-t}	Area under the concentration-time curve from time 0 up to the sampling time corresponding to the last quantifiable concentration
C_{max}	Observed peak drug concentration
C_{min}	Observed minimum drug concentration
eCRF	Electronic case report form
Efinaconazole	Efinaconazole 10% Solution
FOCBP	Females of childbearing potential
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KOH	Potassium hydroxide
LOQ	Limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
T_{max}	Time at which the observed peak drug concentration occurs
US	United States

5 Introduction

Onychomycosis is a chronic and recurring fungal infection of the fingernails or toenails that accounts for about half of all nail disorders. Onychomycosis is usually caused by dermatophytes, either *Trichophyton rubrum* (71%) or *Trichophyton mentagrophytes* (20%). The prevalence of onychomycosis in the United States (US) may be as large as 13%, with the infection observed predominantly in elderly patients (60%) [1, 2]. Onychomycosis of the toenail can result in permanent toenail deformity and has a significant impact on quality of life due to concerns with the appearance of the toenails and interference with wearing shoes, walking, and participating in various sports activities [3, 4].

Cure rates for topical treatments have been significantly lower than currently available systemic medications [5], presumably because they bind strongly to keratin and do not adequately penetrate the nail unit. However, while effective, oral therapy is limited by safety concerns due to systemic exposure. For example, both oral itraconazole and oral terbinafine have the potential to cause drug-drug interactions and hepatotoxicity. Efinaconazole 10% Solution (efinaconazole) has a low affinity for keratin binding and has a higher binding reversibility than that of other reference drugs. Therefore, efinaconazole appears to be a promising antifungal compound for the topical treatment of onychomycosis.

Efinaconazole is a novel triazole antifungal agent that is active in vitro against a wide range of pathogenic fungi and is expected to be effective in the treatment of mild to moderate onychomycosis.

Efinaconazole has been shown to be efficacious in vitro against a panel of fungal species that invade human skin, hair, and nails including dermatophytes Trichophyton, Microsporum, Epidermophyton, and the yeast, Malassezia species, responsible for tinea unguium (onychomycosis), tinea corporis, tinea pedis, tinea capitis, and pityriasis versicolor. Efinaconazole has been shown to be fungicidal against *Candida albicans* and other Candida species responsible for the major yeast (nondermatophyte) form of onychomycosis and cutaneous candidiasis. In vitro studies against dermatophytes showed that efinaconazole was more potent than clotrimazole, but less potent than butenafine.

Efinaconazole has successfully treated experimentally induced dermal candidiasis, tinea corporis, tinea pedis, and tinea unguium in vivo in guinea pig models. It has generally out performed reference drugs in these models, and in particular out performed the marketed drugs for tinea unguium: ciclopirox olamine (approved for the topical treatment of onychomycosis in the US), amorolfine (available outside the US as a topical nail lacquer), and terbinafine (available in the US in oral form).

The safety and efficacy of once daily use of efinaconazole for the treatment of onychomycosis of the toenail were assessed in two 52-week prospective, multicenter, randomized, double-blind

clinical studies. These studies were conducted in subjects 18 to 70 years of age with 20% to 50% clinical involvement of the target great toenail, without dermatophytomas or lunula (matrix) involvement (n = 870 in Study 1 and n = 781 in Study 2) [6]. These studies evaluated 48-weeks of treatment with efinaconazole relative to vehicle solution. At Week 52 (4-weeks after completion of therapy), efinaconazole was superior to vehicle solution in both studies and thus demonstrated efficacy in the treatment of onychomycosis. The most common adverse reactions (ie, reactions with incidences > 1%) reported in the studies were ingrown toenails, application site dermatitis, application site vesicles, and application site pain.

Efinaconazole was approved by the US Food and Drug Administration in June 2014 for the topical treatment of onychomycosis of the toenail(s) due to *T rubrum* and *T mentagrophytes* (Jublia® [efinaconazole] topical solution, 10% [6]). The approved drug is intended for topical application to affected toenails once daily for 48 weeks. During application, the toenail, toenail folds, toenail bed, hyponychium, and undersurface of the toenail plate are to be completely covered.

The current clinical study is designed to evaluate the safety and pharmacokinetics (PK) of once daily topical application of efinaconazole in the treatment of pediatric subjects with mild to severe onychomycosis of the toenails. Application and use of the study drug is consistent with the approved package insert. The evaluations included in the current study are consistent with the evaluations conducted in the development of the approved drug.

6 Study Objectives and Purpose

The primary objectives of this study are to evaluate: 1) safety of once daily topically administered efinaconazole 10% for 48 weeks in pediatric subjects (6-16 years, 11 months of age) with at least mild onychomycosis of the toenails, and 2) pharmacokinetics PK (4 weeks) of once daily topically administered efinaconazole 10% in pediatric subjects (12-16 years, 11 months of age) with moderate to severe onychomycosis of the toenails.

7 Investigational Plan

7.1 Investigators and Study Administrative Structure

Approximately 20-25 investigational centers are planned to participate in this study. Each clinical investigator will be required to provide a copy of his/her curriculum vitae and medical license, complete a financial disclosure statement, and generate a list of study personnel who will be involved in the study, with a summary of their roles and qualifications.

The Sponsor has designated a Contract Research Organization to assume responsibility for activities related to the conduct of the study. The Sponsor also has designated central laboratories to analyze biological samples related to clinical safety, pharmacokinetics, and mycology. A

listing of the organizations involved in the conduct of the study is provided under Personnel Section in the front of the protocol. A complete description of the Sponsor's and delegates' study-related roles/responsibilities, including key personnel, is contained within the Sponsor's study project plan.

7.2 Summary of Study Design

This is an open label, single-arm study designed to evaluate the safety and PK of a once daily topical application of efinaconazole in the treatment of pediatric subjects with mild to severe onychomycosis of the toenails. The study will include a total of 60 subjects, 40 of whom will be 6 to 16 years of age, inclusive, and PK assessments will be performed on approximately 20 subjects 12 to 16 years of age, inclusive (referred to throughout the protocol as the PK subset). All subjects must have onychomycosis of at least 1 great toenail; subjects in the PK subset must have onychomycosis of both great toenails and at least 4 other toenails. Efforts will be made to enroll subjects into the PK subset such that the subjects are evenly distributed across the required age range.

For subjects not participating in the PK subset, the study will consist of 14 scheduled visits, including Screening (up to Day -42), Baseline (Day 1), 12 treatment visits (Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). Subjects included in the PK subset **MUST** decide at time of consent whether to participate in the 4-Week trial, attend the scheduled visits up to Week 4 (Day 29) for collection of the final PK sample and exit the study **OR** participate in the 52-Week trial treatment through week 48 with additional visits at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). The PK assessments will be performed under maximal use conditions.

At the Screening Visit, subjects and their parents/legal guardians will sign an informed consent/assent form and a photography consent/assent form, provide their medical histories, report their previous and concomitant medications, and be evaluated against the inclusion/exclusion criteria. Females of childbearing potential (FOCBP) will have urine pregnancy tests performed. During this visit, subjects will undergo an examination of their feet to visually ascertain the presence of onychomycosis in at least 1 great toenail for subjects not included in the PK assessments, and on both great toenails and at least 4 other toenails for subjects included in the PK assessments. Additionally, the percent involvement of the affected great toenail(s) will be recorded. Specimen will be obtained from the great toenail(s) to ship to the mycology lab. Both toenails may be sampled if both are suspected of manifesting onychomycosis (at least 20% involvement). Blood and urine specimens will be collected for serum chemistry, hematology, and urinalysis evaluations. At relevant post-Screening Visits, the target great toenail will be trimmed back to the distal groove before the clinical evaluations are performed and before photographs are taken.

If a subject fails screening, either at the Screening or Baseline visit (prior to enrollment to treatment), the subject may be rescreened at a later date. Subjects who are rescreened, will be assigned a new screening number, must be re-consented, and undergo all screening procedures per protocol.

At the Baseline Visit (which should be scheduled after KOH and fungal culture results have been obtained from the mycology lab), subjects and/or their parents/legal guardians will update their medical histories and concomitant medication uses, and the inclusion/exclusion criteria will be confirmed. Subjects will undergo abbreviated physical examinations, clinical laboratory evaluations, assessments of vital signs (sitting blood pressure, respiration, pulse, and temperature), and measurements of height and weight. All FOCBP will have urine pregnancy tests performed. For the purposes of efficacy assessments, 1 target great toenail will be selected from the study-eligible great toenail(s), including subjects in the PK subset for whom both great toenails must be involved. Where both great toenails are study-eligible, the toenail with the greater percent of affected area will be selected for mycologic data and for inclusion in the efficacy analysis. In the instance where the percent of affected area is the same for both study-eligible great toenails, the investigator may select either great toenail as the target toenail. The target great toenail will be identified and recorded for each subject, photographs of the target great toenail will be obtained, and a transverse notch will be inscribed in the target great toenail adjacent to the proximal toenail fold (as a marker for measuring toenail growth at subsequent visits). Assessments of all other nontarget toenails, including the other involved toenails of subjects in the PK subset, will also be conducted to assess the presence or absence of onychomycosis on each toenail. This assessment will continue throughout the study visits through week 52.

After confirming eligibility at the Baseline Visit (Day 1), subjects will be enrolled in the treatment period. Subjects or their parents/legal guardians will apply the first dose of study drug to the qualified toenails at the investigational center under the supervision of designated study personnel. Any local skin reactions that occur at the study drug application site, along with any adverse events (AEs), will be recorded. Subjects and their parents/legal guardians will receive weighed study drug bottles and given verbal and written instructions for treatment application. Specifically, subjects who are not included in the PK subset will be instructed to apply the study drug to the affected toenails once daily at bedtime for 48 weeks. Subjects who are included in the PK subset will be instructed to apply the study drug to all 10 toenails once daily at bedtime for 4 weeks. Following the PK blood collections on Days 28 and 29, PK subjects that consented to the 52-Week trial will continue treatment with study drug to **only** the affected toenails. and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). All subjects or their parents/legal guardians will also

receive diaries, with instructions to complete a record of all applications and to note any missed applications of the study drug.

Subjects in the PK subset will not apply study drug the night prior to the Week 4 (Day 28) visit. Following the Day 28 study procedures, subjects in the PK subset will undergo timed blood collections to assess plasma concentrations of efinaconazole and metabolites (H3 and H4). Assessments will require collection of approximately 4 mL of whole blood at each time point (approximately 20 mL total). Within 1 hour after the predose blood sample is drawn, the subjects/parents/legal guardians will apply study drug to all 10 toenails at the investigational center. Subsequent blood collections will occur 2, 4, and 12 hours postdose on Day 28. The subjects will go home after Day 28, but will not apply study drug on the night of the Day 28 visit. All PK subjects in the 4-Week trial will return to the investigational center the following day (Day 29) for collection of a 24-hour postdose blood sample, and exit the study. PK subjects that consented 52-week trial will continue treatment with study drug to only the target great toenail and the other affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52)

Safety will be assessed by reviewing the occurrence of AEs and local skin reactions, assessing vital sign measurements and abbreviated physical examination findings, and noting any additions or changes in concomitant medication uses. Blood samples will be collected at Screening, at Week 4 (Day 28) only for PK subjects who have consented to only 4 weeks of treatment, and at Week 48 for routine safety laboratory evaluations (serum chemistry, hematology, and urinalysis); urine pregnancy tests will be obtained for all FOCBP at each study visit. Efficacy assessments will be performed throughout the study. Efficacy analyses will be based on microscopic examination and mycological culture results for the target great toenail, the percent involvement of the target great toenail, the length of the unaffected part of the target great toenail, the growth of the target great toenail, and the number of affected nontarget toenails.

A post-treatment follow-up visit will occur 4 weeks after the last treatment visit for each subject who continues through Week 48 (ie, at Week 52). Subjects who discontinue from the study prior to Week 48 will return to complete the Week 48 study procedures.

The study design and schedule of assessments is presented in Table 1

Table 1: Study Design and Schedule of Assessments

		Treatment Period														Post-Treatment
Visit	1-SCR	2-BL	3	3A [a]	4	5	6	7	8	9	10	11	12	13	14 [b]	15
Week	Up to Day -42	Day 1	4 (Day 28)	4 (Day 29)	8	12	16	20	24	28	32	36	40	44	48	52
PROCEDURES																
Obtain Informed Consent/Assent and Photography Consent/Assent	X															
Review Medical History	X	X [c]														
Review Previous Therapies	X	X [c]														
Review Inclusion/Exclusion Criteria	X	X [c]														
Conduct Urine Pregnancy Test (all females of childbearing potential) [d]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Clip Toenails [e]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Notch Target Great Toenail [f]		X														
Measure Target Great Toenail Growth (from the PNF to the notch) [f]			X		X	X	X	X	X	X	X	X	X	X	X	X
Conduct Target Great Toenail Assessments [g]	X	X				X			X			X			X	X
Conduct Nontarget Toenail Assessments [h]	X	X				X			X			X			X	X
Obtain Photography		X							X						X	X
Perform KOH Examination [i]	X					X			X			X			X	X
Sample for Fungal Culture [i]	X					X			X			X			X	X
Conduct Abbreviated Physical Exam [j]		X	X[t]												X	
Obtain Vital Signs [k]		X	X[t]			X			X			X			X	
Collect Blood and Urine Samples for CBC/Diff, Chemistry, and Urinalysis	X [p]		X[t]												X [l]	

		Treatment Period														Post-Treatment
Visit	1-SCR	2-BL	3	3A [a]	4	5	6	7	8	9	10	11	12	13	14 [b]	15
Week	Up to Day -42	Day 1	4 (Day 28)	4 (Day 29)	8	12	16	20	24	28	32	36	40	44	48	52
PROCEDURES																
Enroll Qualified Subjects		X														
Review Dosing Instructions		X	X		X	X	X	X	X	X	X	X	X	X		
Apply First Dose in Clinic		X														
Weigh/Dispense Study Drug		X	X[mu]		X	X	X	X	X	X	X	X	X	X		
Apply Study Drug		X[q]	◄	─	─	─	─	─	─	─	─	─	─	─	►	
Collect/Weigh Study Drug			X		X	X	X	X	X	X	X	X	X	X	X	
Review Compliance			X		X	X	X	X	X	X	X	X	X	X	X	
Dispense Diary		X	X[ou]		X	X	X	X	X	X	X	X	X	X		
Collect/Review Diary			X		X	X	X	X	X	X	X	X	X	X	X	
PK Blood Sample Collection [m]			X[m]	X[m]												
Review Local Skin Reactions		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exit Study				X[t]												X

Abbreviations: BL = Baseline Visit; CBC/Diff = complete blood count/differential; KOH = potassium hydroxide; PK = pharmacokinetic; PNF = proximal toenail fold; SCR = Screening Visit

Note: Post-baseline visits are to be scheduled in reference to Visit 2 (Baseline Visit) and within a window of ± 5 days.

[a] Visit 3A (Day 29) is only to be conducted for subjects in the PK subset.

[b] For all Non-PK subjects and PK subjects in 52 week trial, all Week 48 procedures are to be completed for subjects who discontinue from the study during the treatment period (ie, Early Termination).

[c] Confirmation of evaluations conducted at the Screening Visit.

[d] Urine pregnancy tests are required to have a minimum sensitivity of 25 mIU of human chorionic gonadotropin per mL of urine.

[e] Toenails are clipped prior to conducting the assessments.

[f] The transverse notch inscribed at the Baseline Visit is enhanced, as needed, at subsequent visits to allow continued measurement of toenail growth over the course of the study. In cases where the initial notch grows out or is clipped away, a new notch is inscribed in the toenail adjacent to the proximal toenail fold and measurements of toenail growth (ie, proximal toenail fold to notch) will continue using the new notch.

[g] Assessments include calculation of the percent involvement of the toenail affected by onychomycosis and measurement of the distance from the proximal toenail fold to the proximal onychomycotic border.

[h] Assessment of nontarget nails for presence or absence of onychomycosis.

[i] At the Screening visit, KOH specimens for KOH and fungal cultures will be shipped to the mycology lab. At all subsequently indicated study visits, specimens for KOH examinations and fungal cultures are obtained from the target great toenail.

[j] The abbreviated physical examination at the Baseline Visit and Week 48 includes height and weight,

[k] Vital sign measurements at each visit include temperature, pulse, respirations, and sitting blood pressure.

[l] Any clinically significant laboratory abnormality present at Week 48 (or Early Termination) is to be followed to resolution or until clinically stable as determined by the investigator.

[m] A subset of enrolled subjects will be assigned to PK evaluations. At the Week 4/Day 28 Visit, subjects in the PK subset will undergo timed blood sampling on Days 28 to 29

n Study drug should be weighed and dispense at Visit 3A for PK subjects

o Diary should be dispensed with study drug at Visit 3A for PK subjects.

[p] Collection of Screening safety labs may be postponed until after positive Screening mycology results are received, only if the subject/parent are willing to return to the research site for safety lab collection prior to the end of the 42-day screening window. Screening safety lab results must be received within the 42-day screening visit window.

[q] The subject or their parent/legal guardian will apply the first dose of study drug in the investigational center, with guidance from study staff.

Visit	3					3A[u]
Day (Week)	28 (4)					29 (4)
PROCEDURES	Predose	-1 h Following Pre-dose Sample	2 h (± 5 min)	4 h (± 5 min)	12 h (± 15 min)	24 h (± 30 min)
PK Subset - Collect Blood for Plasma Concentrations	X[r]		X	X	X	X
PK Subset - Study Drug Application		X[s]				

[r] The predose blood sample is to be collected after all Day 28/Week 4 study procedures are completed.

[s] Study drug application on Day 28/Week 4 will occur at the investigational center within 1 hour after collecting the predose blood sample. This will be the last application of study drug to all 10 toenails for subjects in the PK subset. For PK subjects that have consented to continuing treatment through week 48: After Day 28, subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) once daily at bedtime for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s).

[t] Applies only to PK subjects in who consented to 4 week trial

[u] Not applicable for PK subjects who consent to only the 4 week trial.

8 Selection and Withdrawal of Subjects

S.1 Subject Inclusion Criteria

Subjects meeting all of the following criteria will be eligible for study entry:

1. Male or female subjects of any race, 6 to 16 years of age (inclusive) at Screening.
   - **PK Subset**: Male or female subjects of any race, 12 to 16 years of age (inclusive) at Screening.
2. Verbal and written informed consent/assent obtained from the subject and/or their parent or legal guardian.
3. Good general health, as assessed by the investigator, based on the subject's medical history, physical examination, and safety laboratory tests.
4. At least 1 great toenail (the "target great toenail") with clinically diagnosed distal lateral subungual onychomycosis involving at least 20% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. There is no specific upper limit for percent involvement. Up to 6 toenails may have onychomycosis in subjects not participating in the PK subset.
   - **PK Subset**: Both great toenails with clinically diagnosed distal lateral subungual onychomycosis involving at least 50% of the affected great toenail at the Screening and Baseline Visits (as determined by the investigator), without dermatophytomas or lunula (matrix) involvement. There is no specific upper limit for percent involvement. Subjects must also have at least 4 toenails other than the great toenails with onychomycosis.
5. Target great toenail for all subjects, and both great toenails for subjects in the PK subset, must have evidence of toenail growth, per subject's report that monthly clipping is needed.
6. Within 42 days prior to the Baseline (Day 1) Visit, have a positive KOH examination (results will be provided by the central the mycology lab) of the target great toenail for all subjects
7. Within 42 days prior to the Baseline (Day 1) Visit, have a positive dermatophyte culture for *T rubrum* or *T mentagrophytes* (at the central mycology laboratory) from the target great toenail in all subjects
   - **PK Subset**: Prior to the Baseline Visit, the great toenail designated for efficacy assessments as the target great toenail must have both a positive KOH examination (results will be provided by the central mycology lab) and a positive fungal culture.
8. All FOCBP must have a negative urine pregnancy test at the Screening and Baseline Visits and must agree to use an effective method of contraception throughout the

study. Effective contraception is defined as use of an intrauterine device, condom with spermicide, diaphragm with spermicide, abstinence (subject is not sexually active), or stable use of a hormonal contraceptive (oral, implant, injection, or transdermal patch) for at least 3 months prior to the Baseline Visit.

9. Subjects and their parents/legal guardians are willing to comply with study instructions and return to the investigational center for all required visits (a visit schedule with the length of each visit will be provided to ensure that the subject can meet the requirements and have adequate transportation).
10. Subjects and parents/legal guardians agree that the subject will avoid the use oftoenail polish, cosmetic toenail products, and pedicures during the study period.

S.2 Subject Exclusion Criteria

Subjects meeting any one of the following criteria will be excluded from the study:

1. Females who are pregnant, nursing an infant, or planning a pregnancy during the study period.
2. History of immunosuppression and/or clinical signs indicative of possible immunosuppression, as determined by the investigator, or known human immunodeficiency virus infection.
3. History of diabetes that is uncontrolled as determined by the investigator (diabetes that is controlled by diet or medication does not exclude a subject).
4. Presence of any toenail infection other than or in addition to dermatophytes, such as *Scytalidium* as determined by the investigator (candidal onychomycosis infection, concurrent with a positive dermatophyte culture, is acceptable).
5. Presence of any of the following: dermatophytoma, fungal "spikes" within 3 mm of the proximal toenail fold on the target great toenail, infection extending to the matrix, or only lateral toenail disease in the target great toenail.
6. Presence of severe moccasin tinea pedis at the Screening or Baseline Visits, as determined by the investigator. If the subject has interdigital tinea pedis that requires treatment, the subject must agree to use only an investigator-approved topical antifungal therapy.
7. Presence of any disease/condition that might cause toenail abnormalities or may interfere with the evaluation of the study drug as determined by the investigator (eg, open sores or ulceration on the toes of affected toenails, psoriasis, immune dysfunction, collagen-vascular diseases, lichen planus, peripheral vascular disease, or traumatic onychodystrophy due to chronic physical stimuli).
8. Any previous surgery on the target great toenail.
9. Presence of onychomycosis of the fingernail.
10. History of immunodeficiency as determined by the investigator.
11. Presence of 1-hand, 2-foot syndrome, or fingernail dermatophytosis.

12. Target great toenail (including toenail plate and any subungual debris) thicker than 3 mm at the Screening and Baseline Visits.
13. Presence of onychodystrophy that could interfere with clinical assessments as determined by the investigator.
14. History of hypersensitivity or allergic reactions to azole derivatives or any of the study drug constituents.
15. Presence of any underlying disease that, in the opinion of the investigator, could present a safety concern for the subject by participating in the study.
16. Subject has received treatment for any type of cancer in the previous 6 months, except for nonmelanoma skin cancer (eg, basal cell carcinoma or nonmetastatic squamous cell carcinoma) that was treated successfully.
17. Presence of any dermatological condition on the feet that could interfere with clinical evaluations as determined by the investigator.
18. Presence of any underlying disease or dermatological condition other than onychomycosis that requires the use of interfering topical or systemic therapy and would make evaluations inconclusive as determined by the investigator, or subject requires treatment with a topical product on the toenails other than the study drug during the study.
19. Subjects using the following topical preparations within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following topical preparations during the study:

- Toenail polish or cosmetic toenail products: 1 day
- Other topical prescription or over-the-counter medications to the toenails (with the exception of bland emollients): 2 weeks
- Topical prescription or over-the-counter antifungal therapy for the toenails, including devices to treat onychomycosis: 4 weeks

20. Subjects using the following systemic medications within the indicated time prior to the Baseline Visit, or requires concurrent use of any of the following systemic medications during the study:

- Systemic antifungal therapy: 4 weeks
- Systemic immunosuppressive agents: 6 months

21. Subject has previously been nonresponsive to systemic antifungal therapy for onychomycosis.
22. Subject is unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.

23. Use of any investigational drug or device within 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit, or concurrent participation in another clinical study with an investigational drug or device.

S.3 Subject Withdrawal Criteria

When possible, subjects who discontinue from the study prior to completing the 48-week treatment period should return to the investigational center to perform the assessments scheduled for Week 48. If appropriate, discontinued subjects may be placed on other conventional therapy upon request or whenever clinically necessary, as determined by the Investigator. The End of Study source documents and all relevant data should be entered into the electronic case report form (eCRF) system at the time the subject discontinues from the study.

Reasons for subject withdrawal may include, but are not limited to, the following:

- Onychomycosis progression, as determined by the investigator, which requires treatment with a prohibited therapy
- Either at the investigator's discretion for safety reasons (eg, severe adverse reactions or unauthorized concomitant therapy), or at the subject's request for personal reasons
- When the requirements of the protocol are not followed
- When a concomitant therapy likely to interfere with the results of the study is reported or required by the subject (the investigator will report all such information on the source documents/eCRFs and decide, in accordance with the Sponsor, whether the subject is to be withdrawn)
- When a subject is lost to follow-up; the investigator (or designee) will try twice to reach the subject by telephone, and will send a follow-up letter by certified mail before considering the subject as lost to follow-up; these actions will be documented in the source documents and recorded on the End of Study eCRF, with a copy of the follow-up letter maintained in the investigator's file
- If a subject becomes pregnant during the treatment period, the study drug will be discontinued immediately, the subject will be discontinued from the study, and the investigator will notify the sponsor. The pregnancy will be followed to term with the outcome reported to the sponsor.

9 Treatments Planned

9.1 Methods of Assigning Subjects to Treatment Groups

This is a single-arm, open label study. After confirming eligibility at the Baseline Visit, subjects will be enrolled in the treatment period and will receive efinaconazole in accordance with the protocol (Section 10).

9.2 Randomization and Blinding

Randomization and blinding do not apply.

PK assessments will be performed on a subset of the study population. Efforts will be made to enroll subjects into the PK subset such that they are evenly distributed across the required age range.

9.3 Treatment Compliance

Subjects and their parents/legal guardians will be dispensed an initial bottle of study drug at Baseline (Day 1). Subjects and their parents/legal guardians will be instructed on the importance of returning the subject's study drug bottle(s) at the next study visit. If a subject does not return his/her study drug bottle, he/she will be instructed to return it at his/her next study visit. A new study drug bottle will be dispensed to the subjects at each post baseline study visit through Week 44. Subjects in the PK subset will be dispensed 2 bottles of study drug at Baseline (Day 1), and will be dispensed one bottle of study drug at each subsequent study visit through Week 44. All used and unused study drug bottles will be collected at Week 48.

The investigational center staff will weigh and record each bottle of study drug before dispensing to the subject and their parent/legal guardian and following return by the subject. Bottle weights will be recorded in the individual study drug log and in the appropriate eCRF.

At each post baseline study visit, subjects and/or their parents/legal guardians will be asked to report any missed doses of study drug, and provide the date and an explanation for each missed dose. A subject who has deviated from the once daily dosing regimen will be counseled in the presence of their parent/legal guardian. The dates of any missed doses of study drug will be recorded in the subject's source document and appropriate eCRF.

9.4 Treatment Administration

Subjects and their parents/legal guardians will receive both verbal and written instructions on the application of the study drug. The subject and/or their parent/legal guardian will apply the first dose of study drug at the investigational center during the Baseline Visit. All of the remaining study drug doses will be applied by the subject at home. The subjects and their parents/legal guardians will be instructed to wait for the toenails to air-dry thoroughly before touching with clothing.

Dosing for Subjects NOT Included in the PK Subset: Subjects and their parents/legal guardians will be instructed to apply their assigned study drug to the target great toenail and all other affected toenail(s) (if any) once daily at bedtime. Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study,

subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be instructed to apply the study drug by completely covering the target great toenail, including the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate. The study drug will be applied to each of the other infected toenails in a similar manner.

Dosing for Subjects Included in the PK Subset:
Days 1 to 2S - Subjects and their parents/legal guardians will be instructed to apply study drug to all 10 toenails, once daily at bedtime. During this period, all PK subjects will be instructed to apply the study drug by completely covering each toenail and 0.5 cm of adjacent skin, including the toenail folds, toenail bed, hyponychium, undersurface of the toenail plate. The subjects will not apply study drug the night prior to the Week 4 (Day 28) visit, nor will they apply study drug on the night of the Week 4/Day 28 Visit. Within 1 hour after the predose blood sample is drawn on Day 28, subjects will apply study drug to all 10 toenails in the manner described above at the investigational center.

Days 29 to Week 4S (only PK subjects consenting in the 52-Week Trial):):
After completion of the PK portion of the study, if the subject consented to the 52-Week trial, , subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) once daily at bedtime for the entire treatment period, even if the disease clears and no affected area is observed on the target great toenail. If other affected toenails treated since baseline clear during the course of the study, subjects and/or their parents/legal guardians will be encouraged to continue treatment on those toenails for the duration of the study. In addition, if new toenails become infected during the study, the subject will be instructed to start treating the additionally affected toenail(s). All subjects and their parents/legal guardians will be given instructions regarding how to apply the study drug, ie, by completely covering the target great toenail, including the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate (if onychomycosis is present). The study drug will be applied to each of the other infected toenails in a similar manner.

9.5 Concomitant Medications

Concomitant medications/therapies refer to all medications/therapies used by the subject during the study. During the course of the study, if appropriate, every attempt should be made to keep the dosing and regimen of concomitant medications/therapies constant, and any change to a medication/therapy during the study must be recorded. Information on concomitant medications/therapies (including indication, dosing, and start and stop dates) will be recorded in the source document and on the appropriate eCRF. All concomitant medications/therapies

(including foot care products) used during the study will be recorded under Concomitant Medications.

All prior medications (those used within 30 days prior to the Screening Visit) and previous antifungal medications used by the subject, including any recent over-the-counter topical treatments (those used within 60 days prior to the Screening Visit) will be recorded under Prior and Concomitant Medications in the eCRF (eg, aspirin, acetaminophen, birth control pills, vitamins, herbal products, homeopathic preparations).

During the study, all foot care products used by the subject will be recorded under Prior and Concomitant Medications.

9.5.1 Allowed Medications/Therapies

Concomitant medications (prescription or over-the-counter) that are considered necessary for the subject's welfare and do not interfere with study assessments and evaluations will be allowed during the study at the investigator's discretion.

If, during the study, a subject requires topical antifungal therapy for tinea pedis, the investigator is to document the problem and the investigator-approved treatment on the AE and concomitant therapy eCRFs, respectively, and to ensure that the subject avoids application of the concomitant therapy to the toenails or adjacent surrounding skin surface.

9.5.2 Prohibited Medications/Therapies

No topical treatments/products will be allowed on the toes or feet other than the study drug during the study, except for investigator-approved treatments. The subject may use any topical antifungal therapy the Investigator approves for use. Use of the following topical treatments is prohibited within the indicated time prior to the Baseline Visit:

Toenail polish or cosmetic toenail products	1 day
Other topical prescription or over-the-counter medications to the toenails (with the exception of bland emollients)	2 weeks
Topical prescription or over-the-counter antifungal therapy for the toenails, including devices used to treat onychomycosis	4 weeks

Use of the following systemic medications is prohibited within the indicated time prior to the Baseline Visit and for the duration of the study:

Systemic antifungal therapy	4 weeks
Systemic immunosuppressive agents	6 months

In addition, use of any investigational drug or device within 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit, or concurrent participation in another clinical study with an investigational drug or device during the study period is not allowed.

If a specific medication/therapy has the potential to interfere with the treatment effect of the study drug or interpretation of the study results, the investigator should contact the medical monitor prior to use (if possible).

Any subject using a prohibited therapy during the course of the study that could interfere with the treatment effect of the study drug or interpretation of the study results (including, but not limited to, those listed above) may be withdrawn from the study at the discretion of the investigator and/or sponsor. However, the investigator should not withdraw a subject without first confirming it with the sponsor.

9.6 Protocol Deviations and Violations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the sponsor and the institutional review board (IRB) or independent ethics committee (IEC) and agreed to by the investigator. Deviations usually have an impact on individual subjects or a small group of subjects and do not involve inclusion/exclusion or primary endpoint criteria.

A protocol violation occurs when there is nonadherence to the protocol that results in a significant, additional risk to the subject, when the subject or investigator has failed to adhere to significant protocol requirements (inclusion/exclusion criteria) and the subject was enrolled without prior sponsor approval, or when there is nonadherence to US Food and Drug Administration regulations and/or International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline.

The investigator or designee must record and explain in the subjects' source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the sponsor for agreement, to the IRB/IEC for review and approval, and to the regulatory authorities, if required.

10 Study Drug Materials and Management

The study drug will be provided to the investigational centers by the sponsor and will be dispensed to the subject and their parent/legal guardian by the pharmacy or an appropriately qualified member of the study staff assigned by the investigator.

All laboratory kits containing materials necessary to collect blood and urine for routine clinical laboratory tests, urine pregnancy tests, fungal cultures, and PK analyses will be supplied to the investigational centers by the designated central laboratories.

10.1 Study Drug

A description of the study drug is included in Table 2.

Table 2. Study Drug Identification

	Investigational Product
Drug Name	Efinaconazole 10% solution for topical administration
Name of Active Ingredient	Efinaconazole
Manufacturer	Valeant Pharmaceuticals
Chemical Name	(2R,3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol
Chemical Formula/Molecular Weight	$C_{18}H_{22}F_2N_4O$ / 348.39 amu
Therapeutic Category	Antifungal
Appearance	Clear to yellow solution
Inactive Ingredients	Alcohol, anhydrous citric acid, butylated hydroxytoluene, C12-15 alkyl lactate, cyclomethicone, diisopropyl adipate, disodium edetate, and purified water.

10.1.1 Packaging and Labeling

Efinaconazole will be provided to the investigational centers in 10 mL bottles containing 8 mL of study drug per bottle. Individual bottles will be supplied to the investigational center. The subjects and their parents/legal guardians will be dispensed 1 bottle at the Baseline Visit and 1 bottle at each subsequent study visit through Week 44. Subjects in the PK subset will be dispensed 2 bottles of study drug at the Baseline Visit, and will be dispensed one bottle of study drug at each subsequent study visit through Week 44.

The label on each bottle of study drug will identify the product as "Efinaconazole". The label on the study drug bottles will contain the following information:

- Protocol number
- Kit number
- Product identification (Efinaconazole 10% Solution)
- Subject number_____
- Subject initials_____
- Date dispensed _____
- A statement indicating the volume of the contents as 8 mL
- Instructions to keep bottle tightly closed and store in an upright position at room temperature (20°C to 25°C [68°F to 77°F]), with excursions permitted between 15°C and 30°C (59°F and 86°F)

- Lot number/expiration date
- Sponsor name and address
- A statement indicating, "Caution: New Drug - Limited by Federal Law to Investigational Use"
- A statement indicating that the drug should be kept out of reach ofchildren

Additional information may be included on the bottle label as necessary.

10.1.2 Storage, Handling, and Disposal of Study Drug

Study drug should be stored in a secure area at the investigational center according to local regulations, in an upright position at controlled room temperature (20°C to 25°C [68°F to 77°F]), with excursions permitted between 15°C and 30°C (59°F and 86°F).

Subjects and their parents/legal guardians will be instructed to keep their study drug bottle at room temperature, out of the reach of children, not to share the study drug with anyone else, and to use it only on the affected toenails as directed by the investigator. Subjects and their parents/legal guardians will be asked to notify the investigational center immediately if a study drug bottle is damaged or lost.

All used and unused study drug supplies will be returned to the sponsor for destruction.

10.1.3 Study Drug Preparation

Not applicable; subjects and/or their parents/legal guardians will apply the study drug directly from the study drug bottles.

10.2 Study Drug Accountability

The Investigator or designee will be responsible for keeping current and accurate records of the amount of study drug received and dispensed, and its disposition. The study drug must be stored under the appropriate conditions in a secure area and is to be dispensed only to subjects enrolled in the study, in accordance with the conditions specified in this protocol. During the course of the study, the Investigator or designee must maintain an inventory of all study drug dispensed to or returned by the subject, including subject identifiers.

A study drug accountability log will be completed by the investigator or designee to document the receipt, dispensation, and return of study drug bottles.

All supplies sent to the Investigators will be accounted for and, in no case, used in any unauthorized situation. Bottles will be weighed (with the cap on) before dispensing to and upon return by the subjects, and weights will be recorded on the pharmacy log and appropriate CRF. All used and unused supplies will be returned to sponsor/designee for destruction at the conclusion of the study.

11 Study Procedures and Evaluations

11.1 Schedule of Evaluations and Procedures

All subject information and data obtained during the study visit procedures must be recorded in the source documents, applicable study logs, and eCRFs.

11.1.1 Screening Visit (Visit 1, Up to Day -42)

After signing the informed consent/assent, subjects will undergo the screening procedures to confirm eligibility to participate in the study.

Newly screened PK subjects will decide at the time of signing consent whether they will consent to the 4-Week trial or participate in the 52-Week trial.

Note: *Subjects that consent to 4 -Week trial will not be allowed to extend their study consent to 52 weeks. Subsequently, PK subjects who consent to the 52-Week trial will be considered discontinued/Early Terminated if he/she discontinues prior to the Week 52 visit.*

The following procedures will be conducted at this visit:

1. Review and explain the nature of the study. Provide a visit schedule with the length of each visit to ensure that the subject can meet the requirements and has adequate transportation.
2. Obtain verbal and written informed consent/assent from the subject and the subject's parent(s) or legal guardian(s) prior to performing any study-related procedures. Provide signed copies of the consent and assent forms to the subject/parent(s) or legal guardian(s).
3. Obtain photography consent/assent from subject and/or the subject's parent(s) or legal guardian(s).
4. Assign a 6-digit study number, which includes the 3-digit investigational center number plus a unique 3-digit subject number beginning with 001 (eg, 001-001, 001-002, 001-003). Numbers must be assigned in chronological order.
5. Record subject's demographic information (sex, date of birth, age, ethnicity, and race).
6. Record subject's medical history including diabetes history.
7. Collect a detailed history of onychomycosis, including an estimated start date of infection, duration of current infection in the potential target great toenail, and all previous therapies used for onychomycosis treatment.
8. Review all prior medications (those used within 30 days prior to the Screening Visit) and previous antifungal medications used by the subject, including any recent over-the-counter topical treatments (those used within 60 days prior to the Screening Visit).
9. Review inclusion/exclusion criteria.

10. Examination of toenails for clinical presence of onychomycosis in at least 1 great toenail, within the definition of eligibility criteria. For subjects in the PK population, both great toenails and 4 other toenails must meet eligibility criteria
11. Examination of all other toenails for presence or absence of onychomycosis on each toenail.
12. Examination of both feet for presence of symptomatic tinea pedis; treat as appropriate using investigator approved topical antifungal therapy
13. Clip the toenails (before performing nail measurements). Remind subject and their parent/legal guardian not to clip toenails at home in between visits.
14. Perform the investigator's assessment of the great toenail(s) with a calculation of the percentage of toenail affected with disease, after clipping the unhealthy toenail. If the great toenail has been clipped proximal to the distal groove, the entire area to the distal groove should be included. The investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail (this is optional at this visit since photography is not done at this visit; outlining should be done if beneficial to performing assessments).
    - Subjects not included in the PK subset must have at least 1 great toenail with 2 20% involvement
    - Subjects included in the PK subset must have both great toenails involved with 2 50% involvement in each great toenail.
15. Obtain specimen from the great toenail(s) to ship to the mycology lab. Both great toenails may be sampled if both are suspected of manifesting onychomycosis (at least 20% involvement).
16. Perform a urine pregnancy test[1] for all FOCBP.[2] Exclude the subject if the pregnancy test result is positive.

    Urine pregnancy testing is mandatory for all FOCBP at the Screening Visit, Baseline Visit, and at all subsequent study visits. The decision may be made by the investigator to do additional urine pregnancy tests during the course of the study.

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[1] Urine pregnancy tests must have a minimum sensitivity of 25 mIU of human chorionic gonadotropin per mL of urine. Urine pregnancy test kits will be provided by the sponsor.

[2] FOCBP include any female subjects who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal (defined as amenorrhea for > 12 consecutive months or women on hormone replacement therapy with documented plasma follicle-stimulating hormone levels > 35 mLU/mL). Even a female subject who is using an oral, implanted, injectable, or transdermal contraceptive hormone, an intrauterine device, a condom with spermicide, or a diaphragm with spermicide to prevent pregnancy, or is practicing abstinence, should be considered of childbearing potential.

17. Collect blood and urine samples for routine safety laboratory analysis (hematology, serum chemistry, and urinalysis). Process and ship the samples to the central safety laboratory per instructions provided in the laboratory manual.

    Note: Collection of Screening safety labs may be postponed until after positive Screening mycology results are received, only if the subject/parent are willing to return to the research site for safety lab collection prior to the end of the 42-day screening window. Screening safety lab results must be received within the 42-day screening visit window.

18. Schedule subject to return for the Baseline Visit (Visit 2, Day 1).

    If a subject fails screening, either at the Screening or Baseline visit (prior to enrollment to treatment), the subject may be rescreened at a later date. Subjects who are rescreened will be assigned a new screening number, must be re-consented, and undergo all screening procedures per protocol.

11.1.2 Baseline Visit (Visit 2, Day 1)

If the Baseline Visit is more than 42 days after the Screening Visit, the subject must be reported as a screen failure and then may be rescreened (with a new subject number) at the investigator's discretion.

The following procedures will be conducted at this visit:

1. Record any AEs (query subjects and their parents/legal guardians, "Are there any changes in your health since the last visit?").
2. Confirm positive KOH and culture results from the central mycology laboratory.
    - All subjects (including those in PK subset) must have at least 1 great toenail with positive KOH (performed at central mycology lab) and positive dermatophyte culture for *T rubrum* or *T mentagrophytes*.
3. Review the safety laboratory test results.

    If any safety laboratory test results obtained at the Screening Visit, are abnormal and clinically significant as determined by the investigator, the investigator should discuss with the medical monitor whether it is in the subject's best interest to participate in the study.
4. Confirm the subject's medical history and prior medication uses.
5. Review all concomitant medications and new medications started since the last study visit.
6. Obtain vital sign measurements. Vital signs will be measured after the subject is seated for at least 5 minutes, and will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.
7. Measure height and weight.
8. Conduct an abbreviated physical examination (excluding urogenital/reproductive systems).

9. Perform a urine pregnancy test for all FOCBP. Exclude the subject if the pregnancy test result is positive.
10. Clip the toenails to the distal groove (before performing toenail measurements and close-up photography).
11. Conduct the investigator's assessment of the great toenail (s), with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
    - Subjects not included in the PK subset must have at least 1 great toenail with 2 20% involvement
    - Subjects included in the PK subset must have both great toenails involved with 2 50% involvement in each great toenail.
12. Select target great toenail in each eligible subject for efficacy assessments. Where both great toenails are study-eligible (including percent involvement, KOH-positive, and culture-positive results), the toenail with the greater percent affected area at the Baseline Visit will be selected as the target great toenail prior to enrollment in the treatment period. In the instance where the percent affected area is the same for both study-eligible great toenails at the Baseline Visit, the investigator may choose either great toenail to be the target great toenail.
13. Inscribe a transverse notch in the great toenail at the proximal nail fold with a file or scalpel. This will be used as a marker at subsequent visits for determining new toenail growth.
14. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis. Subjects in the PK subset must have at least 4 toenails other than the great toenails with onychomycosis.
15. Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
16. Review inclusion/exclusion criteria. If the subject continues to meet all inclusion criteria and none of the exclusion criteria, enroll the subject in the treatment period.
17. Obtain 1 bottle of study drug and weigh the bottle. Record the assigned bottle number for the study drug in the subject's source document and on the appropriate eCRF. Dispense the bottle to the subject and their parent/legal guardian (complete the label and required records). For subjects in the PK subset, 2 bottles of study drug should be obtained. The bottles should be weighed separately and recorded as separate entries, as described above.
18. Instruct the subject and their parent/legal guardian on diary completion and dispense diary.
19. The subject or their parent/legal guardian will apply the first dose of study drug in the investigational center. Instruct the subject and their parent/legal guardian in theproper

application technique for the study drug and provide the appropriate Subject Instruction Sheet with dosing instructions (ie, for non-PK or PK subjects), depending on whether the subject is enrolled in the PK subset. Record any AEs following the initial treatment application.

20. Record local skin reactions. Instruct the subject and their parent/legal guardian to report local skin reactions (if any) at each study visit.
21. Schedule the next study visit (Visit 3 [Week 4, Day 28]) in 28 days (± 5 days).

Note: (± 5 days) only applies to Non-PK subjects, PK subset only has a (± J day) visit window

- For subjects in the PK subset, Visit 3 (Week 4, Day 28) to Visit 3A (Week 4, Day 29) remind subjects not to apply study drug the night prior to their Visit 3 (Week 4, Day 28) visit.

11.1.3 Visit 3 (Week 4, Day 2S [± 5 days]), Visit 4 (Week S [± 5 days]), Visit 6 (Week 16 [± 5 days]), Visit 7 (Week 20 [± 5 days]), Visit 9 (Week 2S [± 5 days]), Visit 10 (Week 32 [± 5 days]), Visit 12 (Week 40 [± 5 days]), Visit 13 (Week 44 [± 5 days])

Visits are to be scheduled in reference to Visit 2 (Baseline).

The following procedures will be conducted at this visit:

1. Record any AEs (query subjects and their parents/legal guardians, "Are there any changes in your health since the last visit?").
2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Clip the toenails.
5. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch). If the most recently applied notch has grown out or has been clipped off, inscribe a new notch adjacent to the proximal nail fold.
6. Collect the diary and study drug bottle from the subject and/or their parent/legal guardian. Weigh the used bottle of the study drug. Record the number of missed doses from the subject diary and review compliance with the subject.
7. Conduct a urine pregnancy test on FOCBP subjects (discontinue any subject from the study who has a positive test result)
8. Obtain 1 bottle of study drug and weigh the bottle, complete the label and drug log, and dispense the bottle to the subject and their parent/legal guardian. Review the dosing instructions with the subject. (Subjects in the PK subset will not be dispensed study drug this day).
9. Dispense diary. (Subjects in the PK subset will not be dispensed a diary this day.)
10. Schedule the next study visit.

Note: PK subjects exiting the study on Day 29 (consented to only the 4-Week trial), the following procedures will be conducted in addition to the procedures listed above.

11. Collect blood and urine samples for routine safety laboratory analysis (hematology, serum chemistry, and urinalysis). Process and ship the samples to the central safety laboratory per instructions provided in the laboratory manual.
12. Measure height and weight.
13. Conduct an abbreviated physical examination (excluding urogenital/reproductive systems).

For subjects in the PK subset at Visit 3 only:

- Collect a predose blood sample after all other study procedures are completed.
- Apply the study drug to all 10 toenails at the investigational center within 1 hour after collecting the predose blood sample.
- Collect postdose blood samples at approximately 2 hours (± 5 min), 4 hours (± 5 min), and 12 hours (± 15 min) after study drug application.
- Instruct the subject to return the following morning for their 24-hour blood sample (Visit 3A (Day 29). Subject will not dose on the evening of Day 28.

11.1.4 Visit 3A (Week 4, Day 29) - Additional Visit for Subjects in the PK Subset

The following procedures will be conducted at this visit:

1. Record any AEs (query subject "Are there any changes in your health?").
2. Record local skin reaction scores reported by the subject.
3. Review concomitant medications.
4. Collect a blood sample 24 hours (± 30 min) after study drug application at Visit 3.
5. Obtain 1 bottle of study drug and weigh the bottle, complete the label and drug log, and dispense the bottle to the subject and their parent/legal guardian. Review the new dosing instructions with the subject (application to only the target great toenail and to any other affected toenails) and provide a copy of new dosing instructions to the subject.
6. Dispense a new diary that includes the new dosing instructions.

Note: PK subjects who consented to only the 4 Week trial will exit the study on Day 29. Drug and subject diary will not be dispensed and urine pregnancy test will not be collected at this visit. .

11.1.5 Schedule the PK subset subject (if consented to the 52-Week trial) for the next study visit. Visit 5 (Week 12 [± 5 days]), Visit S (Week 24 [± 5 days]), Visit 11 (Week 36 [± 5 days])

Visits are to be scheduled in reference to Visit 2 (Baseline).

The following procedures will be conducted at these visits:

1. Record any AEs (query subject and their parent/legal guardian "Are there any changes in your health since the last visit?").
2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Conduct a urine pregnancy test on FOCBP subjects (discontinue any subject from the study who has a positive test result).
5. Clip the toenails.
6. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch). If the most recently applied notch has grown out or has been clipped off, inscribe a new notch adjacent to the proximal nail fold.
7. Conduct the investigator's assessment of the target great toenail, with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
8. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis.
9. Obtain specimens from the target great toenail for fungal culture and KOH examination and send to the mycology central lab per instructions provided in the laboratory manual.
10. Obtain vital sign measurements. Vital signs will be measured after the subject is seated for at least 5 minutes and will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.
11. At Visit 8/Week 24 only: Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
12. Collect the diary and study drug bottle from the subject and/or their parent/legal guardian. Weigh the used bottle of the study drug. Record the number of missed doses from the subject diary and review compliance with the subject and parent/legal guardian.
13. Obtain 1 bottle of study drug and weigh the bottle, complete the label and drug log, and dispense the bottle to the subject and parent/legal guardian.
14. Review the dosing instructions with the subject.

15. Dispense diary.
16. Schedule the subject for the Visit 6 (Week 16 [± 5 days]) study visit, and instruct the subject to return at the same time of day as the Baseline Visit. The Visit 7 (Week 20 [± 5 days]) and Visit 8 (Week 24 [± 5 days]) study visits will follow Visit 6.

11.1.6 Visit 14 (Week 4S [± 5 days]) / Early Termination Visit

The following procedures will be conducted at this visit:

1. Record any AEs (query subject and their parent/legal guardian "Are there any changes in your health since the last visit?").
2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Clip the toenails.
5. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch). If the most recently applied notch has grown out or has been clipped off, inscribe a new notch adjacent to the proximal nail fold.
6. Conduct the investigator's assessment of the target great toenail, with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
7. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis.
8. Obtain specimens from the target great toenail for fungal culture and KOH examination and send to the mycology central lab per instructions provided in the laboratory manual.
9. Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
10. Conduct an abbreviated physical examination (excluding urogenital/reproductive systems).
11. Measure height and weight
12. Obtain vital sign measurements. Vital signs will be measured after the subject is seated for at least 5 minutes, and include systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature.
13. Collect the diary and study drug bottle from the subject and/or parent/legal guardian. Weigh the used bottle of the study drug. Record the number of missed doses from the subject diary and review compliance with the subject and parent/legal guardian.
14. Conduct a urine pregnancy test on FOCBP subjects (if positive test result, the subject should return for Visit 15 [Week 52]

15. Collect blood and urine samples for routine safety laboratory analysis (hematology, serum chemistry, and urinalysis). Process and ship the samples to the central safety laboratory per instructions provided in the laboratory manual.
16. If this is the Early Termination Visit, record the reason for subject discontinuation from the study and complete the Week 48 eCRF. If this is not an Early Termination Visit, the subject should be scheduled to return for the Visit 15 (Week 52) study visit.

11.1.7 Visit 15 (Week 52 [± 5 days]) Post-Treatment Follow-up Visit / Study Exit

For all subjects who continue through the Week 48 visit, this visit should occur 4 weeks after the last treatment visit.

The following procedures will be conducted at this visit:

1. Record any AEs (query subject and their parent/legal guardian, "Are there any changes in your health since the last visit?").
2. Record local skin reaction scores reported by the subject and parent/legal guardian.
3. Review concomitant medications.
4. Clip the toenails.
5. Measure the target great toenail growth since the Baseline Visit (distance from proximal nail fold to transverse notch).
6. Conduct the investigator's assessment of the target great toenail, with a determination of the percentage of toenail affected with disease. Measure the distance from the proximal nail fold to the proximal onychomycotic border.
7. Perform the investigator's assessment of the nontarget toenails for the presence or absence of onychomycosis.
8. Obtain specimens from the target great toenail for fungal culture and KOH examination and send to the mycology central lab per instructions provided in the laboratory manual.
9. Take close-up photographs of the target great toenail. The first photograph will be taken after toenail clipping. After that photograph is taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. When the marker ink has dried, a second close-up photograph will be taken.
10. Conduct a urine pregnancy test on FOCBP subjects.
11. Exit the subject from the study.

11.1.S Unscheduled Visits

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional exams should be fully documented in the source documents and on Unscheduled Visit eCRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit range, are not unscheduled visits. In these cases, the visit data will be collected and transcribed to the appropriate scheduled visit eCRF.

11.1.9 Missed Visits

If a subject misses any scheduled visit and cannot be seen prior to the start of the allowed visit range for the next scheduled follow-up visit, the visit is considered missed.

11.1.10 Subject Completion

A subject has completed the study when Visit 15 (Week 52) has been completed and the subject has been exited from the study. Subjects who require further follow-up for an AE following completion of the study will be followed according to Section 12.0.

11.2 Study Evaluations

11.2.1 Local Skin Reactions

Tolerability will be evaluated through assessment of local redness, swelling, burning, itching, and vesiculation in the selected treatment areas on the toes. Each sign or symptom is to be reviewed with the subjects and their parents/legal guardians after the first application of the study drug at the Baseline Visit and at each follow-up visit through Week 52. The subjects and their parents/legal guardians should assess each reaction based on the worst reaction experienced since the prior visit using the following scales:

Reaction	Score
Redness, Swelling	0 = None 1 = Mild 2 = Moderate 3 = Severe
Burning, Itching, and Vesiculation	Yes or No

Occurrence of vesiculation will always be reported as an AE. Any other sign or symptom will be reported as an AE only if it requires concomitant therapy or results in a temporary interruption or permanent discontinuation of the study drug due to discomfort.

11.2.2 Clinical Laboratory Tests

Blood and urine samples will be collected for routine safety laboratory tests (hematology, serum chemistry, and urinalysis) at the Screening and Week 48/Early Termination visit. Any subject with a screening laboratory abnormality that is determined by the investigator to be clinically significant must be approved for inclusion in the study by the medical monitor. All results will be reported, including abnormal results. Clinically significant changes in lab results from Screening, in the opinion of the investigator, should be reported as AEs. Clinically significant changes present at Week 48/Early Termination are to be followed to resolution or until clinically stable as determined by the investigator. If an AE should require laboratory testing, the results of the test must be obtained by the investigational center and filed in the subject's documentation.

Materials for sample collection will be provided to the investigational centers by the sponsor or central laboratory. Instructions for processing and shipping samples to the central laboratory are contained in the study laboratory manual.

For all FOCBP, urine pregnancy testing will be performed at the Screening and Baseline Visits, as well as at each subsequent study visit. FOCBP is defined as any female subject who has experienced menarche. The results at the Screening and Baseline Visits must be negative for a subject to enter the study. Materials for pregnancy testing will be provided to the investigational centers by the sponsor or central laboratory.

11.2.3 Vital Sign Measurements

Measurement of vital signs will be performed at the Baseline Visit, as well as at Weeks 12, 24, 36, and 48/Early Termination. After the subjects have been sitting for at least 5 minutes, systolic and diastolic blood pressures, pulse rates, respiration rates, and oral temperatures will be recorded.

11.2.4 Physical Examinations

An abbreviated physical examination will be performed at the Baseline Visit and at Week 48/Early Termination. Height and weight will be measured at the Baseline Visit and at the Week 48/Early Termination Visit.

11.2.5 Efficacy for Assessing Treatment Compliance and Safety

Efficacy assessments will be performed throughout the study. The efficacy analyses will be based on microscopic examination and mycological culture results for the target great toenail, the percent involvement of the target great toenail, the length of the unaffected part of the target great toenail, the growth of the target great toenail, and the number of affected nontarget toenails.

Investigators/evaluators will be trained by the sponsor to ensure consistency across investigational centers regarding toenail clipping, evaluations and measurements, as well as collection of sufficient material for KOH examinations and fungal cultures. Evaluators must be pre-approved by the sponsor and must have appropriate documented experience and training, or have a waiver obtained from the sponsor based on experience (or through additional training organized by the sponsor).

Every effort should be made to have the same sponsor-approved evaluator perform the target great toenail assessments and measurements for a particular subject at the Baseline Visit and each follow-up visit.

11.2.5.1 KOH Examination and Fungal Culturing

The KOH examination and fungal culturing of toenail scraping and subungual debris will be performed for study-eligible great toenail(s) at the Screening Visit and for the target great toenail only (as determined at the Baseline Visit) at Weeks 12, 24, 36, 48/Early Termination, and 52 (the

4-week post-treatment follow-up) study visits. At the Screening visit, specimens for KOH and fungal cultures are obtained from study-eligible great toenails at this visit and sent to the central mycology laboratory for testing.

Toenail specimens will be taken by clipping the toenail to the point of attachment (removing unhealthy nail) and obtaining any crumbling subungual debris from under the distal edge of the target great toenail using a disposable curette. All target great toenail plate clippings and "distal" subungual debris should be discarded. Only the soft nail bed keratin beneath the clipped edge of the nail should be collected and used as a specimen for both the KOH examination and the fungal culture. Careful specimen collection in this manner will minimize toenail specimen contaminants and maximize dermatophytic pathogen isolation.

Materials for sample collection will be provided to the investigational centers by the sponsor or central mycology laboratory. Instructions for processing and shipping samples to the central laboratory are contained in the study laboratory manual.

11.2.5.2 Target Great Toenail Assessments

The percent of the affected toenail area and healthy (unaffected) toenail measurements for the target great toenail will be evaluated by the investigator/evaluator at the Screening and Baseline Visits, and at Weeks 12, 24, 36, 48/Early Termination, and 52 (the 4-week post-treatment follow-up) study visits.

Percent of Affected Target Great Toenail Area

The affected area of the toenail will be estimated as the percent of toenail area (nail and nail bed) involved (the distal margin for determining area will be the distal groove after the toenail has been clipped).

Healthy (Unaffected) Target Great Toenail Measurement and Growth

The healthy (unaffected) toenail measurement will be defined as the distance (in mm) between the proximal nail fold and a transverse line on the healthy part of the toenail immediately proximal to the nail infection. At each evaluation, this distance will be measured from the proximal nail fold to the proximal onychomycotic border.

Toenail growth will be measured by inscribing a transverse notch in the nail of the target great toenail adjacent to the proximal nail fold at the center of the nail at the Baseline Visit, and measuring nail growth from that point forward. At every subsequent visit, the distance (in mm) between the proximal nail fold and the notch will be measured and recorded. The notch should be enhanced as needed at subsequent visits to allow continued measurement of toenail growth over the course of the study. If the initially applied notch inscribed at the Baseline Visit has grown out or is clipped away, inscribe a new notch in the toenail adjacent to the proximal nail fold, and continue with measurements using the new notch.

11.2.5.3 Nontarget Toenail Assessment

An assessment of both feet will be made for assessing the presence or absence of onychomycosis of nontarget toenails at the Screening, Baseline, Weeks 12, 24, 36, 48/Early Termination, and 52 (the 4-week post-treatment follow-up) study visits. All nontarget toenails will be assessed for the presence or absence of onychomycosis. Subjects in the PK subset must present with onychomycosis on at least 4 toenails besides the great toenails.

11.2.6 Evaluation of Pharmacokinetics

The PK assessments will be performed on a subset of the study population who will receive treatment under maximal use conditions for 28 days. Plasma samples for determination of efinaconazole and metabolite levels will be collected at the following time points:

- Visit 3 (Day 28): Predose (after all Day 28 procedures are completed). Study drug must be applied within 1 hour after the predose sample is collected. Samples are then collected at 2 (± 5 min), and at 4 (± 5 min), and at 12 (± 15 min) hours postdose.
- Visit 3A (Day 29): 24 (± 30 min) hours after Day 28 study drug application.

Materials for sample collection will be provided to the investigational centers by the sponsor or central laboratory. Instructions for processing and shipping samples to the bioanalytical laboratory are contained in the study laboratory manual.

11.2.7 Photography

At all investigational centers, close-up photographs of the target great toenail will be taken at the Baseline, Weeks 24, 48/Early Termination, and 52 (the 4-week post-treatment follow-up) study visits. One photograph will be taken after toenail clipping. After the first photograph has been taken, the investigator/evaluator will use a fine tipped marker to outline the area affected on the target great toenail. After the ink has dried, a second photograph will be taken. The collected photographs will be used for documentation purposes only and will not be used for determinations of eligibility, efficacy, or any study-related activities. Before photographs are taken, the study subject and their parent(s)/legal guardian(s) must consent/assent to photography. If the photography consent/assent is declined, the subject may still participate in the study.

11.3 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the study drug. Thus, AEs include any unfavorable and unintended illness, sign, symptom, clinically significant laboratory test abnormality, or disease temporally associated with the use of a medicinal product that has appeared or worsened during the course of the clinical study, regardless of causal relationship to the study drug(s) under study. The collection of nonserious

AEs and serious adverse events (SAEs) should begin following the subject's completion of the consent/assent process to participate in the study.

11.3.1.1 Definition of Serious Adverse Events

All AEs will be assessed as either serious or nonserious. An SAE or serious adverse reaction is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is immediately life threatening, (the term "life threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires in subject hospitalization or prolongation of existing hospitalization (hospitalization for elective surgery for a baseline condition is not considered an AE).
- Results in persistent or significant disability/incapacity (permanent or substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the above listed outcomes.

Important medical events that may not have resulted in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization is a criterion for assessment of seriousness. To qualify as serious under the criteria of "hospitalization," a hospital admission of at least a 24-hour period is required. If a subject is retained the emergency room greater than 24 hours, but not admitted for medical care, these cases should be evaluated individually, as criteria such as "medically significant" may also apply.

Hospitalization without a medical AE should not be considered either serious or an AE. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality).
- Hospitalization for a purpose unrelated to the study (eg, "planned" or elective surgery scheduled prior to study participation) would not ordinarily need to be reported, unless a complication occurred which otherwise caused prolongation of this hospitalization.
- Protocol-specified admission or procedure (eg, cataract surgery required by a study protocol; or overnight stay for monitoring due to protocol required surgery, *with no associated SAE or complication necessitating prolonged stay*)
- Social admission (eg, social hospitalization for purposes of respite care)

Note: A spontaneous abortion will be considered an SAE, and must be reported to the sponsor within 24 hours of your awareness of the event.

11.3.1.2 Assessment of Severity

The severity assigned to an AE should be determined by the maximum severity of the AE. The categories described below should be used to estimate the severity of AEs:

- Mild: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- Moderate: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.
- Severe: Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization or prolongation of current hospitalization possible; may be incapacitating or life threatening.

11.3.1.3 Assessment of Causality

The investigator should assess the relationship of the AE, if any, to the study drug as either "Related" or "Not Related".

- **Related:** There is at least a reasonable possibility that the AE/SAE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.
- **Not Related:** There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists.

The following should be taken into account when assessing AE/SAE causality:

- Positive temporal relationship to study drug, such as if the study drug was withdrawn and the SAE resolved or the event recurred after re introduction.

- If there is a reasonable possibility that the AE is associated with an underlying or concomitant illness.
- Possible association with previous or concomitant therapy.
- No temporal relationship to the study drug and/or a more likely alternative etiology exists.
- If the AE is directly related to study procedures or there is a lack of efficacy.

11.3.1.4 Procedures for Reporting Adverse Events and Serious Adverse Events

The period of observation for collection of AEs extends from the time the subject and parent/legal guardian gives informed consent/assent until the last study visit or discontinuation from the study. The first concern will be the safety of the subject, and appropriate medical intervention will be made.

The Investigator or designee will elicit reports (ie, via direct questioning, observation, clinical evaluation) of AEs from the subject at each study visit and record all AEs. The Investigator will document the dates of onset, progress, outcome, and resolution of such AEs. The Investigator will also provide an assessment of all AEs as to the severity, causal relationship to study drug, and causal relationship to study protocol.

It is the investigator's responsibility to document all AEs that occur during the study. The AEs should be documented as a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject and/or their parent/legal guardian at each study visit.

All AEs occurring after the subject and their parent/legal guardian signs the assent/informed consent through the last study visit must be reported, regardless of whether or not the AEs are considered drug-related. All AEs, whether in response to a query, observed by the study site personnel, or reported spontaneously by the subject and/or their parent/legal guardian, will be recorded.

At each visit during the study, the subject will be assessed for the occurrence of new and ongoing AEs. Cutaneous tolerability signs and symptoms that result in the subject's requiring a concomitant therapy or discontinuation from the study will be reported as an AE. The following data will be collected on all AEs and recorded on the appropriate eCRF:

- Event name (diagnosis preferred, if unknown, record the signs/symptoms).
- Onset date and end date.
- Maximum intensity (severity).
- Seriousness.

- Action taken regarding study drug.
- Corrective treatment, if given.
- Outcome.

In addition, the investigator's assessment of causality will be recorded.

Any SAE must be reported to the Sponsor, independent of the circumstance or suspected cause, within 24 hours from the time the event was reported to the Investigator. All SAEs experienced from the date of consent through at least 30 days after the last dose of study drug must be reported to the Sponsor regardless of the relationship to the study drug or the protocol. For events occurring beyond the minimum 30-day period after the last dose of study drug, or for any timeframe afterward deemed medically significant, only SAEs considered related to the study drug should be reported promptly to the Sponsor.

Within 24 hours of notification the Investigator will fax or email a completed Serious Adverse Event Report to the Sponsor:

MedTrials Safety:
Fax: [redacted]
**Please follow up with an email notification to
[redacted] to confirm the faxed submission.

Investigators should not wait to receive additional information to document the event before notifying the sponsor of an SAE. If only limited information is initially available, follow-up reports are required. If the Investigator becomes aware of any new information regarding a SAE (ie, resolution, change in condition, or new treatment), a new SAE Form must be completed and faxed/emailed to the Sponsor within 24 hours. The original SAE form is not to be altered. The report should be marked as a "follow-up report" and describe whether the event has resolved or continues and how the event was treated. Additional relevant information such as hospital records and autopsy reports should be provided to the sponsor as soon as they are available.

Should the investigator become aware of an SAE (regardless of its relationship to investigational product) that occurs within 30 days after stopping the study drug, the SAE must be reported in accordance with procedures specified in this protocol.

The investigator should take all appropriate measures to ensure the safety of the subjects, notably he/she should follow a subject with an SAE until the event has resolved or the condition has stabilized. This may imply that follow-up will continue after the subject has left the study, and that additional investigations may be requested by the sponsor.

11.3.1.5 Submitting an Expedited Safety Report to the IRB (Central or Local)

Any suspected unexpected serious adverse reaction (SUSAR) warrants expedited reporting. In addition, any unexpected SAE related to a subject's participation in the study (or conduct of study), regardless if the study drug was administered, will be evaluated by Global Pharmacovigilance and Risk Management (GPRM) to determine if expedited reporting is required. For example, an unexpected, serious and severe reaction which could be associated to the study procedures, and which could modify the study conduct requires expedited reporting. Each expedited safety report will routinely include a brief cover memorandum, the completed MedWatch Form FDA 3500A or Council for International Organizations of Medical Sciences I Form, a clinical analysis of the event with any similar events that have occurred with the product, and any additional pertinent information recommended by the study Medical Monitor. Once the report is compiled by GPRM, the site Investigator must submit the expedited safety report to the local IRB/EC within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available. The site principal Investigator must retain a complete copy of each expedited safety report as it was submitted to the IRB. It is important that the principal Investigator review these expedited reports, as they contain safety information that may be relevant to each of the participating subjects.

11.3.2 Pregnancy

All female subjects of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of contraceptive failure is minimized. Abstinence is allowed as a birth control method.

Before enrolling a female subject of childbearing potential in this clinical study, the investigator must review the following information about study participation:

- Informed consent/assent requirements.
- Contraceptives in current use.

Following review of this information and appropriate counseling for the subject and their parent/legal guardian, the investigator or designee and the subject and parent/legal guardian must sign the assent/informed consent before study enrollment.

During the study, all female subjects of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to study enrollment, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study drug and must not be enrolled in the study. If pregnancy is suspected while the subject is receiving study treatment, the study drug

must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued and the subject will be followed until the pregnancy comes to term. A Pregnancy Report form will be submitted to the sponsor, initially and at the end of the pregnancy, which includes the outcome of the pregnancy and any complications occurring during the pregnancy or the delivery.

12 Statistics

12.1 Assessment of Safety

12.1.1 Adverse Events

All AEs that occur during the study will be recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are those AEs that occur or worsen on or after the date of first study drug application. All TEAEs will be summarized by the number of subjects reporting each TEAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the safety, PK, and non-PK populations. Each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category.

All SAEs will be summarized by the number of subjects reporting each SAE, the associated system organ class and preferred term, the severity, and the relationship to study drug for the safety, PK, and non-PK populations.

All information pertaining to AEs noted during the study will be listed by subject and will include the verbatim term given by the investigator, the associated system organ class and preferred term, the start and stop (if stopped) dates, the seriousness, and the severity of the event. Additionally, any action taken with the study drug, any corrective treatment administered, the outcome, and the relationship to study drug as well as a list of subjects who prematurely discontinue from the study due to an AE will be provided.

12.1.2 Local Skin Reactions

Local skin reaction scores (redness, swelling, burning, itching, and vesiculation) at each visit will be summarized using frequency tables for the safety, PK, and non-PK populations. Additionally, redness and swelling severity scores will be summarized using descriptive statistics (mean, standard deviation [SD], median, and minimum, and maximum). Subjects with a severity score worse than baseline will also be summarized at each post-baseline visit. The worst score and the last score during the post-baseline period will also be summarized.

12.1.3 Clinical Laboratory Tests

Results of safety laboratory parameters will be summarized at each study visit using descriptive statistics or frequencies and percentages, as appropriate, for the safety, PK, and non-PK populations. Changes from baseline in safety laboratory values will be summarized by treatment group at Week 48 using descriptive statistics. In addition, changes from baseline in safety laboratory values will be summarized using shift tables according to normal ranges.

12.1.4 Vital Signs

Results of vital sign measurements will be summarized at Weeks 12, 24, 36, and 48 using descriptive statistics or frequencies and percentages, as appropriate, for the safety, PK, and non-PK populations. Changes from baseline in vital sign measurements will be summarized at these visits.

12.1.5 Concomitant Medications

All previous therapies and concomitant medications will be classified based on terminology from the World Health Organization Drug Dictionary. Previous therapies and concomitant medications data will be presented in data listings.

12.1.6 Efficacy for Assessing Treatment Compliance

This primary objective of this study is to assess the safety of the study drug. Descriptive efficacy statistics for the endpoints will assist in evaluating compliance with treatment for the purposes of safety assessment. The efficacy variables evaluated in this study include microscopic KOH examination and mycological culture outcomes of the target great toenail, percent involvement of the target great toenail, growth of the target great toenail, and assessments of the nontarget toenails. The efficacy endpoints include the following:

- Complete Cure, defined as 0% clinical involvement of the target toenail and negative KOH and fungal culture at Week 52
- Complete or Almost Complete Cure at Week 52, defined as :: 5% toenail involvement
- The Clinical Efficacy rate at Week 52, defined as an affected target great toenail area of < 10%
- The Mycologic Cure rate at Week 52, defined as a negative KOH examination anda negative fungal culture of the target great toenail sample

The Complete Cure rate, the Complete or Almost Complete Cure rate, the Clinical Efficacy rate, and the Mycologic Cure rate will be presented using descriptive statistics (sample size n, frequency counts, and percentages) for the safety, PK, and non-PK populations. In addition, the growth of the target great toenail at each study visit and the change from baseline in the number of affected nontarget toenails will be summarized descriptively.

A last observation carried forward (LOCF) imputation will be used to impute missing values for the efficacy variables at Week 52 for the non-PK population analyses. No sensitivity analyses will be conducted.

12.2 Assessment of Pharmacokinetics

The PK objectives will be considered met when approximately 16 evaluable subjects are treated under maximal use conditions through day 28 and PK samples collected at predose and 2, 4, 12 hrs postdose on Day 28 and 24 hrs postdose on Day 29. .

No imputations will be made for missing data. Plasma concentrations that are reported as below the limit of quantitation (BLQ) in the data transfer file and will be set to zero for the summaries of concentrations as well as calculation of PK parameters. Missing values will be treated as if they were never drawn. Plasma concentrations and PK parameters will be summarized for the PK analysis set using descriptive statistics (n, mean, SD, standard error of the mean [SEM], coefficient of variation [CV], median, minimum, and maximum). Geometric means will also be used to summarize C_{max}, C_{min}, $AUC_{(0-t)}$ and $AUC_{(0-24h)}$.

Plasma concentrations of efinaconazole and metabolite (H3 and H4) at each scheduled sampling time point will be summarized using descriptive statistics. The individual plasma concentrations will be listed for each subject. Concentrations BLQ will be displayed as BLQ in the listings.

The mean plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will be presented graphically for Days 28 and 29 in both linear and logarithmic scales. Individual subject plasma concentration time profiles for efinaconazole and metabolites (H3 and H4) will also be created.

Plasma PK parameters for efinaconazole and metabolites (H3 and H4) will be calculated using noncompartmental analysis. The PK parameters will be calculated for each subject using actual sampling times. The maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) will be taken directly from the data.

The following PK parameters will be calculated from the individual plasma concentrations on Days 28 and 29 when possible:

- C_{max} (observed peak drug [efinaconazole and metabolites] concentration)
- T_{max} (time at which C_{max} occurs)
- C_{min} (observed minimum drug concentration)
- AUC_{0-t} (area under the concentration-time curve from time 0 up to the sampling time corresponding to the last quantifiable concentration)
- AUC_{0-24h} (area under the concentration-time curve from time 0 through 24 hours [corresponding to the dosing interval])

Additional PK parameters may be calculated as appropriate.

12.3 Subject Disposition

Subject disposition will be summarized for each analysis population.

12.4 Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized using descriptive statistics for each analysis population.

12.5 Protocol Deviations

All protocol deviations will be reported to the sponsor and recorded throughout the study. A tabulation of protocol deviations will be included in the final study report.

12.6 Compliance

Efficacy evaluations are being conducted to assess treatment compliance. Information regarding the evaluations and their analyses are presented in Section 12.1.6.

Study drug compliance will be calculated for each subject by taking into account whether a subject took all doses of study drug as instructed. Calculation of study drug compliance will be documented in the analysis plan.

12.7 Interim Analyses

An interim analysis will be performed to summarize available safety data at a predefined date to be determined by the sponsor. It will be performed for all available data on the PK and non-PK portion of the study. This interim analysis will contain all tables and all listings just like the final analysis, using the locked data for the interim analysis.

12.S Additional Statistical Considerations

All statistical processing will be performed using SAS® version 9.3 or higher unless otherwise stated. No hypothesis testing will be conducted in this study. A statistical analysis plan, describing all statistical analyses, will be provided as a separate document prior to data analysis.

12.S.1 Analysis Populations

All subjects who receive at least 1 confirmed dose of study drug will be included in the safety population.

All subjects in the PK subset who receive at least 1 confirmed dose of study drug and have any PK data on Days 28 and 29 will be included in the PK population.

All safety population subjects who are not in the PK subset will be included in the Non-PK population.

12.S.2 Sample Size Determination

Approximately 60 subjects will be enrolled and receive treatment with study drug. Approximately 20 of the 60 subjects will be enrolled in the PK subset. These sample sizes were based on PK and clinical considerations; no formal sample size calculation was performed. The numbers of planned subjects are considered adequate for determining the safety profile and the PK parameters of efinaconazole in a pediatric population of subjects aged 6 to 16 years 11 months with mild to severe onychomycosis of the toenails.

12.S.3 Handling of Missing Data

No imputations will be made for analyses of safety or PK endpoints. The efficacy endpoints at Week 52, which are used to assess treatment compliance will have missing data imputed with the last observation carried forward (LOCF) for non-PK population analyses.

12.S.4 Multicenter Issues

The study will be conducted at multiple investigational centers in the US and the Caribbean with the intention of pooling the results for analysis.

12.S.5 Multiplicity Issues

Not applicable.

12.S.6 Windowing Rules

The timing of all study visits is relative to the Baseline (Day 1) visit. Visit 3 (Week 4) should occur within 5 days of Day 28, (except for the PK-subset; Visit 3 should occur within 1 day of Day 28) and Visit 3A (Week 4) should occur 1 day after Visit 3. The Week 8 and all subsequent visits should occur within 5 days of the targeted times.

13 Quality Control and Quality Assurance

This study will be conducted under the sponsorship of Valeant, in conformation with all appropriate local and federal regulations as well as ICH guidelines.

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, GCP guidelines, and applicable regulatory requirements. In addition, the sponsor will be responsible for securing agreement from all involved parties to ensure direct access to all study-related sites, source data/documents, eCRFs, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

Central laboratory services will be performed by a qualified, licensed facility that will be listed on the US Food and Drug Administration Form 1572. Copies of all normal values

(as applicable), laboratory certifications, and the director's curriculum vitae will be provided to each investigational center and to the sponsor.

13.1 Study Monitoring

The conduct of the study will be closely monitored. Sponsor representatives must be permitted to visit all study site locations to assess the data, quality of study performance, and study integrity in a manner consistent with applicable health authority regulations and the procedures described in this protocol.

Prior to the start of the study, the Sponsor or its designee(s) will review the protocol, eCRFs, regulatory obligations, and other material or equipment relevant to the conduct of the study with the Investigator/Sub/Co Investigator and relevant study site personnel.

Monitoring visits and telephone consultations will occur as necessary, or per the study monitoring plan, during the course of the investigation to verify the following:

- The rights and well-being of subjects are protected
- The conduct of the investigation is in compliance with the currently approved protocol/amendment, ICH GCPs, and IRB/EC requirements
- The integrity of the data is maintained, including adequate study documentation
- The facilities remain acceptable
- The Investigator and site personnel remain qualified and able to conduct the study
- Study drug accountability is documented properly

During the course of the study, if the Sponsor determines that an Investigator is non-compliant with the study plan and/or applicable regulatory requirements, the Sponsor will take action to secure or reinstate compliance. In addition, the Sponsor may terminate the Investigator's participation in the study if appropriate, or if the Investigator remains non-compliant despite the remedial actions of the Sponsor.

13.2 Audits and Inspections

Interim and end of study audits of raw data, study files, and the final report may be conducted by the sponsor's quality assurance department or its designee. A certificate attesting to the audit(s) will be issued as applicable. In addition, inspections or on-site audits may be carried out by local authorities. The investigators will allow the sponsor's representatives and any regulatory agency to examine all study records and logs, eCRFs, corresponding subject medical records, study drug dispensing records, study drug storage area, and any other documents considered source documentation. The investigators agree to assist the representative, if required.

13.3 Data Quality Assurance

All assessments performed will be accurately documented in the subject's source documents and eCRFs. The investigator or designee will enter the information required by the protocol into the source documents and eCRFs provided by the sponsor or designee. Subjects will be identified in the eCRFs by their assigned subject number and initials only.

The investigators must read the protocol thoroughly and must follow the instructions exactly. Any deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate written protocol amendments made prior to effecting the agreed upon changes. Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB/IEC before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

14 Ethics and Administrative Issues

14.1 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, ICH guidelines, GCP guidelines, and in compliance with local and federal regulatory requirements. The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP.

14.2 Ethics Review

This protocol, proposed informed consent/assent form and other information to the subjects, and all appropriate amendments, will be properly reviewed, and approved by an IRB/IEC. A signed and dated notification of the IRB/IEC approval will be provided to the sponsor and investigator prior to study initiation. The name and occupation of the chair and members of the IRB/IEC will be supplied to the sponsor. The investigator will provide required progress reports and report all SAEs to the IRB/IEC as required.

14.3 Written Informed Consent

Written informed consent/assent, in accordance with local clinical investigation regulations, must be obtained prior to participation in the study. The investigator or designee will discuss the purpose of the study with each subject and their parent(s)/legal guardian(s) and will provide a description of the study drug (including any potential and possible side effects) and the study procedures. Information must be given both in oral and written form. The subject information provided will be in a language understandable to the subject and their parent(s)/legal guardian(s) and may not include any language that appears to waive any of the subject's legal rights or appears to release the investigator, the sponsor, or the institution from liability or negligence.

The investigator or designee will provide the prospective subject and the subject's parent(s) or legal guardian(s) sufficient time to consider whether to participate, minimizing the possibility of coercion or undue influence and will discuss any questions the subject and/or their parent(s)/legal guardian(s) may have. The investigator or designee will explain to the subject and their parent(s)/legal guardian(s) that participation in the study is voluntary and that withdrawal from the study is possible at any time without detriment to care. The consent must include acknowledgment that medical records and medical data derived from the study may be forwarded to the sponsor or to the responsible authorities or federal authorities.

No subject can enter the study or have any study-related procedures performed before his/her written informed consent/assent has been obtained. Subjects under the age of consent must sign an assent form and their parents/legal guardians must sign the informed consent form. Subjects over the age of consent must sign the informed consent form. Subjects and their parents/legal guardians will also provide written consent/assent to obtain photographs of the target great toenail. The original signed and dated informed consent and assent forms will be retained with the study records, and a copy of the signed forms will be given to the subject and their parent or legal guardian as applicable.

An informed consent/assent template will be supplied by the sponsor to the investigator. Any changes to the informed consent/assent form must be agreed to by the sponsor prior to submission to the IRB/IEC, and a copy of the approved version must be provided to the sponsor after IRB/IEC approval.

14.4 Subject Data Protection

Subject data will be protected by ensuring that no captured data contain subject names, addresses, telephone numbers, email addresses, or other direct personally identifying information. It is acknowledged that subject initials, demographics (including birthdates), medical histories, and prior concomitant medication uses, along with the name and address of the enrolling investigator may allow for personal identification of study participants. Other than where necessary to meet regulatory requirements, all data collected in this study will be presented in tabulated (ie, aggregate) form and listings containing information that could be used to identify an individual subject will not be included in any public disclosures of the study data or the study results.

14.5 Data Monitoring Committee

Not applicable.

14.6 Financial Disclosure

Financial disclosures will be obtained from all investigators in order to document any potential conflicts of interest.

14.7 Essential Documents

Investigator must maintain essential documents during the conduct of the study and retain these documents after the completion of the study in accordance with the Sponsor's record retention instructions. The Investigator agrees to adhere to the document retention procedures when signing the protocol Investigator Statement of Approval.

Essential documents include, but are not limited to, the following:

- IRB approvals for the study protocol, all amendments, ICF(s), and advertisements
- IRB annual study review
- IRB correspondence and reports (eg, SAE reports, protocol deviations, and safety updates)
- Regulatory documents (eg, financial disclosure and delegation of authority forms)
- All source documents
- CRFs
- Subject's signed ICF
- FDA Form 1572
- Accountability records for the study drug
- Correspondence from and to sponsor
- Any other documents relevant to the conduct of the study

In the event that the Investigator withdraws from the study (eg, retirement or relocation), study records will be transferred to a mutually agreed upon designee (eg, another Investigator or site IRB/EC). The Investigator will provide notice of such transfer in writing to the sponsor

14.S Investigator Obligations

The investigators must read the protocol thoroughly, complete and sign the protocol signature page, and must follow the instructions exactly. Whenever possible, any planned deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate documentation of sponsor approval prior to effecting the agreed upon changes. Any deviations should be reported to the sponsor and reported to the IRB/IEC according to the requirements of the IRB/IEC.

14.9 Changes to the Protocol

Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB before it may be implemented. No change in the conduct of the study can be instituted without prior written approval from the sponsor.

14.10 Confidentiality/Publication of the Study

All the data furnished to the investigator and his/her staff and all data obtained through this protocol will be regarded as confidential and proprietary in nature and will not be disclosed to any third party, except for the US Food and Drug Administration or other regulatory body, without written consent from the sponsor.

The results of the study may be published or presented by the Investigator(s) after the review by, and in consultation and agreement with the Sponsor, and such that confidential or proprietary information is not disclosed. Prior to submission for publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Sponsor or its designee for review and comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to the Sponsor products and activities receive fair, accurate, and reasonable presentation.

14.11 Study Termination

The sponsor reserves the right to discontinue the study overall or at a particular study site at any time for reasons including but not limited to:

- Emergence of effects that do not justify the benefit/risk relationship to the study population as a whole.
- Failure to comply with the protocol, GCP, or any other violation disturbing the appropriate conduct of the study.
- Failure to meet enrollment goals overall or at a particular study site.

If a study is terminated, the Sponsor will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects and their parents/legal guardians within a reasonable timeframe agreed upon by the Sponsor. All study materials must be collected and all eCRFs completed to the greatest extent possible

15 Data Handling and Record Keeping

15.1 Inspection of Records

Investigators must maintain detailed records on all study subjects who are enrolled in the study or who undergo screening. Data will be recorded in the subject's source documents and in applicable study logs provided by the sponsor. Source documents include subject's medical

records, hospital charts, clinic charts, and the investigator's subject study files, as well as the results of diagnostic tests (eg, laboratory tests). All medical information obtained at each study visit must be recorded in the subject's source documentation in real time as it is collected and then entered onto the eCRF by site personnel.

Subject-completed forms such as diaries and questionnaires are also considered source data. Only subjects are to record information in subject diaries and questionnaires. In no instance, should an Investigator or study site personnel record any data or make changes to subject completed forms. The Investigator or designee should review subject-completed forms during study visits. If an entry is found to be illegible or a mistake is found (eg, an incorrect year was recorded), the subject should be instructed to edit the entry by drawing a single line through the original entry, entering the new information, dating, and writing subject's year of birth to acknowledge.

Upon study completion or at any other time specified by the sponsor or designee, the appropriate study documents must be submitted to the sponsor.

Telephone conversations and electronic mail with the subject, the sponsor, or the sponsor's designee concerning the study must be recorded or kept on file. All source documents must be made available to the sponsor and the sponsor's designated monitor upon request.

15.2 Case Report Forms

Subject data required by this protocol are to be recorded on eCRFs. Subject data recorded on eCRFs during the study will be documented in a coded fashion. The subject will only be identified by the subject number and by their year of birth if also required. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

The Investigator and study site personnel will be responsible for completing the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

The study monitor will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. The eCRFs will be submitted to Valeant or its designee(s) for quality assurance review, and statistical analysis.

A copy of the eCRFs will be retained by the Investigator at the conclusion of the study, who must ensure that it is stored in a secure place

15.3 Retention of Records

The investigator should properly store and maintain all study records in accordance with sponsor directives. All records relating to the conduct of this study are to be retained by the investigator until notified by the sponsor in writing that the records may be destroyed.

16 References

1. Elewski BE. Onychomycosis: pathogenesis, diagnosis, and management. Clin Microbiol Rev. 1998;11(3):415-29.
2. Levy L. Epidemiology of onychomycosis in special-risk populations. J Am Podiatr Med Assoc. 1997;87(12):546-50.
3. Zaias N, Tosti A, Rebell G, Morelli R, Bardazzi F, Bieley H, et al. Autosomal dominant pattern of distal subungual onychomycosis caused by Trichophyton rubrum. J Am Acad Dermatol. 1996;34(2 Pt 1):302-4.
4. Trepanier EF, Amsden GW. Current issues in onychomycosis. Ann Pharmacother. 1998;32(2):204-14.
5. Gupta AK, Tu LQ. Therapies for onychomycosis: a review. Dermatol Clin. 2006;24(3):375 9.
6. Jublia (efinaconazole) topical solution, 10%. [US Prescribing Information]. Valeant Pharmaceuticals North America, LLC; 2014.

Protocol Study V01-10SA-401

A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails

Sponsor:

Dow Pharmaceutical Sciences, a wholly owned subsidiary of Valeant Pharmaceuticals International
1330 Redwood Way, Suite C
Petaluma, CA 94954

SUMMARY OF CHANGES
Amendment 2, 18 August 2017

Section	Page	Description of Change or Clarification	Rationale
Signature page	**2**	**Replaced:** [redacted] **with** [redacted]	New safety personnel
Synopsis **7.2**	**5-10** **20 - 22**	**1 -Revised From:** "Subjects included in the PK subset will attend the scheduled visits up to Week 4 and an additional study visit at Day 29 for collection of the final PK blood sample. The PK assessments will be performed under maximal use conditions. Once PK assessments are complete at Day 29, the PK subset of subjects will continue treatment through week 48 with additional visits at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52)." **TO** "Subjects included in the PK subset **MUST** decide at time of consent whether to participate in the 4-Week trial, attend the scheduled visits up to Week 4 (Day 29) for collection of the final PK and exit the study **OR** participate in the 52-Week trial, with the same scheduled visits as in the 4-Week trial followed by continued treatment through week 48 with additional visits at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). The PK assessments will be performed under maximal use conditions" **2-Revised From:** "Subjects who are included in the PK subset will be instructed to apply the study drug to all 10 toenails once daily at bedtime for 4 weeks.	To meet the study timeline, enrollment requirement was redefined to allow PK subset to participate in the 52-Week trial or exit the study at week 4 once PK samples are collected.

		Following the PK blood collections on Days 28 and 29, these subjects will be instructed to continue treatment with study drug to only the affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). **TO** "Subjects who are included in the PK subset will be instructed to apply the study drug to all 10 toenails once daily at bedtime for 4 weeks. Following the PK blood collections on Days 28 and 29, PK subjects that consented to the 52-Week trial will continue treatment with study drug to **only** the affected toenails. **3- Revised From:** "PK subjects will return to the investigational center the following day (Day 29) for collection of a 24-hour postdose blood sample. PK subjects will continue treatment with study drug to only the target great toenail and the other affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-Week post-treatment follow-up visit (Week 52). **TO** All PK subjects in the 4-Week trial will return to the investigational center the following day (Day 29) for collection of a 24-hour post dose blood sample and exit the study. PK subjects that consented to the 52-Week trial will continue treatment with study drug to only the target great toenail and the other affected toenails and return to the investigational center at Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48), and a 4-week post-treatment follow-up visit (Week 52). **4- Revised From:** After completion of the PK portion of the study, subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) once daily at bedtime. Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail for the entire treatment period **TO** After completion of the PK portion of the study, if the subject consented to participate in the 52-Week trial, subjects and their parents/legal guardians will be instructed to apply the assigned study drug to the subject's target great toenail and all other affected toenail(s) once daily at bedtime for the entire treatment period **5 -Revised From:** "Blood and urine samples will be collected for routine clinical laboratory tests (hematology, serum chemistry, and urinalysis) within	

		the 42 day Screening visit window and at Week 48." **TO** Blood and urine samples will be collected for routine clinical laboratory tests (hematology, serum chemistry, and urinalysis) within the 42 day Screening visit window. These samples will be collected again at Week 48, or at Day 28 for PK subjects who consented to only 4 weeks of treatment. **6- Revised From:** Vital sign measurements (sitting blood pressure, respiration, pulse, and temperature) will be obtained at Baseline and Weeks 12, 24, 36, and 48. An abbreviated physical examination will be performed at Baseline and Week 48; as part of the examination, height and weight will be measured at Baseline and Week 48. **TO** Vital sign measurements (sitting blood pressure, respiration, pulse, and temperature) will be obtained at Baseline and weeks 12, 24, 36, and 48; for PK subjects who consented to only 4 weeks of treatment, these procedures will be done at Day 28. An abbreviated physical examination will be performed at Baseline and Week 48, and at Day 28 for PK subjects who consented to only 4 weeks of treatment; as part of the examination, height and weight will be measured at Baseline and Week 48.	
Table 1	26	Updated footnotes p to r Updated footnote r to s Added footnotes t "Applies only to PK subjects who consented to 4 week trial" u "Not applicable for PK subjects who consent to only the 4 week trial."	Duplicate footnotes Clarification to study procedures
Section 9.4 (Days 29 to Week 48)	32	**Added**: After completion of the PK portion of the study, if the subject consented to the 52-Week trial, **Deleted:** Subjects and their parents/legal guardians will be instructed to continue applying the study drug to the target great toenail	Clarification
11.1.1	37	**Added:** Newly screened PK subjects will decide at the time of signing consent whether they will consent the 4-Week trial or the 52-Week trial. **Note:** *Subjects that consent to 4-Week trial will not be allowed to extend their study consent to 52 weeks. Subsequently, PK subjects who consent to the 52-week trial will be considered discontinued/Early Terminated if he/she discontinues prior to the Week 52 visit.*	To further define enrollment requirements
11.1.3	42	**Added:** Note: PK subjects exiting the study on Day 29 (consented to only 4-Week trial), the following	To further define study procedures

		procedures will be conducted in addition to the procedures listed above. 11. Collect blood and urine samples for routine safety laboratory analysis (hematology, serum chemistry, and urinalysis). Process and ship the samples to the central safety laboratory per instructions provided in the laboratory manual. 12. Measure height and weight. 13. Conduct an abbreviated physical examination (excluding urogenital/reproductive systems).	
11.1.4	42	**Added:** Note: PK subjects who consented to only 4 Week trial will exit the study on Day 29. Drug and subject diary will not be dispensed and urine pregnancy test will not be collected at this visit.	To further define study procedures
11.1.6	45	**Revised From:** If this is the Early Termination Visit, record the reason for subject discontinuation from the study and complete the Week 48 eCRF. All other subjects should be scheduled to return for the Visit 15 (Week 52) study visit **TO** If this is the Early Termination Visit, record the reason for subject discontinuation from the study and complete the Week 48 eCRF. If this is not an Early Termination Visit, the subject should be scheduled to return for the Visit 15 (Week 52) study visit.	To further define study procedures
12.1.1	55	**Revised From:** Treatment-emergent adverse events (TEAEs) are those AEs with an onset on or after the date of first study drug application **TO** Treatment-emergent adverse events (TEAEs) are those AEs that occur or worsen on or after the date of first study drug application.	To match the language in the SAP
12.1.6	57 (last para,)	**Added:** "for the non-PK population analyses"	Clarification
12.2	57	**Revised From:** The PK objectives will be considered met when approximately 16 evaluable subjects are treated under maximal use conditions through day 28 of the PK evaluation **TO** The PK objectives will be considered met when approximately 16 evaluable subjects are treated under maximal use conditions through day 28 and PK samples collected at predose and 2, 4, 12 hrs postdose on Day 28 and 24 hrs postdose on Day 28 and 24 hours postdose Day 29.	Clarify maximal use

12.7	58	**Deleted:** No interim analyses are planned **Added:** An interim analysis will be performed to summarize available safety data at a predefined date to be determined by the sponsor. It will be performed for all available data on the PK and non-PK portion of the study. This interim analysis will contain all tables and all listings just like the final analysis, using the locked data for the interim analysis.	To meet FDA requirements
12.8	58	**Deleted:** When approximately 40 evaluable subjects have been treated for 48 weeks meeting the primary safety objective (regardless if subjects in the PK subset are continuing), a data cut will be done and the study report will be written. Once all subjects in the PK subset completes the study, database lock will be performed and the study report amendment will be written.	The plan for this analysis has been revised. It is now described in Section 12.7 (Interim Analyses).
12.8.3	59	**Revised From:** No imputations will be made for missing safety or PK data. As indicated previously, the efficacy endpoints, which are used to assess treatment compliance, will have missing data imputed with LOCF for non-PK population analyses. Missing efficacy data will not be imputed for safety and PK population analyses. **TO:** No imputations will be made for analyses of safety or PK endpoints. The efficacy endpoints at Week 52, which are used to assess treatment compliance will have missing data imputed with the last observation carried forward (LOCF) for non-PK population analyses.	To be consistent with the SAP