



## CLINICAL PROTOCOL

**Protocol Number:** TAV-ONYC-401

**Protocol Title:** An Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of KERYDIN<sup>®</sup> (tavaborole) topical solution, 5% in the Treatment of Onychomycosis of the Toenail in Pediatric Subjects Ages 6 to 16 Years and 11 Months

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**Sponsor:** Anacor Pharmaceuticals, Inc.  
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**SPONSOR PROTOCOL APPROVAL**

**TITLE:** An Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of KERYDIN<sup>®</sup> (tavaborole) topical solution, 5% in the Treatment of Onychomycosis of the Toenail in Pediatric Subjects Ages 6 to 16 Years and 11 Months

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**STUDY DRUG:** KERYDIN<sup>®</sup> (tavaborole) topical solution, 5%

**IND NUMBER** 71,206

**SPONSOR:** Anacor Pharmaceuticals, Inc.  
1020 East Meadow Circle  
Palo Alto, California 94303

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**Sponsor Signature of Agreement for Protocol TAV-ONYC-401**

I certify that I have the authority to approve this Protocol on behalf of the Sponsor, Anacor Pharmaceuticals, Inc. The study will be conducted in accordance with this protocol and all applicable laws, rules, and regulations including the principles of Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki, and regulations of the United States Food and Drug Administration.

Signature: PPD [REDACTED] Date: PPD [REDACTED]

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**INVESTIGATOR SIGNATURE PAGE**

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein according to the principles of Good Clinical Practices (GCP), applicable laws and regulations, and the ethical principles that have their origin in the Declaration of Helsinki, and will make a reasonable effort to complete the study within the time designated.

I agree to personally conduct or supervise the described study.

I agree to inform any subject that the study drug is being used for investigational purposes and I will ensure that the requirements related to obtaining informed consent in accordance with International Conference on Harmonization (ICH) guidelines for GCP and local regulatory requirements.

I agree to report adverse events that occur during the course of the study to the Sponsor in accordance with ICH guidelines for GCP and local regulatory requirements.

I have read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the study drug.

I agree to promptly report to the Ethics Committee (EC)/Institutional Review Board (IRB) all changes in the research activity and all unanticipated problems involving risks to subjects. I will not make any changes to the conduct of the study without EC/IRB and Sponsor approval, except when necessary to eliminate apparent immediate harm to subjects.

I agree to maintain adequate and accurate records and make those records available for inspection in accordance with ICH guidelines for GCP and local regulatory requirements.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are qualified and informed of their obligations in meeting the above commitments.

I understand that the study may be terminated or enrollment suspended at any time by Anacor Pharmaceuticals, with or without cause, or by me if it becomes necessary to protect the best interest of the subjects.

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Investigator's Name (Printed): \_\_\_\_\_

## 1.0 SYNOPSIS

<b>Title:</b>	An Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of KERYDIN <sup>®</sup> (tavaborole) topical solution, 5% in the Treatment of Onychomycosis of the Toenail in Pediatric Subjects Ages 6 to 16 Years and 11 Months
<b>Protocol Number:</b>	TAV-ONYC-401
<b>Phase:</b>	4
<b>Number of Sites:</b>	Up to 20 study centers
<b>Study Population:</b>	
Male or female pediatric subjects ages 6 to 16 years and 11 months with distal subungual onychomycosis (DSO) involving at least 20% of the total area of the target great toenail (TGT), accompanied by a positive potassium hydroxide (KOH) wet mount and a positive fungal culture for the dermatophytes <i>Trichophyton rubrum</i> ( <i>T. rubrum</i> ) or <i>Trichophyton mentagrophytes</i> ( <i>T. mentagrophytes</i> ) during the Screening period.	
<b>Sample Size:</b>	
The study will enroll subjects ages 6 to 16 years and 11 months with at least 40 subjects ages 12 to 16 years and 11 months. All subjects will be assigned to receive active treatment with KERYDIN <sup>®</sup> (tavaborole) topical solution, 5%. At least 16 evaluable subjects ages 12 to 16 years and 11 months will be studied under maximal use conditions (PK subgroup).	
<b>Study Objective:</b>	
The primary objective of this study is to assess the safety and tolerability of KERYDIN (tavaborole) topical solution, 5% applied once daily for 48 weeks in pediatric subjects ages 6 to 16 years and 11 months with onychomycosis of the toenails. The secondary objective is to perform pharmacokinetic (PK) assessments in a subgroup of at least 16 evaluable subjects ages 12 to 16 years and 11 months following topical administration under maximal use conditions.	
<b>Duration of Subject Participation:</b>	
<ul style="list-style-type: none"><li>• Screening period: up to 10 weeks (maximum duration of 70 days)</li><li>• Treatment period: 48 weeks</li><li>• Post-treatment follow-up period: 4 weeks</li></ul>	
<b>Study Treatment:</b>	
KERYDIN (tavaborole) topical solution, 5% will be applied topically once daily for 48 weeks.	

**Study Design:**

This is an open-label study to evaluate the safety, tolerability, and pharmacokinetics of KERYDIN (tavaborole) topical solution, 5% in treating distal subungual onychomycosis (DSO) of the toenails in pediatric subjects ages 6 to 16 years and 11 months. An eligible subject will have a TGT with at least 20% involvement with a positive KOH wet mount and positive fungal culture for *T. rubrum* or *T. mentagrophytes* from a sample obtained during the Screening period for one of the great toenails with DSO. KOH and fungal culture will be sent to a central mycology laboratory for eligibility determination. Both great toenails can be sampled at Screening.

Eligible subjects will apply KERYDIN (tavaborole) topical solution, 5% once daily to all affected toenails (the TGT as well as all other toenails identified by the Investigator at the Baseline visit as having the clinical characteristics of onychomycosis) throughout the 48-week treatment period.

Subjects will be evaluated at Screening, Baseline (Day 1), and at Weeks 2, 4, 8, 16, 24, 32, 40, 48, and 52. Each evaluation will include vital signs and a clinical assessment of adverse events (AEs) and a local tolerability evaluation.

Additional procedures are performed as follows:

- Mycology sampling at Screening, Week 24, and Week 52/early termination (ET)
- Clinical involvement of the TGT at Screening, Week 24, and Week 52/ET
- Safety laboratory testing at Baseline, Week 24, and Week 52/ET
- Digital photography at Screening, Week 24, and Week 52/ET
- Urine pregnancy tests (UPTs) will be performed on all postmenarchal females at all scheduled visits starting at Baseline.

Subjects will start a diary at Baseline (Day 1) and will complete the diary as instructed.

In this study, there will be at least 16 evaluable subjects ages 12 to 16 years and 11 months studied under maximal use conditions (PK subgroup). Subjects in this maximal use subgroup will apply the study drug on all 10 toenails, including up to 2 mm of the surrounding skin. On Day 15, a pre-dose PK sample will be collected to assess steady state trough level. On Day 29, the study drug application will be done at the study site, and PK samples will be collected prior to dosing, as well as 4, 6, 8, and 24 hours post-dose on Days 29-30. After PK sampling is complete, study drug will be applied only to the affected toenails.

**Inclusion Criteria:**

Subjects must meet all of the following criteria to be eligible for this study:

1. Male or female subjects, ages  $\geq 6$  years and  $\leq 16$  years and 11 months at the time of enrollment
2. Have a parent or guardian able to understand, to agree to, and to sign the study informed consent form; subject has the ability to give assent based on their age, maturity, and psychological state at the time of parental/guardian consent
3. A clinical diagnosis of DSO affecting either great toenail with positive KOH and *T. rubrum* or *T. mentagrophytes* culture from the TGT confirmed by a central

<p>mycology laboratory during the Screening period</p> <ol style="list-style-type: none"> <li>DSO involving at least 20% of the TGT</li> <li>TGT capable of growing, as assessed by the Investigator or qualified designee</li> <li>Subject and parent/guardian (if applicable) are willing and able to comply with study drug instructions, comply with study instructions, and commit to attending all visits</li> <li>Postmenarchal females must agree to use a medically accepted method of contraception for the entire study period</li> </ol>
<p><b>Exclusion Criteria:</b></p> <p>Subjects with the following characteristics will be excluded from entering this study:</p> <ol style="list-style-type: none"> <li>One or more of the following conditions affecting the TGT: <ul style="list-style-type: none"> <li>Proximal subungual onychomycosis</li> <li>Onychomycosis involving the lunula</li> <li>Superficial white onychomycosis, dermatophytoma, exclusively lateral disease, or yellow/brown spikes</li> <li>Screening culture results that demonstrate co-infection with <i>Scopulariopsis</i> spp., <i>Scytalidium</i> spp. or other nondermatophyte molds (exception: <i>Candida</i> spp. and <i>Epidermophyton floccosum</i> are permitted)</li> </ul> </li> <li>Anatomic abnormalities of the toe(s) or toenail(s) to be treated including, but not limited to: genetic nail disorders, pigmentary disorders, onychogryphosis, trauma to the toenail(s) to be treated, or other abnormality that in the Investigator's opinion may interfere with clinical evaluation of the toenail(s) or would indicate that the subject is unlikely to respond to a topical treatment for DSO</li> <li>Current or past history of chronic moccasin-type tinea pedis (involving the sides or dorsum of the foot)</li> <li>Current or past history of psoriasis or lichen planus involving the skin, nails or mucous membranes</li> <li>History of any significant chronic fungal disease other than onychomycosis (eg, chronic mucocutaneous candidiasis)</li> <li>Known diagnosis of type I or type II diabetes</li> <li>Concurrent use of or have used any of the following topical or systemic medications within the indicated timeframe prior to Screening: <ul style="list-style-type: none"> <li>Topical antifungals applied to the toenails: 2 weeks</li> <li>Systemic corticosteroids (including intramuscular injections): 4 weeks</li> <li>Systemic immunosuppressive agents: 4 weeks</li> <li>Systemic antifungals for treatment of onychomycosis or with known activity against dermatophytes: 24 weeks</li> </ul> </li> <li>Any significant active or past medical condition which, in the Investigator's opinion, may expose the subject to unacceptable risk by study participation, confound the evaluation of treatment response or AEs, or interfere with the</li> </ol>

<p>subject's ability to complete the study</p> <p>9. History of any known immunodeficiency</p> <p>10. Known to be allergic to the study drug or excipients in the study drug</p> <p>11. History of drug or alcohol abuse (current or within the past 6 months)</p> <p>12. Participated in any other trial of an investigational drug or device within 30 days prior to Screening or participation in a research study concurrent with this study</p>
<p><b>Criteria for Evaluation:</b></p>
<p>Safety:</p> <ul style="list-style-type: none"> <li>• Frequency and severity of local tolerability reactions (LTRs), including burning/stinging, induration/edema, oozing and crusting, pruritus, erythema, and scaling</li> <li>• Frequency and severity of treatment-emergent adverse events (TEAEs) other than LTRs</li> <li>• Incidence of serious adverse events (SAEs)</li> <li>• Observed values and changes in vital signs and safety laboratory test parameters</li> </ul> <p>Pharmacokinetics:</p> <ul style="list-style-type: none"> <li>• Blood samples will be collected according to schedule, and descriptive statistical analysis of steady state systemic concentrations of tavaborole performed in a subgroup of 16 evaluable subjects ages 12 to 16 years and 11 months on Day 15 and Day 29</li> </ul> <p>Efficacy:</p> <ul style="list-style-type: none"> <li>• Clinical assessment of disease severity of TGT</li> <li>• Mycology (KOH wet mount and fungal culture)</li> </ul>
<p><b>Efficacy Endpoints:</b></p> <p>The following definitions will be applied to the clinical and mycological response to treatment in the TGT:</p> <p><u>Clinical and mycological characteristics:</u></p> <ul style="list-style-type: none"> <li>• <b>Completely Clear Nail (CN):</b> no clinical evidence of onychomycosis as evidenced by normal toenail plate, no onycholysis, and no subungual hyperkeratosis</li> <li>• <b>Almost CN:</b> no more than minimal evidence of onychomycosis as evidenced by toenail plate dystrophic or discolored <math>\leq 5\%</math> of the distal aspect, with minimally evident onycholysis and subungual hyperkeratosis</li> <li>• <b>Mild onychomycosis:</b> onychomycosis as evidenced by toenail plate dystrophic or discolored <math>&gt; 5\%</math> to <math>\leq 20\%</math> of the distal aspect, with clearly evident onycholysis and subungual hyperkeratosis</li> <li>• <b>Moderate onychomycosis:</b> onychomycosis as evidenced by toenail plate</li> </ul>



dystrophic or discolored  $> 20\%$  to  $\leq 50\%$  of the distal aspect, with clearly evident onycholysis and subungual hyperkeratosis

- **Severe onychomycosis:** onychomycosis as evidenced by a toenail plate dystrophic or discolored  $> 50\%$  of the distal aspect, with pronounced onycholysis and subungual hyperkeratosis
- **Negative mycology:** negative KOH wet mount and negative fungal culture

**Treatment Outcomes:**

- **Complete cure:** completely CN and negative mycology
- **Almost complete cure:** almost CN and negative mycology
- **Treatment success:** completely CN or almost CN

**Primary Efficacy Endpoint:**

The primary efficacy endpoint for this study is the complete cure rate of the TGT at Week 52

**Secondary Efficacy Endpoints:**

- Complete or Almost complete cure of the TGT at Weeks 24 and 52
- Treatment success (Clinical Efficacy rate) of the TGT at Weeks 24 and 52 defined as completely CN or almost CN
- Negative mycology (Mycological Cure rate) of the TGT at Weeks 24 and 52 defined as negative KOH wet mount and negative fungal culture
- Negative fungal culture of the TGT at Weeks 24 and 52

**Statistical Methods:**

All subjects who receive at least one confirmed dose of study drug and have at least one post-baseline safety assessment will be included in the Safety population. The PK population will include evaluable subjects from the maximal use subgroup with available PK data.

The efficacy assessments are intended to assess compliance with treatment for the purposes of the safety assessment. Efficacy endpoints will be summarized descriptively for the safety population.

**Background and Demographic Characteristics:**

Subject demographic and Baseline characteristics will be summarized for the safety and PK populations.

**Efficacy:**

The primary and secondary efficacy endpoints will be summarized with descriptive statistics including sample size, frequency count, and percentage.

**Safety:**

All AEs occurring during the study will be recorded and classified on the basis of *Medical Dictionary for Regulatory Activities* terminology. TEAEs are those with an onset on or after the time of the first study drug administration. For the safety population, all reported TEAEs will be summarized by system organ class (SOC), preferred term, severity, relationship to study drug, and seriousness. When summarizing TEAEs by causality and severity, each subject will be counted only once within an SOC or a preferred term using the event with the closest relationship to study drug and the greatest severity within each classification.

SAEs will be summarized by severity and relationship to study drug, and individual SAEs will be listed by subject. A list of subjects who prematurely discontinued from the study due to an AE will also be provided.

LTRs will be evaluated with frequency tables for each visit. Additionally, LTRs will be summarized by descriptive statistics (mean, standard deviation, median, and minimum and maximum).

**Pharmacokinetics:**

Pharmacokinetics of tavaborole will be summarized by collection day.

The following PK parameters will be calculated for Day 15 and Day 29 ( $\pm$  specified window):

- $C_{\max}$ : maximum observed plasma concentration
- $T_{\max}$ : time to maximum observed plasma concentration
- $AUC_{0-24}$ : area under the plasma concentration-time curve from Hour 0 to Hour 24, calculated using the linear trapezoidal rule
- $AUC_{0-\infty}$ : area under the plasma concentration-time curve extrapolated to infinity
- $\lambda_z$ : elimination rate constant
- $t_{1/2}$ : elimination half-life

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## 2.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AUC <sub>0-24</sub>	Area Under the plasma Concentration-time curve from Hour 0 to Hour 24
AUC <sub>0-∞</sub>	Area Under the plasma Concentration-time curve from Hour 0 extrapolated to infinity
CN	Clear Nail
C <sub>max</sub>	maximum observed plasma concentration
CRF	Case Report Form
DSO	Distal Subungual Onychomycosis
EC	Ethics Committee
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hERG	human ether-à-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
KOH	potassium hydroxide
$\lambda_z$	elimination rate constant
LTR	Local Tolerability Reactions
PK	Pharmacokinetic
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedures
t <sub>1/2</sub>	elimination half-life
TEAE	Treatment-Emergent Adverse Event
TGT	Target Great Toenail
T <sub>max</sub>	time to maximum observed plasma concentration
UPT	Urine Pregnancy Test
w/w	weight for weight



### 3.0 BACKGROUND AND RATIONALE

KERYDIN<sup>®</sup> (tavaborole) topical solution, 5%, the first oxaborole antifungal agent, was approved by the Food and Drug Administration (FDA) for the topical treatment of onychomycosis of the toenails on 07 July 2014 (NDA 204427). This present study is being conducted to fulfill the postmarketing requirement for a pharmacokinetic (PK)/safety trial of KERYDIN (tavaborole) topical solution, 5% in pediatric subjects with onychomycosis of the toenails.

#### 3.1 Disease Information

Dermatophytes are a group of fungi that can infect the keratinous layers of the skin, hair, and nails. Very superficial infections with the dermatophytes are found only in the top layer, the stratum corneum, or scaly part of the skin. Dermatophytes are ubiquitous in the environment, commonly found in the soil. While all humans come into contact with dermatophytes in their environment, only a small percentage of the population develops symptomatic disease, leading some to conclude that dermatophytosis is an infectious disease but not a contagious disease.

Dermatophyte infections of the skin are seen as tinea pedis (skin infection of the toes, more commonly known as athlete's foot), tinea manuum (infection of the skin of the hand), tinea faciei (infection of facial skin), tinea cruris (infection of the groin area, more commonly known as jock itch), and tinea corporis (ringworm).

When dermatophytes infect the nail unit, the resulting condition is referred to as onychomycosis. The characteristics of onychomycosis include onycholysis (separation of the nail plate from the nail bed), subungual hyperkeratosis (thickening of the nail bed), as well as changes in the nail plate which include thickening, changes in color, and brittleness.

The clinical manifestations of onychomycosis can vary depending on what part of the nail unit is infected: the nail plate, the nail bed, and/or the paronychia (skin that surrounds the nail plate). Recognized clinical types of onychomycosis include superficial white onychomycosis in which only the surface of the nail plate is infected, proximal subungual onychomycosis in which the proximal portion of the nail is infected, and the most common distal subungual onychomycosis (DSO) in which the distal nail plate and nail bed are infected.

Onychomycosis is the most common nail disorder in adults, affecting 2% to 13% of the adult population.<sup>1</sup> It is more prevalent in older adults, with 28% to 40% of adults over the age of 60 years having some nail involvement with dermatophytes.<sup>1</sup>

Onychomycosis in the pediatric population has been described as uncommon, unusual, and rare.<sup>5,6</sup> The low frequency of pediatric onychomycosis has been attributed to factors

such as a faster nail growth compared to the adult population, a smaller contact surface that offers less chance for trauma and fungal colonization, infrequent exposure to fungi in public places, and a lower prevalence of tinea pedis (all of which are risk factors for onychomycosis). Reports in the literature confirm a low prevalence of onychomycosis in the pediatric population, ranging between 0.2% and 2.6%, and indicate that onychomycosis is mainly reported after puberty.<sup>7</sup>

Several approved oral and topical treatments are available for onychomycosis, including KERYDIN (tavaborole) topical solution, 5%.<sup>2,3</sup> Oral medications, the most effective current treatment for onychomycosis, are associated with potential hepatotoxicity or cardiotoxicity.<sup>2</sup>

### 3.2 Investigational Drug

KERYDIN (tavaborole) topical solution, 5% contains 5% tavaborole (w/w) in a clear, colorless alcohol-based solution for topical use. The active ingredient, tavaborole, is an oxaborole antifungal with the chemical name of 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. KERYDIN (tavaborole) topical solution, 5% is approved by the FDA for the topical treatment of onychomycosis. The drug vehicle consists of alcohol, propylene glycol, and edetate calcium disodium. Refer to the Investigator's Brochure<sup>4</sup> (IB) or package insert for further information on the characteristics of KERYDIN (tavaborole) topical solution, 5%.<sup>8</sup>

Tavaborole shows broad spectrum activity against the major dermatophytes that cause onychomycosis, *Trichophyton rubrum* (*T. rubrum*) and *Trichophyton mentagrophytes* (*T. mentagrophytes*), as well as against yeasts and molds. The drug's novel mechanism of action is the inhibition of an aminoacyl-tRNA synthetase. Tavaborole forms an adduct with tRNA<sup>Leu</sup> in the editing site of leucyl-tRNA synthetase. Data from both *ex vivo* human cadaver nails and human PK studies demonstrate good penetration of tavaborole into and through the nail plate with low systemic exposure.

### 3.3 Nonclinical Data

Tavaborole has been tested in an extensive battery of toxicology studies with systemic administration in rats, rabbits, and dogs and with topical administration in mice, guinea pigs, rabbits, and minipigs. Tavaborole is not genotoxic, is not a sensitizer, and has a low potential of causing toxicity after single or repeated administration. The major finding after repeated oral administration was irritation of the nonglandular stomach in rats, and the major finding after repeated topical administration was local dermal irritation in minipigs. Tavaborole has been found to be non-carcinogenic in 2-year studies in rats (oral) and mice (topical). Based on its human ether-à-go-go-related gene (hERG) tail current inhibition (1 µM), tavaborole can be classified as a low-potency hERG-channel blocker. Fetal skeletal malformations were observed following very high oral doses of tavaborole in a rat embryo-fetal developmental toxicity study. Tavaborole did not affect

fertility or reproductive performance and did not affect prenatal and postnatal development or maternal function when dosed orally to rats.

Tavaborole has a relatively short half-life in rats following oral administration. Radiolabeled studies with  $^{14}\text{C}$ -tavaborole showed extensive metabolism, including a major biotransformation pathway involving oxidative oxaborole ring cleavage, followed by further oxidation, glucuronidation, or sulfation.

### 3.4 Clinical Experience

Refer to the IB<sup>4</sup> or package insert<sup>8</sup> for further information on the clinical experience with KERYDIN (tavaborole) topical solution, 5%.

### 3.5 Summary of Known and Potential Risk and Benefits

Details about specific benefits and risks for subjects participating in this clinical trial can be found in the IB<sup>4</sup>, package insert<sup>8</sup>, and in the sample informed consent form (ICF) document. KERYDIN (tavaborole) topical solution, 5% has not been studied in pediatric patients; thus, the safety of the drug has not been established in the patient population that will be enrolled in this trial.

### 3.6 Dose Rationale

The NDA for KERYDIN (tavaborole) topical solution, 5% was approved by FDA in July 2014 for the treatment of onychomycosis of the toenails due to *T. rubrum* or *T. mentagrophytes*. KERYDIN (tavaborole) topical solution, 5% applied daily for 48 weeks was studied in two Phase 3 registration studies. Data from the studies showed a statistically significant therapeutic effect compared with vehicle with no safety concerns. This 48-week long, open-label PK/safety trial will enable the study of the safety profile of KERYDIN (tavaborole) topical solution, 5% in subjects ages 6 to 16 years and 11 months with onychomycosis of the toenails.

The dosing regimen for the pharmacokinetic analysis is based on a Phase 1 maximal use absorption study in adults<sup>9</sup>. In this Phase 1 study, elevated plasma concentrations of tavaborole in adult subjects with onychomycosis were achieved through once daily application to all 10 toenails and up to 2 mm of surrounding skin.

While the Phase 1 maximal use study in adults required onychomycosis of at least 4 involved toenails, including at least 1 great toenail with 50-75% nail involvement, this degree of disease severity in the pediatric population is exceedingly rare, and will therefore not be a study requirement. The maximal dosing regimen of once daily application to all 10 toenails and up to 2 mm of surrounding skin is expected to produce elevated plasma concentrations in this pediatric population.

### 3.7 Statement of Compliance

This study will be conducted in compliance with the protocol approved by the appropriate Institutional Review Boards (IRB) and Ethics Committees (EC), according to International Committee on Harmonization (ICH) and local Good Clinical Practice (GCP) standards, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

### 3.8 Population

Male or female subjects ages 6 to 16 years and 11 months with DSO involving at least 20% of the total area of the target great toenail (TGT), accompanied by a positive potassium hydroxide (KOH) wet mount and a positive fungal culture for the dermatophytes *T. rubrum* or *T. mentagrophytes* during the Screening period. A PK subgroup of at least 16 evaluable subjects ages 12 to 16 years and 11 months will be studied under maximal use conditions.

### 3.9 Number of Sites

Up to 20 study centers are planned.

## 4.0 STUDY OBJECTIVES

The primary objective of this study is to assess the safety and tolerability of KERYDIN (tavaborole) topical solution, 5% applied once daily for 48 weeks in pediatric subjects ages 6 to 16 years and 11 months with onychomycosis of the toenails.

The secondary objective is to perform PK assessments in at least 16 evaluable subjects ages 12 to 16 years and 11 months following topical administration under maximal use conditions.

## 5.0 STUDY DESIGN

This is an open-label study to evaluate the safety, tolerability, and pharmacokinetics of KERYDIN (tavaborole) topical solution, 5% in treating DSO of the toenail in pediatric subjects ages 6 to 16 years and 11 months. An eligible subject will have a TGT with at least 20% involvement with a positive KOH wet mount and positive fungal culture for *T. rubrum* or *T. mentagrophytes* from a sample obtained during the Screening period for one of the great toenails. KOH and fungal culture will be sent to a central mycology laboratory for eligibility determination. Both great toenails can be sampled at Screening.

The mycological confirmation of eligibility will be performed as follows:

1. Initial sample is KOH (+) and culture (+) for *T. rubrum* or *T. mentagrophytes*, with or without co-infection with *Candida* spp. or *E. floccosum*, subject is eligible for enrollment within the maximum period of 10 weeks (i.e., within 70 days) from the Screening visit.
2. Initial sample is KOH (–) or initial sample is KOH (+) and culture (–): The sample may be repeated and will be assessed as follows:
  - If a repeat sample is KOH (+) and culture (+) for *T. rubrum* or *T. mentagrophytes* with or without co-infection with *Candida* spp. or *E. floccosum*, for enrollment as long as the subject is enrolled within the maximum period of 10 weeks (i.e., within 70 days) from the Screening visit.

Eligible subjects will apply KERYDIN (tavaborole) topical solution, 5% once daily to all affected toenails (the TGT as well as all other toenails identified by the Investigator at the Baseline visit as having the clinical characteristics of onychomycosis) throughout the 48-week treatment period.

Subjects will be evaluated at Screening, Baseline (Day 1), and at Weeks 2, 4, 8, 16, 24, 32, 40, 48, and 52. Each evaluation will include a clinical assessment of the adverse events (AEs) and local tolerability evaluation.

Additional procedures are performed as follows:

- Mycology sampling at Screening, Week 24, and Week 52/early termination (ET)
- Clinical disease severity of the TGT at Screening, Week 24, and Week 52/ET
- Safety laboratory testing at Baseline, Week 24, and Week 52/ET
- Digital photography at Screening, Week 24, and Week 52/ET
- Urine pregnancy tests (UPTs) will be performed on all postmenarchal females at all scheduled visits starting at the Baseline visit.

Subjects will start diaries at Baseline (Day 1) and will complete the diary as instructed.

In this study, there will be a PK subgroup of at least 16 evaluable subjects ages 12 to 16 years and 11 months studied under maximal use conditions. Subjects in this maximal use subgroup will apply the study drug on all 10 toenails, including up to 2 mm of the surrounding skin, for 28 days ( $\pm 7$  days). On Day 15, a pre-dose PK sample will be collected to assess steady state trough level. On Day 29, the study drug application will be done at the study site, and PK samples will be collected prior to dosing, as well as 4, 6, 8, and 24 hours post-dose on Days 29-30. After PK sampling is complete, study drug will be applied only to the affected toenails.

## **5.1 Study Endpoints**

### **5.1.1 Safety Endpoints**

- Frequency and severity of local tolerability reactions (LTRs), including burning/stinging, induration/edema, oozing and crusting, pruritus, erythema, and scaling
- Frequency and severity of treatment-emergent adverse events (TEAEs) other than LTRs
- Incidence of serious adverse events (SAEs)
- Observed values and changes in vital signs and safety laboratory test parameters

### **5.1.2 Pharmacokinetic Endpoint**

Blood samples will be collected according to schedule and descriptive statistical analysis of steady state systemic concentrations of tavaborole performed in a subgroup of subjects under maximal use conditions.

### **5.1.3 Efficacy Endpoints**

The primary efficacy endpoint for this study is the complete cure rate of the TGT at Week 52. Complete cure is defined as 0% clinical involvement of the TGT and negative mycology (negative KOH wet mount and negative fungal culture) at Week 52.

The secondary efficacy endpoints include the following:

- Complete or Almost complete cure of the TGT at Weeks 24 and 52
- Treatment success (Clinical Efficacy rate) of the TGT at Weeks 24 and 52 defined as defined as completely Clear Nail (CN) or almost CN
- Negative mycology (Mycological Cure rate) of the TGT at Weeks 24 and 52 defined as negative KOH wet mount and negative fungal culture
- Negative fungal culture of the TGT at Weeks 24 and 52

## **5.2 Blinding and Maintenance of the Blind**

Not applicable to this study.

## **5.3 Study Treatment**

All subjects will receive KERYDIN (tavaborole) topical solution, 5%. Study drug will be applied topically once daily for 48 weeks by the subject and/or parent/guardian.

### 5.3.1 Treatment Administration

Study drug will be applied on all affected toenails daily with a supplied dropper, preferably at bed time, except for the clinic visit days during which the study drug will be applied at the visit. On Day 1, subjects and/or parent/guardian will be given instructions on how to apply the study drug and will apply the study drug at the study site, under the supervision of the Investigator or a qualified designee.

Additionally, subjects in the maximal use PK subgroup will receive a minimum dose of each treatment to all 10 toenails, including up to 2 mm of surrounding skin defined as follows:

- Great toenails: two (2) drops each
- All other toenails: one (1) drop each

KERYDIN (tavaborole) topical solution, 5% is for topical use on toenail(s) only. Contact with mucous membranes (i.e., inside of nostrils, mouth, vagina, urethra, and rectum) and the eyes should be avoided.

### 5.3.2 Labeling

Each bottle and kit will be labeled in accordance with Good Manufacturing Practice and will include the following information:

- Protocol number
- Kit number
- Unique alpha-numeric identifier (batch/lot number)
- Storage requirement
- Investigational use and appropriate caution statements
- Sponsor identification

### 5.3.3 Packaging and Storage

Each treatment kit will contain 2 bottles of KERYDIN (tavaborole) topical solution, 5% and applicators (droppers).

KERYDIN (tavaborole) topical solution, 5% will be supplied in amber glass bottles each containing 10 mL of product. The Sponsor will provide all test preparations/supplies for KERYDIN (tavaborole) topical solution, 5%.

Study drug must be stored at the study site according to label conditions in a secure, limited-access location.

Subjects and/or parents/guardians will be instructed to store the study drug at room temperature (not to refrigerate or freeze), in an upright position.

#### **5.3.4 Duration of Study**

Each subject will participate in the study for up to 62 weeks from the time of signing the ICF through the final contact. After the Screening period of up to 10 weeks (maximum of 70 days), each subject will receive open-label KERYDIN (tavaborole) topical solution, 5% for up to 48 weeks followed by a 4 week post-treatment follow-up visit. The study is expected to have an overall duration of approximately 28 months, including an enrollment period of approximately 12 months.

#### **5.4 Discontinuation of Study by Sponsor**

The Sponsor reserves the right to terminate the study at any time. If the Sponsor elects to discontinue the study because of a safety concern, the Sponsor will immediately notify the sites to discontinue treatment of all subjects currently enrolled in the study and will promptly notify the FDA. If the Sponsor elects to discontinue the study for any other reason, the Sponsor will notify the sites and the sites will notify subjects at their next scheduled visit. The IRB/EC will also be notified.

Reasons for study discontinuation by the Sponsor may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- Sponsor's decision to discontinue investigation in a specific therapeutic area
- Subject enrollment is unsatisfactory

#### **5.5 Discontinuation of Study Site by Sponsor**

The Sponsor reserves the right to terminate a clinical study site from the study at any time. If the Sponsor elects to discontinue a clinical study site from the study because of a safety concern, the Sponsor will immediately notify the site to discontinue treatment of all subjects currently enrolled in the study and will promptly notify the FDA. If the Sponsor elects to discontinue a clinical study site from the study for any other reason, the Sponsor will notify the site, and the site will notify subjects at their next scheduled visit. In all cases, the Investigator must notify the IRB/EC in writing of the site's discontinuation and send a copy of the notification to the Sponsor.



Reasons for study site discontinuation by the Sponsor may include, but are not limited to, the following:

- Subject enrollment at the site is unsatisfactory
- Investigator request to withdraw from participation
- Serious and/or persistent noncompliance by the Investigator with the protocol, the clinical research agreement, or applicable regulatory guidelines in conducting the study
- IRB/EC decision to terminate or suspend approval for the investigation

## **5.6 Product Accountability**

Subjects and/or parents/guardians will be instructed to return all used, unused, and empty study drug bottles at all protocol-specified visits for assessment of study drug accountability.

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The bottles contained in each medication kit will be weighed using a calibrated scale. The number of bottles dispensed and returned will be counted and the weight of the bottles (with cap on) after return will be measured and documented in the subject study drug log and/or site study drug log or an equivalent document and will be verified by the Sponsor's study monitor. The study drug log or equivalent document shall be retained at the study site and a copy supplied to the Sponsor when the study is complete.

All study drug supplies, including all containers of study drug, whether empty or containing unused study drug, must be returned to the Sponsor's designee, unless Investigators are instructed otherwise by the Sponsor or its designee. The Sponsor's study monitor will provide instructions on the return of all study drug supplies.

A final inventory of the total amount of study drug received at each study site against the amount dispensed and returned must be recorded in the site study drug log or an equivalent document.

Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to inspection by the regulatory authorities at any time.

## **5.7 Data Identification**

Electronic case report forms (CRF) will be used to record subject data during the course of the study.

All study data must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subjects' records. The Investigator must therefore agree to allow access to subjects' records, and source data must be made available for all study data. The subjects (or their legal representatives) must also allow access to the subjects' medical records, and they will be informed of this and will be signing their agreement when giving informed consent.

All aspects of the study will be carefully monitored by the Sponsor or authorized representatives of the Sponsor, with respect to current GCP and standard operating procedures (SOPs) for compliance with applicable government regulations. These individuals will have access, both during the trial and after trial completion, to review and audit all records necessary to ensure integrity of the data, and they will periodically review progress of the study with the Investigator.

Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. However, ethical reasons may warrant the failure to obtain and record certain data or to record data at the times specified. If this becomes necessary, the reasons must be clearly documented in the source chart.

## 5.8 Prior and Concomitant Medications

Any prior use of systemic antifungal medication within 24 weeks prior to Screening, all medication taken within 30 days before Screening, and all concomitant medication taken during the study are to be recorded on the source documents and CRF. The identity of the medication and the reason for use must be recorded. The use of any concomitant medication must relate to an AE or the subject's medical history.

### 5.8.1 Medications Prohibited Prior to Screening/Baseline (Day 1) and During the Study

The medications prohibited prior to Screening are listed in the exclusion criteria (Section 6.3) and summarized in Table 1 below.

**Table 1: Medications Prohibited Prior to the Study**

Class of Medication	Washout Period
Topical antifungal agents applied to the toenails	2 weeks prior to and during Screening
Systemic corticosteroids (including intramuscular injections) or immunosuppressive agents, except inhaled corticosteroids, which are allowed throughout the study	4 weeks prior to and during Screening
Systemic antifungal agents for treatment of onychomycosis or with known activity against dermatophytes	24 weeks prior to and during Screening
Any investigational drug	30 days prior to and during Screening

Subjects must not take any of the medications listed in [Table 2](#) during the study.

**Table 2: Concomitant Medications Prohibited During the Study**

Class of Medication	Prohibited During Study, From:
Topical antifungal agents applied to the toenails	Screening
Systemic antifungal treatments	Screening
Any investigational drug other than the study drug	Screening

### 5.8.2 Prohibited Procedures

Over-the-counter treatments, such as tea tree oil or holistic products, applied to the toenails are prohibited. Toenail polish is not allowed during the study. On the day of a study visit, subjects and/or parents/guardians should not apply the study drug or any other products to their feet or toenails until they have either been instructed to apply study drug during the visit or until they have completed the study visit. These restrictions will remain in effect, as applicable, throughout the study.

### 5.8.3 Medications Allowed During the Study

Subjects with tinea pedis may be treated with topical antifungal agents if treatment is indicated. Subjects should apply the topical antifungal to all affected areas as directed by the Investigator, avoiding all toenails. These restrictions will remain in effect, as applicable, throughout the study.

## 5.9 Females of Non-childbearing Potential

Premenarchal female subjects will be considered to be of non-childbearing potential.

## 5.10 Females of Childbearing Potential

Acceptable contraceptive methods for female subjects include one of the following:

- Abstinence
- Oral, transdermal, intrauterine, injected, or implanted hormonal methods of contraception
- Tubal ligation
- Placement of a copper-containing intrauterine device
- Condom with spermicidal foam/gel/film/cream/suppository

- Male partner who has had a vasectomy for at least 4 months
- Sterile (eg, total hysterectomy)

An acceptable method of contraception must be used starting from the Screening visit and continue through the end of the study.

## 6.0 STUDY POPULATION

Male or female subjects ages 6 to 16 years and 11 months with DSO involving at least 20% of the total area of the TGT, accompanied by a positive KOH wet mount and a positive fungal culture for the dermatophytes *T. rubrum* or *T. mentagrophytes*, with or without co-infection with *Candida* spp. or *E. floccosum*, during the Screening period. A PK subgroup of at least 16 evaluable subjects ages 12 to 16 years and 11 months will be studied under maximal use conditions.

### 6.1 Sample Size

The study will enroll subjects ages 6 to 16 years and 11 months with at least 40 subjects ages 12 to 16 years and 11 months. All subjects will be assigned to receive active treatment with KERYDIN (tavaborole) topical solution, 5%. A PK subgroup of at least 16 evaluable subjects ages 12 to 16 years and 11 months will be studied under maximal use conditions.

### 6.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for this study:

1. Male or female subjects, ages  $\geq 6$  years and  $\leq 16$  years and 11 months at the time of enrollment
2. Have a parent or guardian able to understand, to agree to, and to sign the study ICF; subject has the ability to give assent based on their age, maturity, and psychological state at the time of parental/guardian consent
3. A clinical diagnosis of DSO affecting either great toenail with positive KOH and *T. rubrum* or *T. mentagrophytes* culture from the TGT confirmed by a central mycology laboratory during the Screening period
4. DSO involving at least 20% of the TGT
5. TGT capable of growing, as assessed by the Investigator or qualified designee
6. Subject and parent/guardian (if applicable) are willing and able to comply with study drug instructions, comply with study instructions, and commit to attending all visits

7. Postmenarchal females must agree to use a medically accepted method of contraception for the entire study period

### 6.3 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded from entering this study:

1. One or more of the following conditions affecting the TGT:
  - Proximal subungual onychomycosis
  - Onychomycosis involving the lunula
  - Superficial white onychomycosis, dermatophytoma, exclusively lateral disease, or yellow/brown spikes
  - Screening culture results that demonstrate co-infection with *Scopulariopsis* spp., *Scytalidium* spp. or other nondermatophyte molds (exception: *Candida* spp. and *E. floccosum* are permitted)
2. Anatomic abnormalities of the toe(s) or toenail(s) to be treated including, but not limited to: genetic nail disorders, pigmentary disorders, onychogryphosis, trauma to the toenail(s) to be treated, or other abnormality that in the Investigator's opinion may interfere with clinical evaluation of the toenail(s) or would indicate that the subject is unlikely to respond to a topical treatment for DSO
3. Current or past history of chronic moccasin-type tinea pedis (involving the sides or dorsum of the foot)
4. Current or past history of psoriasis or lichen planus involving the skin, nails or mucous membranes
5. History of any significant chronic fungal disease other than onychomycosis (eg, chronic mucocutaneous candidiasis)
6. Known diagnosis of type I or type II diabetes
7. Concurrent use of or have used any of the following topical or systemic medications within the indicated timeframe prior to Screening:
  - Topical antifungals applied to the toenails: 2 weeks
  - Systemic corticosteroids (including intramuscular injections): 4 weeks
  - Systemic immunosuppressive agents: 4 weeks

- Systemic antifungals for treatment of onychomycosis or with known activity against dermatophytes: 24 weeks
8. Any significant active or past medical condition which, in the Investigator's opinion, may expose the subject to unacceptable risk by study participation, confound the evaluation of treatment response or AEs, or interfere with the subject's ability to complete the study
  9. History of any known immunodeficiency
  10. Known to be allergic to the study drug or excipients in the study drug
  11. History of drug or alcohol abuse (current or within the past 6 months)
  12. Participated in any other trial of an investigational drug or device within 30 days prior to Screening or participation in a research study concurrent with this study

#### **6.4 Subject Withdrawal**

Subjects may be withdrawn from the study (eg, from further study treatment) for the following reasons as well as other specified reasons:

- AE (including LTR)
- Lost to follow-up
- Subject did not wish to continue for reasons related or unrelated to study treatment
- Noncompliance with protocol
- Administrative reasons (eg, study terminated, study on hold)
- Pregnancy

In all cases, the reason for and date of withdrawal must be recorded in the CRF and in the subject's source documents. The subject must be followed up to establish whether the reason was an AE, and if so, this must be reported in accordance with the procedures in Section 11.0. If a subject is withdrawn due to pregnancy, refer to Section 11.8 for follow-up procedures.

As far as possible, all examinations scheduled for the final study visit must be performed on all subjects who receive the study drug but do not complete the study according to protocol.

The Investigator must make every effort to contact subjects lost to follow-up. Attempts to contact such subjects must be documented in the subject's records (eg, times and dates of

attempted telephone contact, receipt for sending a registered letter).

## **7.0 STUDY PROCEDURES**

### **7.1 Study Visits**

Subjects will be required to visit the clinic for all scheduled visits (Screening, Baseline, and at Weeks 2, 4, 8, 16, 24, 32, 40, 48, and 52). The PK subgroup will have one extra visit (Visit 4a). The timing of each study visit is relative to Baseline (Day 1). Both the PK and non-PK visits will have a window of  $\pm 7$  days with the exception of PK Visit 3 which will have a +7 day window and PK Visit 4a which must immediately follow the proceeding day to allow for 24-hour PK draw). Additional unscheduled visits may be requested by the subject or Investigator to address any safety concerns.

### **7.2 Study Procedures and Evaluations Schema**

#### **7.2.1 Study Schema**

[Table 3](#) displays the study procedures throughout the study.

**Table 3: Schedule of Events**

Study Visit No.	1 (Screening)	2 (Baseline)	3	4	4a (PK)	5	6	7	8	9	10	11 (or ET)
Study Day ( $\pm 7$ days V4-11, +7 days V3)	Up to -70 days	1	15	29	30							
Study Week			2	4		8	16	24	32	40	48	52
Informed consent	x											
Obtain subject number	x											
Demographics	x											
Medical and medication history	x	x										
Abbreviated physical examination		x										
KOH mount and fungal culture <sup>c</sup>	x							x				x
Review inclusion/exclusion criteria	x	x										
Identify target great toenail (TGT)	x	x										
Identify 'other toes' to be treated		x										
Clinical assessment (% TGT disease severity)	x							x				x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events (AEs)	x	x	x	x	x	x	x	x	x	x	x	x
Safety laboratory tests		x						x				x
Urine pregnancy test (UPT) for postmenarchal females		x	x	x		x	x	x	x	x	x	x
Vital signs (blood pressure, pulse rate, respiratory rate) <sup>a</sup>	x	x	x	x		x	x	x	x	x	x	x
LTR assessment		x	x	x		x	x	x	x	x	x	x
PK subgroup sampling <sup>b</sup>			x	x	x <sup>b</sup>							
Photography of the TGT <sup>c</sup>	x							x				x
Weigh and dispense new study drug kit		x	x	x		x	x	x	x	x		
Study drug collection/weighing/accountability			x	x		x	x	x	x	x	x	
Supervise study drug self-administration <sup>d</sup>		x	x	x		x	x	x	x	x		
Diary review and training/re-training		x	x	x		x	x	x	x	x	x	
Schedule next visit	x	x	x	x		x	x	x	x	x	x	

ET, early termination; KOH, potassium hydroxide; PK, pharmacokinetic; LTR, local tolerability reaction

<sup>a</sup> Vital signs conducted after subject is sitting or supine for at least 5 minutes.

<sup>b</sup> For subjects in the PK subgroup, at Visit 3 (Day 15) a pre-dose sample will be collected and Visit 4 (Day 29), PK samples will be collected prior to dosing, as well as 4, 6, and 8 hours post-dose. At Visit 4a (Day 30), the 24-hour post-dose sample is collected prior to dosing.

<sup>c</sup> Perform photography procedures before mycology procedures.

<sup>d</sup> Application occurs at the site on visit days. For PK subgroup participants, the application for Visit 3 (Day 15) and Visit 4a (Day 30) is to occur after the subject has had their PK specimen drawn.



### 7.2.2 Visit 1: Screening Visit (up to 70 Days Prior to Day 1)

Subjects who have taken prohibited medication(s) within the eligibility criteria exclusionary timeframe will fail Screening, but they may rescreen after the required timeframe has been met. If necessary, the Screening procedures may be completed over 70 days. The following procedures will be performed at the Screening visit (Visit 1):

- Obtain informed consent prior to any study-specific evaluations or procedures
- Obtain subject number
- Collect demographic information
- Verify subject eligibility (inclusion/exclusion criteria)
- Identify the TGT (to be confirmed at Baseline)
- Clinical assessment of the TGT
- Collect medical and medication history including all medication taken within 30 days prior to Screening and any prior use of systemic antifungal agents for treatment of onychomycosis or with known activity against dermatophytes within 24 weeks prior to Screening
- Review and record new AEs occurring after signed ICF
- Obtain vital signs (blood pressure, pulse rate, respiratory rate) after subject is in sitting or supine position for at least 5 minutes
- Take digital photographs (photography procedure is to occur before mycology procedure);
  - Take the first set of photographs after trimming the TGT to within 1 mm distal of the hyponychium or distal groove
  - Mark the TGT with indelible ink pen (distal groove and the proximal mycotic border)
  - Take the second set of photographs after marking the TGT
- Obtain sample for KOH wet mount and fungal culture (Do not perform mycology sampling until after photography procedure is completed)
  - A local KOH wet mount is an optional procedure, and only the central mycology laboratory reading will be used for analysis and eligibility determination.

- Trim toenails as needed: the unattached nail plate of the subject's TGT can be trimmed as far as needed to obtain an adequate sample of subungual debris.
- Schedule next visit

### **7.2.3 Treatment Period (Visit 2 through Visit 10)**

The treatment period consists of Visit 2 (Baseline visit) through Visit 10 (Week 48). An unscheduled visit may occur for follow-up of an AE, LTR, abnormal laboratory evaluation, replacement of lost study drug, or for any reason that, in the judgment of the Investigator, is required to ensure patient safety or study integrity. Procedures relevant to the reason for the unscheduled visit (i.e., repeat laboratory test) should be performed. At treatment period visits, the following assessments will be performed as indicated below.

#### **7.2.3.1 Visit 2: Baseline Visit (Day 1)**

- Verify subject eligibility
- Confirm medical and medication history
- Collect concomitant medication information
- Review and record AEs
- Assess for LTR and grade the severity using the scales provided in [Table 4](#)
- Perform an abbreviated physical examination (prior to enrolling and drug dispense)
- Assess and confirm the identity of the TGT; if both great toenails are eligible, select the one with the greatest involvement
- Assess other toenails (includes assessment of the presence of and visual estimate of the extent of the total toenail area that shows onycholysis and subungual hyperkeratosis) to determine which toenails (other than the TGT) will be treated during the study. For all subjects, assess and document other toenail involvement. However, ALL 10 toenails, affected and unaffected, including up to 2 mm of the surrounding skin, will receive study drug application for 28 days ( $\pm$  specified window) for the subjects in the PK subgroup.
- Obtain vital signs (blood pressure, pulse rate, respiratory rate) after subject is in sitting or supine position for at least 5 minutes
- Draw blood for safety laboratory tests
- Conduct UPT (postmenarchal females only)
- Dispense study drug after weighing and recording the weight of the bottles with caps

- Instruct the subject on drug storage and administration. Supervise self-administration of study drug and re-instruct as needed. Application occurs at the site on visit days.
- Perform diary training
- Schedule next visit. Instruct subject to save all study drug bottles and caps and bring all used and unused study drug bottles and caps to each visit. Remind the subject not to apply study drug or use products on the feet or nails on the day of clinic visits.

#### **7.2.3.2 Visit 3 (Week 2) Through Visit 10 (Week 48)**

- Collect concomitant medication information
- Review and record AEs
- Obtain vital signs (blood pressure, pulse rate, respiratory rate) after subject is in sitting or supine position for at least 5 minutes
- Week 24 only: draw blood for safety laboratory tests
- Week 24 only: Clinical assessment of the TGT
- Week 24 only: take digital photographs (photography procedure is to occur before mycology procedure);
  - Take the first set of photographs after trimming the TGT to within 1 mm distal of the hyponychium or distal groove
  - Mark the TGT with indelible ink pen (distal groove and the proximal mycotic border)
  - Take the second set of photographs after marking the TGT
- Week 24 only: obtain sample for KOH wet mount and fungal culture (Do not perform mycology sampling until after photography procedure is completed)
- Conduct UPT (postmenarchal females only)
- Assess for LTR and grade the severity using the scales provided in [Table 4](#)
- Trim toenails as needed
- Collect study drug, perform accountability, and record the weight of the returned bottles with caps

- Dispense new study drug kit after weighing and recording the weight of the bottles with caps
- Only for subjects in the maximal use subgroup at Visit 3, collect a pre-dose PK sample. At Visit 4 (Day 29) and Visit 4a (Day 30): collect PK samples prior to dosing, as well as 4, 6, 8, and 24 hours post-dose. NOTE: 24 hours post-dose occurs at Visit 4a (Day 30) and occurs prior to application that day.
- Supervise self-administration of study drug and re-instruct as needed. Application occurs at the site on visit days. For PK subgroup participants, the application for Visit 4a (Day 30) occurs after the subject has had their 24-hour PK specimen drawn.
- Review diary and re-train as needed
- Schedule next visit. Instruct subject to save all study drug bottles and caps and bring all used and unused study drug bottles and caps to each visit. Remind the subject not to apply study drug or use products on the feet or nails on the day of clinic visits.

#### **7.2.4 Visit 11 (Week 52) or Early Termination**

- Collect concomitant medication information
- Review and record AEs
- Clinical assessment of the TGT
- Take digital photographs (photography procedure is to occur before mycology procedure);
  - Take the first set of photographs after trimming the TGT to within 1 mm distal of the hyponychium or distal groove
  - Mark the TGT with indelible ink pen (distal groove and the proximal mycotic border)
  - Take the second set of photographs after marking the TGT
- Obtain sample for KOH wet mount and fungal culture (Do not perform mycology sampling until after photography procedure is completed)
- Obtain vital signs (blood pressure, pulse rate, respiratory rate) after subject is in sitting or supine position for at least 5 minutes
- Draw blood for safety laboratory tests
- Conduct UPT (postmenarchal females only)

- Assess for LTR and grade the severity using the scales provided in [Table 4](#)
- Collect study drug, perform accountability, and weigh the bottles and caps returned, if applicable

### **7.3 Explain Study and Obtain Signed Informed Consent Form**

At the Screening Visit, the Investigator or qualified designee will explain the study to the subject and/or parents/guardians, answer all of his/her/their questions, and obtain a signed ICF/assent before performing any study-related procedure. A copy of the signed ICF/assent will be given to the subject and/or parents/guardians.

### **7.4 Demographics**

The subjects' demographics collected at Screening on the CRF will include date of birth (age), sex, ethnicity, and race.

### **7.5 Review Inclusion/Exclusion Criteria**

The inclusion and exclusion criteria will be reviewed at Screening by the Investigator or qualified designee to ensure that the subject qualifies for the study. The inclusion and exclusion criteria will be reviewed again at Baseline to confirm that the subject still meets the criteria to participate in the study.

### **7.6 Medical History and Medication History**

A medical history and medication history will be obtained by the Investigator or qualified designee at Screening and confirmed at the Baseline visit. Subject history should include significant medical information, as well as history of and prior treatment for onychomycosis and any symptoms attributed to onychomycosis. Review of all appropriate medication washout times will be discussed with the subject.

### **7.7 Concomitant Medications**

At all visits, concomitant medication information will be collected.

### **7.8 Physical Examinations**

An abbreviated physical examination will be performed by the Investigator or a qualified designee at Baseline prior to enrollment (and drug dispensing). Abnormal physical examination findings at Baseline will be recorded on the medical history module of the CRF.

### **7.9 Identify Target Great Toenail (TGT) and Other Toenails**

At Screening, the Investigator will perform a visual assessment of the severity of nail involvement of the subject's great toenails to determine if Screening should proceed.

The TGT is defined as the most involved great toenail that meets eligibility criteria. The chosen great toenail (left or right) will be recorded on the CRF.

At Baseline (Day 1) the Investigator will assess all other toenails for the presence of onychomycosis to determine what other toenails will be treated throughout the study.

#### **7.10 Toenail Trimming Procedure**

At Screening, Week 24, and Week 52:

Trimming procedure for photography: trim the TGT to within 1 mm distal of the hyponychium or distal groove. The photography procedure is to be completed prior to mycology trimming and sampling procedure.

Trimming procedure for mycology sampling: after the photography procedure is complete, the TGT may be further trimmed for the purposes of mycology sampling. The unattached nail plate of the subject's TGT can be trimmed as far as needed to obtain an adequate sample of subungual debris.

At all other visits, the subject's toenails can be trimmed, as needed, by the Investigator or a qualified designee.

#### **7.11 KOH Mount and Central Fungal Culture**

Mycology sampling is to occur after all photography procedures for that visit have been completed. At Screening, the Investigator may perform a KOH wet mount at the study site to confirm the clinical diagnosis of onychomycosis prior to obtaining a sample for the central mycology laboratory; however, care must be taken to obtain sufficient subungual debris for the analysis at the central laboratory. The local KOH wet mount is an optional procedure and only the central mycology laboratory reading will be used for analysis and eligibility determination. If both great toenails are potentially eligible by clinical criteria, then both great toenails can be sampled at Screening. A subject that fails mycology criteria may be resampled (see resample criteria in Section 5.0).

A sample of subungual debris will be obtained again at Week 24 and Week 52/ET.

Specimen collection and sample shipment instructions will be provided in the laboratory manual.

#### **7.12 Study Drug Dispensing**

Dispensing occurs at Visits 2-9. Upon opening the study drug kit (carton), study site personnel should verify that each bottle in a given kit is tightly capped and contains study medication. Any information required on the bottle label (i.e., subject identifier) should be completed

before dispensing. The number of bottles contained in each medication kit will be verified and the bottles weighed with cap on before a kit is dispensed to a subject.

### **7.13 Study Drug Self-Administration**

During the Baseline visit (Day 1), subjects will be instructed on how to apply the study medication and will self-administer study drug application at each dispense visit under the supervision of site personnel. The subject will be retrained as needed. The subject will be instructed to self-administer study drug topically, once daily, on all affected toenails (TGT and other toenails identified by the Investigator). Application occurs at the site on visit days. For PK subgroup participants, the application for Visit 4a (Day 30) is to occur after the subject has had their 24-hour PK specimen drawn. Subjects should continue dosing all toenails that were identified as affected at Baseline throughout the study even if some of the affected toenails become clear.

Subjects participating in the PK maximal use subgroup will initially be instructed to apply study medication to all 10 toenails, including up to 2 mm of the surrounding skin, once daily for 28 days ( $\pm 7$  days). Additionally, these subjects will receive a minimum dose of each treatment defined as follows:

- Great toenails: two (2) drops each
- All other toenails: one (1) drop each

After PK assessments are complete, the subject will be instructed to apply study medication to all affected toenails once daily for the remainder of the study.

### **7.14 Dosing Modifications**

If dosing modification is needed due to local irritation, or any other reasons, the Investigator may implement a temporary interruption of study drug to one or more toes as applicable.

### **7.15 Study Drug Collection**

Subjects will be instructed to save all used, unused, and empty study drug bottles and caps and return them at each return visit. The subject will be reminded of these instructions at each visit. The Investigator or a qualified designee will collect study drug and perform accountability (bottle count and weighing the bottles with cap on).

### **7.16 Dosing Diary**

Subjects will start a diary at Baseline (Day 1) and will complete the diary as instructed. The diary will be reviewed at each study visit in order to assess compliance with treatment.

### **7.17 Digital Photography**

At the Screening Visit, Week 24, and Week 52/ET, digital photographs of the TGT will be obtained before performing mycology sampling procedures:

- Take the first set of photographs after trimming the TGT to within 1 mm distal of the hyponychium or distal groove
- Mark the TGT with indelible ink pen (outline the distal groove and the proximal mycotic border)
- Take the second set of photographs after marking the TGT

Photography will occur at selected sites. Photographs will be utilized for purposes of publications. All photos will be sent to the central photography laboratory and photographic equipment will be provided to all sites by the central photography laboratory for use throughout the trial. The Investigator and qualified designees will be trained on the use of the camera and the appropriate lighting and positioning of the toe. Details on the digital photography procedure will be provided in a separate manual.

## **8.0 PHARMACOKINETIC ASSESSMENT**

### **8.1 Collection of Blood Samples for Pharmacokinetic Assessment**

Blood samples for the determination of plasma levels of tavaborole and PK parameters will be obtained under maximal use conditions (once daily application to all 10 toenails, including up to 2 mm of the surrounding skin) from the subgroup of subjects ages 12 to 16 years and 11 months to achieve at least 16 evaluable subjects. Subjects in the maximal use subgroup will apply the study drug on all 10 toenails, including up to 2 mm of the surrounding skin, for 28 days  $\pm$  7 days. At Visit 3 (Day 15) a pre-dose PK sample will be collected to assess steady state trough level. At Visit 4 (Day 29), the study drug application will be done at the study site, and PK samples will be collected prior to dosing, as well as 4, 6, and 8 hours post-dose. At Visit 4a (Day 30) the sample will be collected 24 hours post-dose and prior to the application for that day.

Approximately 24 mL of blood (6 samples, 4 mL each) will be taken from each of the 16 subjects for the PK determination.

### **8.2 Specimen Assays**

Each blood sample will be labeled appropriately and the actual time and date of each sample collection will be entered in the CRF. Procedures for PK sample collection, processing, handling, storage, and shipping will be provided in a separate PK laboratory manual.



## 9.0 EFFICACY ASSESSMENT

The efficacy assessments are intended to assess compliance with treatment for the purposes of the safety assessment.

### 9.1 Clinical Assessment of the Target Toenail Involvement

Clinical involvement of the TGT will be assessed at Screening and Weeks 24 and 52/ET using the following definitions of disease severity:

- **Completely CN:** no clinical evidence of onychomycosis as evidenced by normal toenail plate, no onycholysis, and no subungual hyperkeratosis
- **Almost CN:** no more than minimal evidence of onychomycosis as evidenced by toenail plate dystrophic or discolored  $\leq 5\%$  of the distal aspect, with minimally evident onycholysis and subungual hyperkeratosis
- **Mild onychomycosis:** onychomycosis as evidenced by toenail plate dystrophic or discolored  $> 5\%$  to  $\leq 20\%$  of the distal aspect, with clearly evident onycholysis and subungual hyperkeratosis
- **Moderate onychomycosis:** onychomycosis as evidenced by toenail plate dystrophic or discolored  $> 20\%$  to  $\leq 50\%$  of the distal aspect, with clearly evident onycholysis and subungual hyperkeratosis
- **Severe onychomycosis:** onychomycosis as evidenced by a toenail plate dystrophic or discolored  $> 50\%$  of the distal aspect, with pronounced onycholysis and subungual hyperkeratosis

### 9.2 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is complete cure rate (no clinical evidence of onychomycosis as evidenced by a normal toenail plate, no onycholysis, and no subungual hyperkeratosis and negative KOH wet mount and fungal culture) of the TGT at Week 52.

Treatment Outcomes are defined as follows:

- **Negative mycology:** negative KOH wet mount and negative fungal culture
- **Complete cure:** completely CN and negative mycology
- **Almost complete cure:** almost CN and negative mycology
- **Treatment success:** completely CN or almost CN

The efficacy assessments are intended to assess compliance with treatment for the purposes of the safety assessment.

### 9.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- Complete or Almost complete cure of the TGT at Weeks 24 and 52 defined as (no clinical evidence of onychomycosis as evidenced by a normal toenail plate, no onycholysis, and no subungual hyperkeratosis) or almost CN (no more than minimal evidence of onychomycosis as evidenced by a toenail plate dystrophic or discolored over  $\leq 5\%$  of the distal aspect, with minimally evident onycholysis and subungual hyperkeratosis) of the TGT with negative mycology at Week 52;
- Treatment success (Clinical Efficacy rate) of the TGT at Weeks 24 and 52 defined as completely CN or almost CN ;
- Negative mycology (Mycological Cure rate) of the TGT at Weeks 24 and 52 defined as negative KOH wet mount and negative fungal culture
- Negative fungal culture of the TGT at Weeks 24 and 52

## 10.0 SAFETY ASSESSMENT

Safety assessments will be performed according to the schedule of events shown in [Table 3](#). Safety variables for this study include the frequency and severity of LTRs, frequency and severity of treatment-emergent adverse events (TEAEs) and SAEs (see Section [11.0](#)), and abnormalities in clinical laboratory parameters and vital signs. Adverse events occurring from the informed consent signature up to the completion of the study or the early termination visit, as applicable, will be recorded.

### 10.1 Local Tolerability Reactions (LTRs)

Safety evaluations will include LTRs (burning/stinging, induration/edema, oozing and crusting, pruritus, erythema, and scaling), as reported by the subject and/or evaluated by the Investigator at Baseline and each study visit thereafter. LTRs will be documented on the CRF specifically designed to capture LTR information (local tolerability signs CRF) and not on the AE CRF. LTRs that require treatment (eg, with a concomitant medication or drug interruption or drug discontinuation) are an exception to this guideline; these LTRs should be documented on both the local tolerability signs CRF and on the AE CRF.

The grading of LTRs is presented in [Table 4](#).

**Table 4: Grading of Local Tolerability Reactions (LTRs)**

Grade	Guideline
<b>Burning/Stinging</b>	
0 - None	No stinging/burning
1 - Mild	Slight warm, tingling sensation; not really bothersome
2 - Moderate	Definite warm; tingling/stinging sensation that is somewhat bothersome
3 - Severe	Hot, tingling/stinging sensation that has caused definite discomfort
<b>Induration/Edema</b>	
0 - None	No elevation
1 - Mild	Barely perceptible elevation
2 - Moderate	Clearly perceptible elevation but not extensive
3 - Severe	Marked and extensive elevation
<b>Oozing and Crusting</b>	
0 - None	Absent
1 - Mild	Faint signs of oozing
2 - Moderate	Definite oozing or crust but with 5 or fewer sites per area
3 - Severe	Marked and extensive oozing and crusting
<b>Pruritus</b>	
0 - None	No pruritus
1 - Mild	Occasional, slight itching/scratching
2 - Moderate	Constant or intermittent itching/scratching which is not disturbing sleep
3 - Severe	Severe bothersome itching/scratching which is disturbing sleep
<b>Erythema</b>	
0 - None	No redness present
1 - Mild	Faintly detectable erythema; very light pink
2 - Moderate	Dull red, clearly distinguishable
3 - Severe	Deep/dark red
<b>Scaling</b>	
0 - None	No scaling
1 - Mild	Barely perceptible shedding, noticeable only on light scratching or rubbing
2 - Moderate	Obvious but not profuse scaling
3 - Severe	Heavy scale production

## 10.2 Vital Signs

Vital signs will be measured at each study visit after the subject has been sitting or supine for at least 5 minutes. Vital sign measurements taken will be blood pressure, pulse rate, and respiratory rate.

### 10.3 Clinical Safety Laboratory Parameters and Pregnancy Tests

Clinical safety laboratory parameters will be assessed at Baseline, Week 24, and Week 52/ET, if applicable. Laboratory tests may be repeated more often if clinically indicated. Blood samples may be taken with the subject in a non-fasting state.

All out-of-normal range laboratory values must be evaluated by the Investigator or subinvestigator as to whether they are clinically significant (i.e., require medical intervention or have clinical signs and/or symptoms). Abnormal clinical laboratory parameters that are considered clinically significant by the Investigator will be recorded on the AE CRF except Baseline visit. Clinically significant laboratory abnormalities noted from the Baseline visit will be recorded as medical history. The AE should be reported as a clinical diagnosis when possible. Laboratory tests will be performed by the central laboratory and are presented in [Table 5](#).

UPTs will be performed at each scheduled visit on postmenarchal females starting at Baseline. If a UPT result is positive, the subject must be discontinued (see [Section 11.8](#) for details).

The Sponsor will designate a central laboratory for safety laboratory tests. All samples for clinical laboratory tests must be managed through the central laboratory designated by the Sponsor. Sample management (collection, storage, shipping, etc.) will be done according to the central laboratory instructions.

**Table 5: Safety Laboratory Parameters**

Hematology	Chemistry
Hemoglobin	Blood urea nitrogen
Hematocrit	Creatinine
Red blood cell count	Glucose (nonfasting)
Platelet count	Sodium, Potassium
White blood cell count	Aspartate aminotransferase, alanine aminotransferase
Neutrophils	Total bilirubin
Eosinophils	Alkaline phosphatase
Monocytes	Albumin
Basophils	Total protein
Lymphocytes	Urine pregnancy test (all scheduled visits starting at Baseline)

## 11.0 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 11.1 Definition of Adverse Event

An AE is any untoward medical occurrence or unintended change from the subject's Baseline (pretreatment) condition, including intercurrent illness, that occurs during a clinical trial after treatment has started, whether or not it is considered related to study treatment. An AE can

therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product.

An AE is meant to include events that are either new or represent detectable exacerbations of preexisting conditions, and does not imply any judgment about causality.

AEs will be assessed at each visit. Any AE occurring on or after the date of the dose of study drug administration on Day 1 and up to and including the completion/termination date will be counted as treatment-emergent.

Adverse experiences may include but are not limited to subjective or objective symptoms spontaneously reported by the subject and/or observed by the Investigator or medical staff, including laboratory abnormalities of clinical significance. Preexisting conditions noted as part of the medical history at Screening must be reported on the appropriate medical history CRF page. Stable, ongoing conditions present at Screening should not be recorded as AEs if the severity at Screening remains unchanged during the study. However, preexisting conditions for which an increase in severity is observed after Screening must be recorded as AEs.

Any AE a subject experiences from signing the ICF up to the completion of final study procedures will be reported as described and recorded on the CRF as follows:

- **LTRs:** LTRs assessed at each visit are to be documented on the CRF specifically designed to capture LTR information (local tolerability symptoms CRF) and not on the AE CRF. An exception to this is that LTRs requiring treatment (eg, with a concomitant medication or drug interruption or drug discontinuation) should be documented on both the local tolerability symptoms CRF and on the AE CRF.
- **Life-threatening experience:** An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- **Persistent or significant disability/incapacity:** Any adverse experience that, in the Investigator's opinion, results in a substantial disruption of a person's ability to conduct normal life functions.

- **Unexpected AE:** An AE is considered “unexpected” if it is not listed in the IB or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.
- **Associated with the use of the drug:** A reasonable possibility exists that the experience may have been caused by the drug.

## 11.2 Relationship to Study Drug

The Investigator will assess the causal relation, if any, between the AE and the study drug using the following definitions:

- **Definite:** A reaction or event that follows a reasonable temporal sequence from administration of study drug or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected study drug, and that is confirmed by improvement on stopping or reducing the dosage of study drug and reappearance of the reaction on rechallenge.
- **Probable:** A reaction that follows a reasonable temporal sequence from administration of study drug, that follows a known or expected response pattern to the suspected study drug, and that could not be reasonably explained by the known characteristics of that subject’s clinical state.
- **Possible:** A reaction that follows a reasonable temporal sequence from administration of study drug, that follows a known or expected response pattern to the suspected study drug, but that could readily have been produced by a number of other factors.
- **Unlikely:** A reaction that does not follow a reasonable temporal sequence from administration of study drug. However, causality from the study drug cannot be ruled out.
- **Not related:** A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug.

## 11.3 Severity

The assessment of severity is subjective, and the Investigator should use medical judgment to compare the reported adverse experience to similar type events observed in clinical practice. The guidelines for severity assessment are as follows:

- **Mild:** Symptom(s) barely noticeable to the subject or does not make the subject uncomfortable. The adverse experience does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
- **Moderate:** Symptom(s) of a sufficient severity to make the subject uncomfortable. Performance of daily activities is affected. Severity may lead to temporary cessation of treatment with the study drug. Treatment of symptom(s) may be needed.
- **Severe:** Symptom(s) of a sufficient severity to cause the subject severe discomfort. Severity may lead to cessation of treatment with the study drug. Treatment for symptom(s) may be given.

Grading for LTRs is defined in [Table 4](#).

#### 11.4 Outcome

The outcome of an AE will be assessed as follows:

- Recovered / Resolved
- Not Recovered / Not Resolved
- Recovered / Resolved with sequelae
- Fatal
- Unknown

#### 11.5 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires or prolongs in-patient hospitalization
- Results in persistent or significant disability/incapacity, or
- Results in a congenital anomaly

Medical and scientific judgment should be exercised in determining whether an event that does not meet any of the above criteria is an important medical event. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious 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.

Elective surgeries planned and approved before Screening (eg, joint replacement) will not be considered SAEs if they are due to a preexisting condition and not due to a worsening of a condition during the study.

In the event of death, the cause of death should be recorded and reported as the SAE. "Death" is an outcome and is not an acceptable verbatim term to describe an SAE. The only exception is "sudden death," when the cause of death is unknown at the time of the Investigator's awareness of the event.

### 11.6 Safety Reporting Procedures

Upon awareness of an SAE, the Investigator must contact the Anacor Pharmacovigilance Group immediately by fax and follow up with a written description of the circumstances surrounding the event within 24 hours of becoming aware of the event. The Anacor Pharmacovigilance Group will forward the initial SAE report form to the medical monitor. For SAE reporting:

Anacor Pharmacovigilance Group  
Fax/eFax: PPD

All subsequent information pertaining to the SAE must be reported to the Anacor Pharmacovigilance Group. If required, a safety report will be filed with the appropriate regulatory authorities. All SAEs will be reported promptly to the IRB/EC. In addition to being reported to the Anacor Pharmacovigilance Group and the applicable IRB/EC, all SAEs must be recorded in the subject's medical record and entered in the CRF.

If required, a safety report will be prepared by the Sponsor, sent to all participating Investigators, and filed with the appropriate regulatory authorities.

#### Medical Monitor Contact Information:

If needed, the medical monitor can be contacted directly for consults.

Name: PPD, MD  
Telephone: PPD  
Fax/eFax: PPD  
Email: PPD



All AEs will be followed through the end of the study and will be noted as “ongoing” if not resolved at the last study visit. All SAEs will be followed to resolution or stabilization, as determined by the Investigator.

The Investigator must document his/her efforts to obtain all follow-up information regarding the SAE requested by the Anacor Pharmacovigilance Group.

### **11.7 Laboratory Test Abnormalities**

The Investigator will review all safety laboratory results. All out-of-normal range laboratory values must be evaluated for clinical significance, and clinically significant abnormalities must be reported as AEs except from Baseline visit abnormalities which will be recorded as medical history. Clinically significant laboratory abnormalities are defined as laboratory abnormalities that have clinical manifestations or require medical intervention. Investigators should report clinical diagnoses as AEs rather than list individual laboratory test results when possible.

### **11.8 Pregnancy**

In the event that a subject becomes pregnant during study treatment or follow-up, the Anacor Pharmacovigilance Group and medical monitor must be notified immediately upon the Investigator becoming aware of the pregnancy. The subject will be discontinued from study drug. The outcome of the pregnancy will be collected by the safety group.

## **12.0 STATISTICAL PLAN**

All statistical processing will be performed using SAS<sup>®</sup> unless otherwise stated.

Descriptive statistics will include sample size, mean, median, standard deviation, minimum, and maximum continuous variables. Categorical variables will be tabulated with frequency counts and percentages.

### **12.1 Sample Size**

The study will enroll subjects ages 6 to 16 years and 11 months with at least 40 subjects ages 12 to 16 years and 11 months. All subjects will be assigned to receive active treatment with KERYDIN (tavaborole) topical solution, 5%. A PK subgroup of at least 16 evaluable subjects ages 12 to 16 years and 11 months will be studied under maximal use conditions.

## 12.2 Statistical Analysis

### 12.2.1 Study Populations

The following populations will be used:

- **Safety population:** all subjects who receive at least one confirmed dose of study drug and have at least one post-baseline safety assessment.
- **PK population:** all subjects from the maximal use subgroup with available PK data.

### 12.2.2 Background and Demographic Characteristics

Subject demographic (age, sex, race, and ethnicity) and Baseline characteristics will be summarized for the Safety and PK populations. Age will be represented as both a continuous and as a categorical variable.

### 12.2.3 Efficacy

The primary and secondary efficacy endpoints including Complete cure rate, Complete or Almost complete cure rate, Treatment success (Clinical Efficacy), Mycological Cure rate, and negative fungal culture of the TGT at Week 24 and Week 52 will be summarized for the safety population with descriptive statistics including sample size, frequency count, and percentage.

The efficacy assessments are intended to assess compliance with treatment for the purposes of the safety assessment.

### 12.2.4 Pharmacokinetics

Pharmacokinetics will be tabulated for each collection day using descriptive statistics. Mean plasma concentrations will be plotted through time using both linear and semi-logarithmic scales. Plasma concentrations will also be plotted through time for each subject, using both linear and semi-logarithmic scales. Concentrations below the limit of quantitation will be set to zero for descriptive statistics.

The following PK parameters will be calculated for Day 15 (steady state trough level only) and Day 29 [steady state ( $\pm$ specified window)]:

- $C_{\max}$ : maximum observed plasma concentration
- $T_{\max}$ : time to maximum observed plasma concentration
- $AUC_{0-24}$ : area under the plasma concentration-time curve from Hour 0 to Hour 24, calculated using the linear trapezoidal rule

- $AUC_{0-\infty}$ : area under the plasma concentration-time curve extrapolated to infinity
- $\lambda_z$ : elimination rate constant
- $t_{1/2}$ : elimination half-life

PK parameters will be calculated using actual sampling times.

### **12.2.5 Safety**

No imputation will be made for missing safety data.

#### **12.2.5.1 Extent of Exposure**

The extent of exposure to study drug will be summarized by the total number of days of dosing, total number of applications, and total amount of study drug applied.

#### **12.2.5.2 Local Tolerability and Adverse Events**

LTRs (burning/stinging, induration/edema, oozing and crusting, pruritus, erythema, and scaling) will be evaluated by frequency tables for each visit. Additionally, LTRs will be summarized by descriptive statistics (mean, standard deviation, median, and minimum and maximum).

All AEs occurring during the study will be recorded and classified on the basis of *Medical Dictionary for Regulatory Activities* terminology. TEAEs are those with an onset on or after the time of the first study drug administration. For the safety population, all reported TEAEs will be summarized by system organ class (SOC), preferred term, severity, relationship to study drug, and seriousness. When summarizing TEAEs by causality and severity, each subject will be counted only once within an SOC or a preferred term using the event with the closest relationship to study drug and the greatest severity within each classification.

SAEs will be summarized by severity and relationship to study drug, and individual SAEs will be listed by subject. A list of subjects who prematurely discontinued from the study due to an AE will also be provided.

All information pertaining to AEs noted during the study will be listed by subject, detailing the verbatim term reported by the Investigator, preferred term, SOC, onset date, resolution date, maximum severity, seriousness, action taken regarding study drug, corrective treatment, outcome, and drug relationship. The event onset will also be shown relative (in number of days) to date of first administration of study drug.

#### **12.2.5.3 Laboratory Values and Vital Signs**

Changes from Baseline in vital signs and safety laboratory values will be summarized at each follow-up evaluation using descriptive statistics or frequency tables as applicable.

Additionally, changes from Baseline in safety laboratory values will be summarized using shift tables according to normal ranges. The last laboratory evaluation before the first dose of study drug will be used as Baseline for all laboratory analyses.

#### **12.2.5.4 Concomitant Medications**

Concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced. All medications will be presented in the data listings. A table of concomitant medications by percentage of subjects who used them will also be provided. No statistical tests will be performed.

### **13.0 ETHICAL CONSIDERATIONS**

#### **13.1 Ethical Conduct of the Study**

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of GCP (as defined in the ICH E6 Guideline for GCP). The Investigator and the site personnel are responsible for conducting this study in accordance with US Code of Federal Regulations, GCP, the ethical principles that have their origin in the Declaration of Helsinki, and all other applicable laws and regulations.

#### **13.2 Subject Information, Informed Consent, and Assent**

The Investigator and designated site staff who will perform the consent/assent process are responsible for knowing country-specific regulations and other local requirements with regard to child assent and to ensure that the assent process is conducted in accordance with those requirements.

An initial informed consent (for parent/guardian of adolescent subjects) and assent form (for adolescent subjects, as applicable) will be provided to the Investigator to prepare the ICF and assent documents to be used at the Investigator's site. Updates to the informed consent template must be communicated to the Sponsor or designee prior to IRB/EC approval. Written informed consent and assent, in accordance with local clinical investigation regulations and approved by the IRB/EC, must be obtained prior to participation in the study. The Investigator will not undertake any measures specifically required for the clinical study unless and until valid consent and assent have been obtained.

Information must be given both in oral and written form. For adolescent subjects, written informed consent and assent documents will be given to the parent/guardian and each applicable subject, respectively. Informed consent documents will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The information provided in the informed consent will be in a language understandable to the adult subjects or parent/guardian of adolescent subjects and may not include any language that appears to waive any of the parent/guardian's or subject's legal

rights or appears to release the Investigator, the Sponsor, or the institution from liability or negligence.

The Investigator will provide the parent/guardian and/or prospective subject sufficient time to consider whether to participate. The Investigator will explain to the subject and parent/guardian, as applicable, that withdrawal from the study is possible at any time without detriment to care. The ICF and assent must include acknowledgement that medical records and medical data derived from the study may be forwarded to the Sponsor or to the responsible authorities or federal authorities.

At the first visit, and prior to initiation of any study-related procedures, the parent/guardian (or the subject's legally authorized representative) of adolescent subjects will be asked to give written informed consent, and adolescent subjects will be asked to give assent (and written informed consent at the time they turn 18 years of age during the study), after having been informed about the nature and purpose of the study, participation/discontinuation conditions, and risks and benefits. If the parent/guardian is unable to provide written informed consent, the subject's legally authorized representative may provide written consent as allowed by institution-specific guidelines. The informed consent and assent documents, as applicable, must be signed and dated by the parent/guardian (or the subject's legally authorized representative) and the subject, prior to study participation. Copies of the signed informed consent and assent documents must be provided to the parent/guardian (or the subject's legally authorized representative) and/or the subject.

If the parent/guardian and/or the subject is unable to read, oral presentation and explanation of the ICF and/or assent must be provided to the parent/guardian and/or subject in the presence of an impartial witness or legally authorized representative. After the parent/guardian and/or subject provide oral and if capable written/dated informed consent and/or assent, the witness should sign and date the ICF and/or assent in accordance with the instructions of the relevant IRB/EC. By signing the ICF and/or assent, the witness attests that the written information was accurately explained to, and apparently understood by, the parent/guardian and/or subject, and that informed consent and/or assent was freely given by the parent/guardian and/or subject.

Original signed/dated consent and assent forms (if applicable) must remain in the subject's study file and be available for verification by the Sponsor or their designees at any time.

### **13.2.1 Child Assent Considerations**

The IRB/EC approval letter must clearly document the IRB/EC's assessment of risk in accordance with 21 CFR 50.51–50.54, Subpart D. The ICF should reflect the correct number of signature lines for the parent(s)/guardian(s) in accordance with the IRB/EC's risk assessment of the proposed research (see 21 CFR 50.55).

The IRBs/ECs are required to determine if child assents are appropriate for all studies that include pediatric subjects. The IRB/ECs may opt to waive assent if the subjects are not

capable of understanding (i.e., based on level of intellectual development or maturity) or if the study is in the best interest of the subject (i.e., strong possibility of benefit and no other alternatives are available). If an IRB/EC chooses to waive assent, this must be documented in the IRB/EC approval letter or be documented in the meeting minutes.

The contents of an assent are not mandated by the US FDA; however, assents must be factually correct, written at an age appropriate level, and not include any coercive language. The assent must have a date and signature line for the child. State laws differ in their requirements for subjects who have not reached the legal age of majority and IRB/ECs are responsible for following their local regulations. Use of an assent is not a substitute for parental permission. Parents/guardians must receive a full informed consent to review and sign.

### **13.3 IRB/EC Approval**

This protocol, the informed consent document, and all relevant supporting data, including any advertisement used to recruit study subjects, must be submitted to the IRB/EC for approval, which must be obtained before the study begins. At least once a year, the Investigator is responsible for informing the IRB/EC of the progress of the study and of any changes made to the protocol. The Investigator is also responsible for notifying the IRB/EC of any significant AEs that occur during the study.

### **13.4 Subject Confidentiality**

The Investigator must assure that subject anonymity will be maintained and that subject identity is protected from unauthorized parties. On CRFs and other documents that are submitted to the Sponsor, subjects should be identified by an identification code and not by their names. Electronic data will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the Sponsor, independent IRB/EC, or regulatory authorities may inspect their medical records to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

The Investigator should keep a subject enrollment log showing codes, names, and addresses. All data obtained during the course of this study will be transferred, stored, managed, and analyzed in compliance with applicable privacy policy.

The Sponsor or designee will ensure that the use and disclosure of protected health information obtained during a research study complies with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, if applicable. The HIPAA rule provides federal protection for the privacy of protected health information by implementing standards to protect and guard against the misuse of individually identifiable health information of subjects participating in the clinical trials. Authorization is required from each research subject (i.e., specific permission granted by an individual to a covered entity) for the use or

disclosure of his or her protected health information. A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization may be combined in the informed consent document (approved by the IRB/IEC) or it may be a separate document (approved by the IRB/IEC) or provided by the Investigator or Sponsor (without IRB/IEC). It is the responsibility of the Investigator and institution to obtain such waiver/authorization in writing from the appropriate individual.

## **14.0 DOCUMENTATION AND STUDY MONITORING**

### **14.1 Changes to Protocol**

Any changes or additions to this protocol requiring a protocol amendment must be approved by the Sponsor and the Investigator before implementation. Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the clinical study protocol. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

Amendments affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB/EC and by the regulatory authority. Examples of amendments requiring such approval are as follows:

- An increase in study drug dosage or duration of exposure of subjects
- A significant change in the study design (eg, addition or deletion of a control group)
- An increase in the number of invasive procedures to which subjects are exposed
- Addition or deletion of a test procedure for safety monitoring

These requirements for approval should not prevent any immediate action from being taken by the Investigator or by the Sponsor in the interests of preserving the safety of all subjects included in the study. If the Investigator believes an immediate change to the protocol is necessary and he or she implements this change for safety reasons, the Medical Monitor and the IRB/EC should be notified accordingly.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/EC approval, but the IRB/EC must be informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/EC approval that can be treated as administrative amendments include:

- Changes in analytical methods
- Changes in the staff used to monitor studies (eg, Sponsor or contract research organization staff)

- Minor changes to the inclusion or exclusion criteria used to select study subjects
- Minor changes in the packaging or labeling of study drug

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a coordinating Investigator and the IRB/EC. This also applies to any communication between the Investigator (or coordinating Investigator, if applicable) and the authorities.

## **14.2 Case Report Forms**

Information collected for this study will be entered onto the CRFs at the site. Site personnel will be trained on CRF guidelines prior to initiation of the study. The completed CRF casebook must be reviewed and signed by the Investigator named in the clinical study protocol or by a designated subinvestigator.

## **14.3 Study Monitoring and Auditing**

All aspects of the study will be carefully monitored by the Sponsor or authorized representatives of the Sponsor at regular intervals, and with respect to current GCP and SOPs for compliance with applicable government regulations. These individuals will have access, both during the study and after study completion, to review and audit all records necessary to ensure integrity of the data and verify the entries on the CRF. They will periodically review progress of the study with the Investigator.

Training sessions, regular monitoring of Investigators by designated personnel, data verification, cross-checking, and data audits will be performed and instruction manuals provided to ensure quality of all study data.

The Sponsor's monitor or designee is responsible for inspecting the CRF as defined in the monitoring plan throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of data; and, adherence to local regulations on the conduct of clinical research. The Investigator will ensure that subjects' medical records and other study-related records needed to verify entries on the CRF are available at the Investigator site during monitoring visits. In addition to the monitoring visits, communications (letter, telephone, and fax), by the study monitor will also be used to determine whether the investigation is being conducted according to protocol design and regulatory requirements. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

In accordance with ICH guidelines and GCP, this study may be selected for audit by the Sponsor or designees. Inspection of the site facilities (eg, subject areas, drug storage areas, record storage areas) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH, GCP, and applicable regulatory requirements. The study monitor will perform study close-out procedures.



#### **14.4 Direct Access to Source Data/Documents**

All study data must be verifiable to the source data, which necessitates access to all source documents. Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondence, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Investigator and be made available for inspection by the Sponsor, or representatives of the Sponsor and/or regulatory authorities. The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system for all study-related (essential) documentation, suitable for inspection at any time by the Sponsor or Sponsor's representatives, or applicable regulatory authorities.

The subjects (or their legal representatives) must also allow access to the subjects' medical records, and subjects will be informed of this and will indicate their agreement when giving informed consent.

Data generated in this study must be available for inspection by any regulatory authorities, the Sponsor or designated representatives, and the IRB/EC as appropriate. At a subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Subject medical information obtained during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

#### **14.5 Data Collection**

To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notification will be sent to the site for completion and return to data management.

All clinical information required by the protocol must be entered on the CRF from source documentation by study site personnel as information is available. If edits to entries in the source document or CRF are required, the change must be recorded in a manner that does not obscure the original entry. Additionally, the initials of the person making the change and the date that the change is made must be recorded.

#### **14.6 Document Retention**

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the Investigator for a specified time. Study-related records should be retained by the Investigator until notified by the Sponsor in writing that retention is no longer necessary. Should the Investigator wish to assign the study

records to another party or move them to another location, written notification must be given to the Sponsor or designee.

The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include but are not limited to:

- Signed informed consent/assent documents for all subjects, as applicable
- Subject identification code list, Screening log (if applicable), and enrollment log
- Record of all communications between the Investigator and the IRB/EC
- Composition of the IRB/EC
- Record of all communications between the Investigator and Sponsor (or contract research organization)
- List of subinvestigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study and their signatures
- Copies of CRF and of documentation of corrections for all subjects
- Investigational product accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (subject medical records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the ICH E6 Guideline for GCP (Essential Documents for the Conduct of a Clinical Trial)

#### **14.7 Termination of Study**

The Sponsor may discontinue the study at any time. The Investigator should notify the IRB/EC in writing of the study's completion or early termination and send a copy of the notification to Sponsor.

#### **14.8 Investigator Agreement**

An Investigator agreement will be included with the protocol. The Investigator will be responsible for signing and dating the Investigator agreement to officially note that he or she has read, understands, and agrees to conduct this study in accordance with all stipulations of the protocol and in accordance with applicable law, regulations, and guidelines.

## 15.0 FINANCE AND INSURANCE

Before the start of the study, the Investigator will disclose to the Sponsor any proprietary or financial interests he or she might hold in the investigational products or the Sponsor company as outlined in the financial disclosure form provided by the Sponsor. The Investigator agrees to update this information in case of significant changes during the study or within 1 year of its completion. The Investigator also agrees that, where required by law or regulation, the Sponsor may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations. Similar information will be provided by each subinvestigator to whom the Investigator delegates significant study-related responsibilities.

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

## 16.0 PUBLICATION POLICY

The publication policy is outlined in the Clinical Trial Agreement. The data generated in this clinical trial are the exclusive property of the Sponsor and are confidential. Written approval from Sponsor is required prior to disclosing any information related to this clinical trial. Submission to the Sponsor for review and comment before submission to the publisher will be required. This requirement should not be construed as a means of restricting publication, but is intended solely to assure concurrence regarding data, evaluations, and conclusions and to provide an opportunity to share with the Investigator any new and/or unpublished information of which he/she may be unaware.

The Investigator agrees by his/her participation that the results of this study may be used for submission to national and/or international registration and supervising authorities. If required, these authorities will be provided with the names of Investigators, their addresses, qualifications, and extent of involvement. The Investigator is required to provide the Sponsor with all study data, complete reports, and access to all study records.

## 17.0 REFERENCES

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4. Tavaborole Topical Solution, 5% (formerly AN2690) Investigator's Brochure, version 13 edition. Palo Alto, CA: Anacor Pharmaceuticals; 2013.
5. Gupta A P, Chang P, Del Rosso JQ, et al. Onychomycosis in children: prevalence and management. *Pediatr Dermatol* 1998;15(6):464–71.
6. Huang P-H and Paller A. Itraconazole pulse therapy for dermatophyte onychomycosis in children. *Arch Pediatr Adolesc Med* 2000;154(6):614–8.
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8. KERYDIN (tavaborole) topical solution, 5% [Package Insert]. Palo Alto, CA: Anacor Pharmaceuticals, Inc.; March 2015.
9. Protocol No. P06118. Evaluation of the pharmacokinetics of SCH 900340 in subjects with onychomycosis of the toenails. Schering-Plough Research Institute. Study Report No. 002-CLN PK-003-01.

## APPENDIX A: SUMMARY OF CHANGES

### Summary of changes needed for clarification and consistency from Amendment 2 (dated 15 July 2015) to Amendment 3 (dated 28 March 2016)

The entire document was updated to clarify that subjects studied under ‘maximal use conditions’ are the PK subgroup and to reflect the changes detailed below:

#### Study Objective

Screening period of 4-10 weeks was clarified to read: Screening period: up to 10 weeks (maximum duration of 70 days)

#### Study Design

Local tolerability evaluation was modified to remove ‘of the TGT’ to clarify local tolerability evaluation is of all toes: Subjects will be evaluated at Screening, Baseline (Day 1), and at Weeks 2, 4, 8, 16, 24, 32, 40, 48, and 52. Each evaluation will include vital signs and a clinical assessment of adverse events (AEs) and a local tolerability evaluation.

#### Treatment Outcomes

The following missing definition was added:

- Almost complete cure: almost CN and negative mycology

#### Secondary Efficacy Endpoints

The following text was corrected to remove ‘and negative mycology’ from the definition:

- Treatment success (Clinical Efficacy rate) of the TGT at Weeks 24 and 52 defined as completely CN or almost CN

A secondary end point was added:

- Negative fungal culture of the TGT at Weeks 24 and 52

#### Treatment Administration

The following text was modified to clarify that study drug would be applied during the visit: Study drug will be applied on all affected toenails daily with a supplied dropper, preferably at bed time, except for the clinic visit days during which the study drug will be applied at the visit.

#### Table 3: Schedule of Events

‘Abbreviated’ was added to physical examination for clarification and consistency with Section 7.2.3.1 and Section 7.8.

**Visit 2: Baseline Visit (Day 1)**

‘Abbreviated’ was added and ‘complete’ was deleted in the following bullet in Section 7.2.3.1 to be consistent with the text in Section 7.8:

- Perform an **abbreviated** ~~complete~~ physical examination (prior to enrolling and drug dispense)

**KOH Mount and Central Fungal Culture**

Typo was corrected to remove the word ‘once’ to clarify resampling can occur more than once: A subject that fails mycology criteria may be resampled (see resample criteria in Section 5.0).

**Dosing Diary**

The following text was deleted: The dosing diary will only be utilized to determine the total number of applications. All other dosing data; application date and time relevant for PK analysis and date of first and last application to determine total number of days of dosing will be based on data reported in the site paper source and recorded on the CRF.

**Digital Photography**

The following text was added: Photographs will be utilized for purposes of publications.

**Clinical Safety Laboratory Parameters and Pregnancy Tests**

The following text was modified to clarify that Baseline is recorded as medical history: Abnormal clinical laboratory parameters that are considered clinically significant by the Investigator will be recorded on the AE CRF except Baseline visit. Clinically significant laboratory abnormalities noted from the Baseline will be recorded as medical history.

**Safety Reporting Procedures**

The email address was removed and fax/efax number was added.

**Laboratory Test Abnormalities**

The following text was modified to clarify that Baseline is recorded as medical history: All out-of-normal range laboratory values must be evaluated for clinical significance, and clinically significant abnormalities must be reported as AEs except from Baseline visit abnormalities which will be recorded as medical history.