NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	204427/S-006
Priority or Standard	Priority
Submit Date(s)	2-FEB-2018
Received Date(s)	2-FEB-2018
PDUFA Goal Date	2-AUG-2018
Division/Office	DDDP
Review Completion Date	
Established Name	tavaborole
(Proposed) Trade Name	KERYDIN
Pharmacologic Class	Antifungal
Code name	
Applicant	Pfizer Inc
Formulation(s)	Topical solution
Dosing Regimen	Applied once daily for 48 weeks
Applicant Proposed Indication(s)/Population(s)	Topical treatment of onychomycosis of the toenail due *to T. rubrum* or *T. mentagrophytes* in patients 6 years of age and above
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Topical treatment of onychomycosis of the toenail due *to T. rubrum* or *T. mentagrophytes* in patients 6 years of age and above

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PeRC	Pediatric Review Committee
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The New Drug Application (NDA) for KERYDIN (tavaborole) 5% topical solution was approved by the Agency in 7-July-2014 for the treatment of onychomycosis of the toenails due to *T. rubrum* or *T. mentagrophytes* in adults.

This submission is intended to satisfy a Pediatric Written Request as well as the post-marketing study requirement PMR 2154-1 listed in the NDA 204427 Approval Letter dated 6-JUNE-2014.

KERYDIN (tavaborole) 5% topical solution contains 5% tavaborole (w/w) in a clear, colorless alcohol-based solution for topical use. Tavaborole shows broad spectrum activity against the major dermatophytes that cause onychomycosis, *Trichophyton rubrum* and *Trichophyton mentagrophytes*, as well as against yeasts and molds. The drug's mechanism of action is the inhibition of an aminoacyl-transfer ribo-nucleic acid (tRNA) synthetase.

KERYDIN 5% topical solution applied daily for 48 weeks was studied in two Phase 3 registrational studies. Data from the studies showed a statistically significant therapeutic effect compared with vehicle, with minimal safety concerns.

In the approval letter, pediatric study requirements for ages 0 to 11 years and 11 months were waived because necessary studies are impossible or highly impracticable due to low prevalence in the younger population. Studies for pediatric age group of 12 to 17 years and 11 months were deferred because the product is ready for approval for use in adults and pediatric studies has not been completed. Pediatric study is described as:

PMR 2154-1 Pharmacokinetic/safety study of tavaborole topical solution, 5% in 40 pediatric subjects age 12 to 17 years and 11 months with onychomycosis of the toenails.

Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions.

In addition, the Agency issued a Written Request (WR) for the potential use of KERYDIN in the treatment of pediatric population 6 years to 17 years 11 months old with onychomycosis of the toenails. The PWR articulated the following rationale:

> Onychomycosis of the toenails is predominantly a disease of adults, however, there are several
> publications that describe various types of onychomycosis and treatment

options in children. In
order to determine the age of children appropriate for an onychomycosis study, the Division has considered only data that are reflective of the recommended indication-onychomycosis of the toenail due to dermatophytes (T. rubrum or T. mentagrophytes) and determined that culture-positive onychomycosis is extremely low in patients less than 12 years of age, which was the reason for waiving PREA required studies in this subpopulation.

However, due to the lack of the specific safety concerns with KERYDIN, and presence of sporadic onychomycosis cases in the younger pediatric age group, the Division requests opening enrollment to pediatric patients down to 6 years of age for the purpose of issuing this WR. There were no literature cases describing onychomycosis in neonates, therefore the study in this age group is not required.

Efficacy in the pediatric population can be extrapolated from adults because the course of the disease, the type of the microorganisms that cause onychomycosis and the effect of the drug are anticipated to be the same in adults and children.

To obtain the needed pediatric information on KERYDIN, the Agency issued a Written Request for a clinical study:

Open-label pharmacokinetic/safety study of tavaborole topical solution, 5% in pediatric subjects age 6 to 17 years and 11 months with onychomycosis of the toenails. The PK assessments will be performed on a subset of at least 16 subjects under maximal use conditions. The protocol for this study must be agreed upon with the FDA prior to initiation.

This submission (Supplement-6), includes the completed pediatric study report TAV-ONYC-401 entitled “An Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of KERYDIN® (tavaborole) topical solution, 5% in the Treatment of Onychomycosis of the Toenail in Pediatric Subjects Ages 6 to 16 Years and 11 Months,” intended to satisfy the WR as well as the PMR 2154-1 listed in the NDA 204427 Approval Letter dated 7-JUL-2015. In addition, the applicant submitted a request to add (b) (4) to the USPI.

1.2. Conclusions on the Substantial Evidence of Effectiveness

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Study TAV-ONYC-401 primary objective was to assess the safety and tolerability of KERYDIN (tavaborole) 5% topical solution applied once daily (QD) for 48 weeks in pediatric subjects aged 6 to 16 years and 11 months with onychomycosis of the toenails. The secondary objective of the study was to assess pharmacokinetics in at 16 evaluable subjects aged 12 to 16 years 11 months following topical administration under maximal use conditions. Anacor Pharmaceuticals submitted the proposed pediatric protocol to the pediatric Written Request on 18-July-2015. This protocol was reviewed by the Dr. Doanh Tran from Clinical Pharmacology. The Agency provided comments to the sponsor for the proposed disease severity inclusion criteria in subjects in the PK subgroup:

"We do not agree with your proposed disease severity inclusion criteria for subjects in the PK subgroup. For the PK subgroup, we recommend that you enroll subjects with ≥50% involvement of both great toenails and 4 additional affected toenails. You have not provided sufficient evidence to support that such inclusion criteria are not feasible. You should make an effort to recruit subjects at the upper end of disease severity as recommended to meet maximal use conditions."

Given this advice, the sponsor revised the protocol and submitted the report for the current study with the maximal enrollment criteria of ≥ 4 toenails, including 1 target great toenail.

Fifty-five (55) subjects were enrolled, of which 47 subjects completed the study. Eight (8) subjects discontinued the study: 4 due to being lost to follow-up and 4 due to withdrawal by the subject. Overall, tavaborole 5% topical solution showed efficacy like that seen in previous adult studies. Following daily topical applications of tavaborole 5% topical solution to pediatric subjects under maximal use condition, for 29 days, tavaborole was absorbed into the systemic circulation. Steady state of tavaborole was achieved within the study period. Tavaborole 5% topical solution was safe and well tolerated. No deaths, permanent discontinuations, temporary discontinuations, or dose reductions due to AEs were reported in this study. Complete cure of onychomycosis was reported in 8.5% of pediatric subjects, and complete or almost complete cure was reported for 14.9% of pediatric subjects at Week 52; results that are like those seen in previous adult studies.

In study TAV-ONCY-401, twenty-two subjects had PK results obtained under maximal use conditions, exceeding the minimum number of 16

subjects requested in the PMR and in the written request., and this reviewer recommends APPROVAL of this supplement as conditions of the Written Request have been met. The Maximal Use PK study in adults enrolled a similar severity of onychomycosis. This product had comparable safety for use in the pediatric population as studied.

The review team recommends approval of this supplement, and concludes that the applicant satisfied the elements of the Pediatric Written Request. Labeling will be updated to reflect the safety outcomes of this pediatric study.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Onychomycosis is a chronic fungal infection of toenails and/or fingernails. It is estimated that 15-20% of persons in United States between 40 and 60 years old have onychomycosis. Older age, tinea pedis, and immunodeficiency are some of the risk factors for acquiring onychomycosis. • The most common site of infection is the toenail and the most common type of onychomycosis is distal subungual. Dermatophytes causing distal subungual onychomycosis are *Trichophyton rubrum*, and *Trichophyton mentagrophytes*. Fingernail onychomycosis is more likely to be caused by *Candida albicans*. • The clinical manifestations of onychomycosis include separation of the nail plate from the nail bed (onycholysis), subungual hyperkeratosis, and changes in the nail plate that make it thicker, brittle, and discolored. Symptoms include toenail discomfort when walking including pain and social embarrassment.	Treatment may be indicated from both medical and psychosocial perspectives. Without treatment, the disease can cause damage to the nail unit, and can spread to infect other nails, the skin, or potentially predispose to secondary bacterial infections (in immunocompromised populations).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Current therapeutic approaches include mechanical or chemical nail avulsion, topical therapy, oral therapy, or a combination of these treatment modalities. Treatment choice depends on the clinical pattern of onychomycosis, the thickness of the involved nails, and the number of affected nails as well as patient motivation and preference	Systemic agents include griseofulvin, terbinafine, and itraconazole. Topical therapies in addition to tavaborole include ciclopirox and efinaconazole.
Benefit	• The efficacy and safety in adults was demonstrated in the original NDA application, with approval in 2014. Topical therapy may be a reasonable option for patients with onychomycosis who are unable to tolerate oral antifungal agents or do not wish to undergo more comprehensive podiatric topical treatment required for Penlac® use. The addition of pediatric information would be of benefit for the limited pediatric population with onychomycosis.	This open label study provided some evaluation of treatment effects for the pediatric population who might desire treatment for onychomycosis.
Risk	• No new safety issues were identified that were new or unique to the pediatric population as studied in this trial.	Pediatric PK information will be a useful addition to labeling. The adverse events associated with the drug product, which are primarily local reactions, can be adequately informed by labeling. The label also provides adequate information for instructions for use. A multidisciplinary 915 safety review was conducted in August, 2016 with no recommendations for new safety labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• No REMS or additional safety precautions beyond labeling is recommended. Labeling is sufficient to convey risks.	Approval of this supplement is recommended. Updated labeling to reflect this study is being conveyed to the sponsor.

X David L. Kettl -S

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David Kettl, MD, FAAP
Cross-Disciplinary Team Leader

2 Therapeutic Context

Analysis of Condition

Onychomycosis is a chronic fungal infection of toenails and/or fingernails. It is estimated that 15-20% of persons in United States between 40 and 60 years old have onychomycosis. It is more prevalent in adults than in children (prevalence rate 0.2% to 2.6%). The most common site of infection is the toenail. The most common type of toenail onychomycosis is distal subungual onychomycosis and the most common dermatophytes causing distal subungual onychomycosis are Trichophyton rubrum and Trichophyton mentagrophytes. Fingernail onychomycosis is more likely to be caused by yeasts, most commonly Candida albicans.

The clinical manifestations of onychomycosis include separation of the nail plate from the nail bed (onycholysis), subungual hyperkeratosis, and changes in the nail plate that make it thicker, brittle, and discolored. Symptoms include toenail discomfort when walking, pain and social embarrassment. Without treatment, the disease can cause progressive damage to the nail unit, and can spread to infect other nails, the skin, or potentially predispose to secondary bacterial infections (in immunocompromised populations). The criteria for diagnosis of onychomycosis include clinical evaluation, potassium hydroxide (KOH) microscopic evaluation, and fungal culture.

2.2. Analysis of Current Treatment Options

Therapeutic options for the treatment of onychomycosis include no therapy, palliative care, mechanical or chemical debridement, topical and systemic antifungal agents, or a combination of two or more of these modalities. Factors that influence the choice of therapy include the presentation and severity of the disease, the current medications the patient is taking, previous therapies for onychomycosis and their response, physician and patient preference, and the cost of therapy.

Penlac® (ciclopirox) Nail Lacquer topical solution, 8% is the first approved topical product (1999) in the United States for the treatment of onychomycosis. Ciclopirox lacquer, approved in 1999, has demonstrated modest efficacy in treating mild to moderate onychomycosis not involving the lunula with reported complete cure rates of 8.5%; frequent nail debridement is required when using this product. Another topical product currently available is Jublia® (efinaconazole) 10% topical solution.

Oral treatment has been generally used for onychomycosis, but use may be limited in some patients by drug-drug interactions, especially in the elderly where there is frequent use of

concomitant medications, other safety concerns (e.g., liver toxicity), and by the potential need for laboratory monitoring. Itraconazole (Sporanox®) and terbinafine (Lamisil®) and Griseofulvin have been approved in the US, with respective cure rates of 14% and 38%. Hepatotoxicity is associated with systemic exposure in most oral antifungal medications.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Distribution of KERYDIN in the US is described in this table.

Table 1: Domestic Distribution of KERYDIN

Item	NDC	Description (Brand Name, Dosage Form, Strength, Presentation)	Quantity (Unit Packages)
NA	10377-905-10	KERYDIN Topical Solution, 5%, 10 mL Bottle with Applicator	(b) (4)
NA	10377-905-44	KERYDIN Topical Solution, 5%, 4 mL Bottle with Applicator	
NA	55724-111-22	KERYDIN Topical Solution, 5%, 4 mL Bottle with Applicator, Physician Sample	

Source: Annual Reporting 07-JUL-2016 to 06-JUL-2017

3.2. Summary of Presubmission/Submission Regulatory Activity

KERYDIN (tavaborole) topical solution, 5% was approved by the FDA on 6-June-2014. The Agency issued a Written Request for pediatric study data on 17-APR-2015. The applicant provided a pediatric protocol entitled "An Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of KERYDIN, in the treatment of Onychomycosis of the Toenail in Pediatric Subjects Ages 6 to 16 years and 11 Months." This study is intended to satisfy the Written Request as well as the post-marketing study requirement PMR 2154-1 listed in the NDA 204427 Approval Letter dated 6-JUNE-2014. The study protocol was reviewed by the Agency and recommendations were conveyed. The current supplement provides the completed Clinical Study Report for TAV-ONYC-401.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

N/A. Clinical study site inspections were not requested for this single, open-label study conducted with an approved drug product.

4.2. Product Quality

This study used the approved Kerydin drug product.

No changes were proposed to the CMC-related sections of the labeling (Sections 3, 11, or 16) or to the carton and container labeling. An information request, dated 05-MAR-2018, requested the submission of an Environmental Assessment (EA) or Request for Categorical Exclusion from the requirement of an EA. The response from the applicant was adequate.

There are no outstanding CMC issues related to product quality.

Novel excipients: No
Any impurity of concern: No

4.3. Clinical Microbiology

No additional clinical microbiology claims are being asserted in this supplement.

4.4. Devices and Companion Diagnostic Issues

N/A

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies were submitted. The nonclinical review consisted of a label review only. A few minor changes to the PLLR converted label are suggested below.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology
N/A

Secondary Pharmacology
N/A

Safety Pharmacology
N/A

5.4. ADME/PK

N/A

5.5. Toxicology

5.5.1. General Toxicology

N/A

5.5.2. Genetic Toxicology

N/A

5.5.3. Carcinogenicity

N/A

5.5.4. Reproductive and Developmental Toxicology

N/A

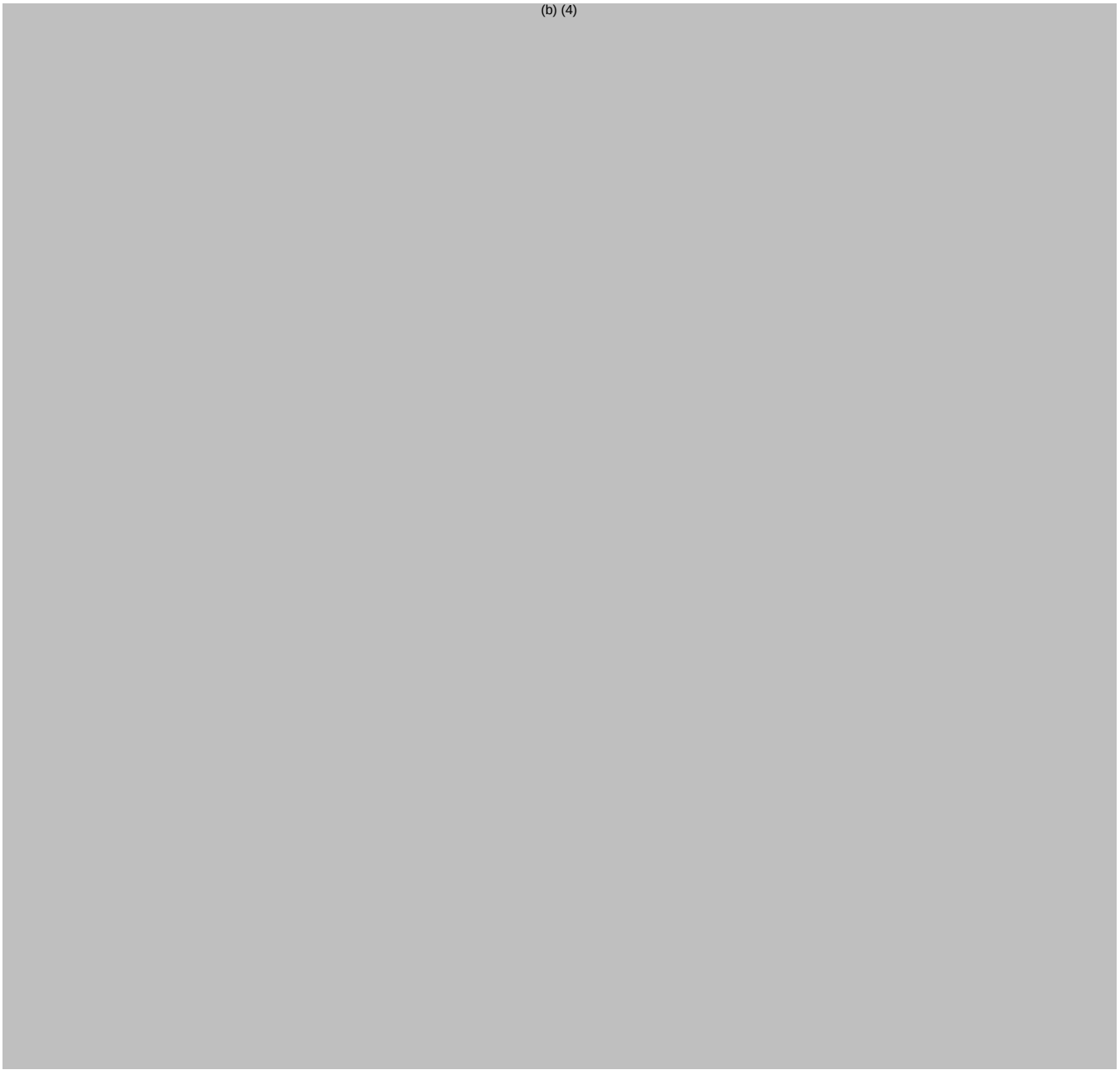
5.5.5. **Other Toxicology Studies**

N/A

5.6. **Nonclinical Labeling**

Strikethrough Version: It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the KERYDIN label reproduced below.

(b) (4)



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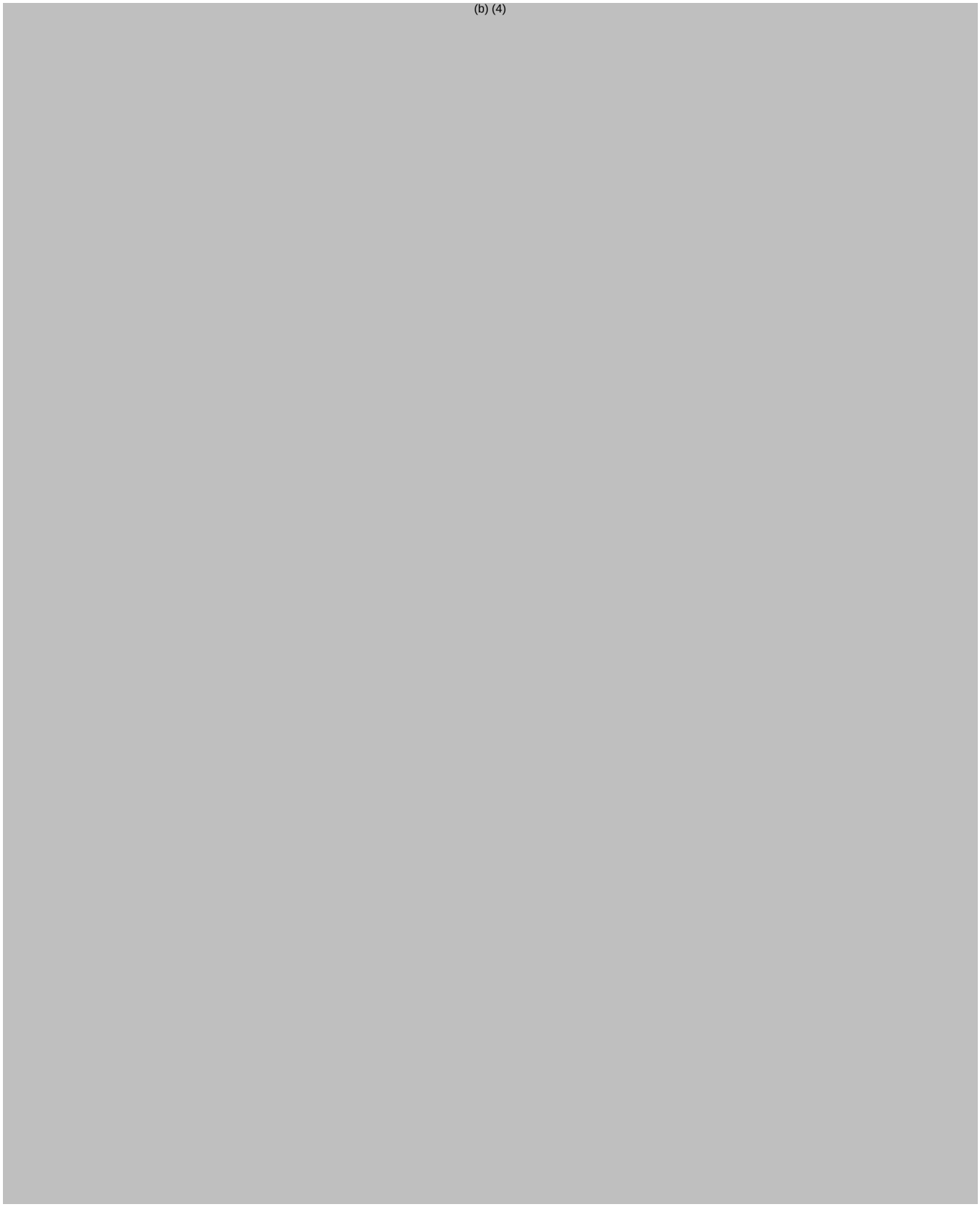

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X Carmen D. Booker -S

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X Barbara A. Hill -S

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Primary Reviewer

Team Leader

APPEARS THIS WAY ON ORIGINAL

6 Clinical Pharmacology

6.1. Executive Summary

KERYDIN® (tavaborole) topical solution, 5% was approved in 2014 for the topical treatment of onychomycosis of the toenails in adults due to *Trichophyton rubrum* or *Trichophyton mentagrophytes*. The approved dosing regimen in adults is once daily application to affected toenails for 48 weeks. The NDA was approved with a post marketing requirement (PMR) to conduct pediatric study as shown below.

PMR 2154-1 Pharmacokinetic/safety study of tavaborole topical solution, 5% in 40 pediatric subjects age 12 to 17 years and 11 months with onychomycosis of the toenails. Pharmacokinetic assessments will be done in at least 16 evaluable subjects under maximal use conditions.

A written request for the potential use of KERYDIN in the treatment of pediatric population 6 years to 17 years 11 months old with onychomycosis of the toenails was issued on 4/17/ 2015 and an amendment of the written request was issued on 7/10/ 2015. Compared to the original written request, the upper age limit of pediatric subjects was changed from 17 years and 11 months to 16 years and 11 months in the amendment.

The applicant conducted a clinical trial (Study TAV-ONYC-401) in pediatric subjects ages 6 to 16 years and 11 months with onychomycosis of the toenails to fulfill the PMR and to satisfy the written request. In this application, the applicant submitted the results of the trial and requested approval for use in patients 6 years of age and older.

In the PMR and the written request, the pharmacokinetics (PK) assessment under maximal use conditions was required in subjects 12 years of age and older. PK assessment of subjects between 6 to 12 years of age was not mandated due to fewer subjects with onychomycosis in this age range. In the completed study with results submitted in this application, twenty-two subjects had PK results obtained under maximal use conditions, exceeding the minimum number of 16 subjects requested in the PMR and in the written request. This application is acceptable from a Clinical Pharmacology perspective.

6.1.1. Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds NDA 204427/S-006 acceptable pending agreement on recommended labeling changes. The efficacy supplement also satisfies PMR 2154-1 as outlined in the approval letter of NDA 204427 dated 7/7/2014 and the revised written request issued on 7/10/2015.

6.1.2. Phase IV Commitments

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Study TAV-ONYC-401 was an open-label study that evaluated the safety, tolerability, and PK of KERYDIN® (tavaborole) topical solution, 5% in the treatment of onychomycosis of the toenail in 55 pediatric subjects 6 to 16 years and 11 months old who had a target great toenail (TGT) with distal subungual onychomycosis affecting at least 20% of the TGT and with a positive potassium hydroxide and positive fungal culture for *Trichophyton rubrum* or *Trichophyton mentagrophytes* from the TGT. The subjects received once daily treatment with the drug product for 48 weeks.

The PK of the drug product was evaluated in 40 subjects aged 11 years to < 17 years. In this subgroup of subjects, the study drug was applied onto all 10 toenails, including up to 2 mm of the surrounding skin once daily during Days 1-29. PK samples were collected at pre-dose on Day 15 and at pre-dose, and at 4, 6, 8, and 24 hours post-dose on Day 29. After Day 29, the subjects continued to receive treatment in the study; however, the study drug was applied only to the affected toenails.

Thirty-seven subjects had evaluable PK data. Thirty-seven subjects with moderate (N=18) or severe (N=19) disease onychomycosis had evaluable PK data. The mean (SD) amount of drug used per dosing day was 0.36 (0.25) grams during this period. Among the 37 subjects, 22 subjects (7 females and 15 males) had at least 3 other toenails with disease involvement in addition to one TGT. Among these 22 subjects, 11 subjects had moderate onychomycosis and the other 11 subjects had severe onychomycosis at baseline; the median (range) involvement of the TGT is 55% (21-85%); the mean (SD) age of these subjects was 14.5 (1.4) years.

Tavaborole concentration was measurable (≥ 0.5 ng/mL) in 21 out of these 22 subjects with a range of 0.983-16.4 ng/mL. A summary of the PK results on Day 29 is shown in Table 2. Steady-state was reached within the PK evaluation period. The mean (SD) values of C_{max} and AUC_{0-24} of tavaborole in the subjects who had at least 3 other toenails with disease involvement in addition to the TGT with at least 20% involvement were 5.9 (4.9) ng/mL and 76.0 (62.5) ng*hr/mL, respectively. These values are similar to those observed in the previous maximal use PK trial conducted in adult subjects with disease involvement in at least 4 toenails, including at least one great toenail with 50-75% affected by the disease.

Table 2: Plasma PK Parameters of Tavaborole on Day 29 Following Once Daily Application of KERYDIN® (tavaborole) Solution, 5% in Pediatric Subjects in Study TAV-ONYC-401.

Study	Current Pediatric Trial TAV-ONYC-401		Previous Adult Trial P06118
Disease Involvement	≥20% target great toenail (all evaluable PK subjects)	≥4 toenails, including one target great toenail with at least 20% involvement	≥4 toenails, including ≥1 great toenail with 50-75% involvement
Number of Subjects	37	22	24
Age (years)	14.2 (1.6)	14.5 (1.4)	51.0 (12.3)
T_{max} (hr)	6 (0-23.9) N=36	5.9 (0-23.9) N=21	8.03 (0.467-24.0)
C_{max} (ng/mL)	5.4 (4.4)	5.9 (4.9)	5.17 (3.47)
AUC_{0-24} (ng*hr/mL)	71 (56)	76.0 (62.5)	75.8 (44.5)*

Source: reviewer's table based on data provided by the applicant.
*AUC_{tau} is presented because PK samples were collected 0-96 hours post dose.

Reviewer's comments: *The applicant obtained evaluable PK information from 37 subjects. Based on the number of toenails affected by disease (i.e. ≥4 toenails, including ≥1 great toenail) that was similar to that in the previous maximal use PK trial conducted in adults, 22 subjects were considered to have evaluable PK results assessed under maximal use conditions, although the minimum involvement of TGT of 20% in pediatric subjects was less than the minimum involvement of 50% in adult subjects. This degree of disease severity in pediatric subjects was discussed within the review team and it was concluded that this would represent maximal use conditions in pediatric subjects aged 12 years and older.*

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The applicant proposed the same dosing regimen that was approved in adults in pediatric population. The proposed regimen is supported by the safety and efficacy data of the completed study (TAV-ONYC-401). Refer to Clinical and Statistics reviews for safety and efficacy findings.

Therapeutic Individualization

No studies were conducted for assessment of the effects of various intrinsic or extrinsic factors on the safety or efficacy of the proposed topical drug in this efficacy supplement application.

Outstanding Issues

None.

Labeling Recommendations

Revisions to the applicant's proposed wording for the clinical pharmacology and related sections of the labeling are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted from the label proposed by the applicant.

(b) (4)

[redacted]

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

See Section 6.2.1.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Not applicable. The pediatric study TAV-ONYC-401 for this topical product included PK information obtained under maximal use conditions which provided information to support the systemic safety of the topical product and not efficacy.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. See Section 7 for details of the evaluation of the effectiveness and safety.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Not applicable.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Not applicable.

X Yanhui Lu -S X — Digitally signed by Yanhui Lu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yanhui Lu -S, 0.9.2342.19200300.100.1.1=2001501324 Date: 2018.07.30 09.45.20 -04'00'

Chinmay Shukla -S — Digitally signed by Chinmay Shukla -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Chinmay Shukla -S, 0.9.2342.19200300.100.1.1=2000377244 Date: 2018.07.24 11:36:00 -04'00'

Primary Reviewer — Team Leader

7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

A single open-label clinical study is submitted in this supplement to satisfy the Written Request and PMR 2154-1 issued by the Agency for KERYDIN (tavaborole) topical solution, 5%.

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Table 3: List of Clinical Studies in this Submission

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
TAV-ONYC-401	An Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Kerydin® (Tavaborole) Topical Solution, 5% in the Treatment of Onychomycosis of the Toenail in Pediatric Subjects 6 to 16 years and 11 months	Applied once daily for 48 weeks In the MAXUSE PK subgroup, treatment will be to all 10 toenails	Treatment outcomes were defined as follows: Negative Mycology: Negative KOH wet mount and negative fungal culture; Complete Cure: Completely CN and negative mycology;	Completion of the study at 52 weeks	55 enrolled 47 completed	Male or female subjects ages ≥ 6 years and ≤ 16 years and 11 months with clinical diagnosis of DSO affecting either great toenail with positive KOH and T. rubrum or T. mentagrophytes culture from the TGT confirmed by central mycology laboratory and at least 20% of the TGT

Source: Clinical Study Report (TAV-ONYC-401)

7.1.2. Review Strategy

Data sources provided for this submission included a single Open-Label study, TAV-ONYC-401. Data submitted is provided in electronic format: \\CDSESUB1\evsprod\NDA204427\204427.enx

Data and Analysis Quality

There were no issues with the data quality or analysis.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. TAV-ONYC-401

Trial Design and Endpoints

TAV-ONYC-401 is an open-label study to evaluate the safety, tolerability, and PK of tavaborole 5% topical solution in treating distal subungual onychomycosis (DSO) of the toenail in pediatric subjects aged 6 to 16 years and 11 months. An eligible subject had a target great toenail (TGT) with at least 20% involvement with a positive potassium hydroxide (KOH) wet mount and positive fungal culture for T. rubrum or T. mentagrophytes from a sample obtained during the Screening period for 1 of the great toenails. KOH and fungal culture were sent to a central mycology laboratory for eligibility determination. Both great toenails were sampled at Screening.

The dosing regimen for the PK analysis was based on a Phase 1 maximal use absorption study in adults. In this Phase 1 study, elevated plasma concentrations of tavaborole in adult subjects with onychomycosis were achieved through QD 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% to 75% nail involvement, the sponsor argued that this degree of disease severity in the pediatric population is rare, and was therefore not in the enrollment criteria. The maximal dosing regimen of QD application to all 10 toenails and up to 2 mm of surrounding skin was expected to produce elevated plasma concentrations in this pediatric population.

Statistical Analysis Plan

This is an Open-Label study; therefore, formal statistical testing for efficacy was performed. The efficacy assessments are intended to assess compliance with treatment for the purposes of the safety assessment.

For the safety population, all subjects who received at least one confirmed dose of study drug and have at least one post-baseline safety assessment will be analyzed.

For the PK population, all subjects from the maximal use subgroup with available PK data at Day 15 and at least one collection on Day 29 will be analyzed.

7.2.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country of conduct, including the archiving of essential documents.

Patient Disposition

A total of 55 subjects were enrolled, of which 47 completed the study. Eight (8) subjects discontinued the study: 4 due to being lost to follow-up and 4 due to withdrawal by the subject. Of the 55 subjects who were enrolled, 54 subjects were included in the safety evaluation. The 1 subject who was excluded from the safety evaluation did not have a postbaseline safety assessment.

Table 4: Subject Disposition

Parameters	Tavaborole (N=55)
Completed the study	
Yes	47 (85.5%)
No	8 (14.5%)
Reason for discontinuation	
Adverse event	0 (0.0%)
Lost to follow-up	4 (7.3%)
Pregnancy	0 (0.0%)
Protocol deviation	0 (0.0%)
Withdrawal by subject	4 (7.3%)
Other	0 (0.0%)

Table of Demographic Characteristics

A total of 37 male subjects and 17 female subjects were treated in the safety population.

Table 5: Summary of Subjects Demographics and Baseline Characteristics (Safety Population)

Demographic Parameters	KERYDIN (N= 54)
Sex	
Male	37 (68.5%)
Female	17 (31.5%)
Age	
Mean years (SD)	13.2 (2.69)
Median (years)	14
Min, max (years)	6.0 to 16.0
Age Group	
6 to < 12 years	13 (24.0%)
12 years to 16 years, 11 months	41 (75.9%)
Race	
White	46 (85.2%)
Black or African American	8 (14.8%)
Asian	0 (0.0%)
American Indian or Alaska Native	0 (0.0%)
Clinical assessment of disease severity of target great toenail	
Complete clear nail	0 (0.0%)
Almost clear nail	0 (0.0%)
Mild onychomycosis	0 (0.0%)
Moderate onychomycosis	30 (55.6%)
Severe onychomycosis	24 (44.4%)
Percent involvement of target great toenail	
Mean (SD)	52.6 (18.37)
Median	50
Min to Max	21.0 to 90.0
Number of other affected toenails	
Mean (SD)	3.6 (2.97)
Median	3.0
Min to Max	0.0 to 8.0

Source: Applicant submission TAV-ONYC-401

Efficacy Results – Primary Endpoint

For this supplement, efficacy is used to evaluate the treatment compliance of the subjects. No formal statistical testing was completed for the efficacy. However, the primary efficacy will be summarized for the safety population.

Table 6: Summary of Clinical and Mycological Characteristics (Safety Population)

Parameters	KERYDIN (N=54)		
Clinical assessment of disease severity on TGT	Baseline	Week 24	Week 52
N	54	50	47
Completely Clear Nail	0	1 (2.0%)	6 (12.8%)
Almost Clear Nail	0	4 (8.0%)	6 (12.8%)
Mild onychomycosis	0	13 (26.0%)	12 (25.5%)
Moderate onychomycosis	30 (55.6%)	27 (54.0%)	16 (34.0%)
Severe onychomycosis	24 (44.4%)	5 (10.0%)	7 (14.9%)
Fungal Culture results (*T. rubrum* and *T. mentagrophytes*)			
N	54	50	47
Positive	54 (100%)	2 (4%)	6 (12.8%)
Negative	0	48 (96%)	41 (87.2%)
KOH result			
N	54	50	47
Positive	54 (100%)	31 (62%)	28 (59.6%)
Negative	0	19 (38%)	19 (40.4%)

Source: Applicant's submission (TAV-ONYC-401) Study Report

Of the 54 subjects, at Week 24, one (1) subject had a completely clear nail (CN), 4 subjects had almost CN and 5 subjects had severe onychomycosis, while at Week 52, 6 subjects each had a completely clear and almost CN, and 7 subjects had severe onychomycosis. The fungal culture result was found to be negative for 48 subjects at Week 24 and 41 subjects at Week 52.

Table 7: Summary of the Primary Endpoint: Complete Cure at Week 52 (Safety Population)

	KERYDIN (N=54)
Complete Cure [a] at Week 52	
N	47
YES	4 (8.5%)
NO	43 (91.5%)

Source: Applicant's submission (TAV-ONYC-401) Study Report
a Complete Cure defined as completely clear nail, negative fungal culture and negative KOH.

In comparison to the adult studies for registration, the complete cure rate is similar (6.5% for study 1 and 9.1% for study 2).

Reviewer's comment: *The efficacy results of this open-label study are qualitatively comparable to the adult registration studies for the original NDA. 0*

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Primary Endpoints

N/A

7.3.2. Integrated Assessment of Effectiveness

N/A. The study was not designed nor conducted to demonstrate statistically significant efficacy results for the pediatric population, as efficacy is extrapolated from that demonstrated in adults

7.4. Review of Safety

7.4.1. Safety Review Approach

The safety review is based on the 54 subjects of the safety population for study TAV-ONYC-401.

7.4.2. Review of the Safety Database

Overall Exposure

The safety population was 54 subjects and the extent of the exposure is summarized in the table below.

Table 8: Overall Exposure (Safety Population)

Total number of dosing days	**KERYDIN (N=54)**
Mean (SD)	316.5 (63.19)
Median	336.0
Min to Max	78 to 358
Total number of applications	
Mean (SD)	269.1 (63.98)
Median	298
Min to Max	61 to 340
Total amount of study drug applied (grams)	
N	31
Mean (SD)	69.2 (39.39)
Median	57.1
Min to Max	15 to 169

Source: Applicant's submission (TAV-ONYC-401) Study Report

For the maximal use exposure data, please refer to the Clinical Pharmacology section of this review.

Relevant characteristics of the safety population:

The demographic of the safety population is described in Table 5.

Adequacy of the safety database:

The safety database of 54 subjects is acceptable for this open-label study.

7.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

None.

7.4.4. Safety Results

Deaths

There was no death among subjects who participated in TAV-ONYC-401.

Serious Adverse Events

One serious adverse event (SAE) was reported. This subject experienced an acute appendicitis and was determined as not related to the investigational drug by both the applicant and this reviewer.

Dropouts and/or Discontinuations Due to Adverse Effects

There were no discontinuations due to an adverse event.

Significant Adverse Events

Thirty (30) of the 54 subjects (55.6%) had at least 1 TEAE reported following treatment with KERYDIN; a total of 65 TEAEs were reported. One (1) 11-year-old female subject ((b) (6)) experienced 2 TEAEs which were considered possibly (paronychia) and probably (application site erythema) treatment-related by the Investigator; the paronychia was reported to have started on Study Day 228 and resolved without treatment 12 days later, while the application site erythema preceded the paronychia with onset date 9 days earlier and resolution after 64 days of onset with the use of Vaseline.

Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported TEAEs by preferred term in the 54-safety population were

nasopharyngitis (13%), contusion (9.3%), sinusitis (5.6%), vomiting (5.6%), influenza (3.7%), concussion (3.7), oropharyngeal pain (3.7), and headache (3.7).

Laboratory Findings

There were no clinical significant trends in the laboratory testing. There were no clinically meaningful changes in the laboratory values over time. One subject, a 16-year-old female subject (b) (6)) had a low hemoglobin and hematocrit at Week 52, which was clinically significant and was reported as an AE.

Reviewer's comment: *Given the age of the female subject ((b) (6) , the reduction in hemoglobin is unlikely related to the investigational product.*

Vital Signs

No changes in vital signs were clinically significant over time.

7.4.5. Analysis of Submission-Specific Safety Issues

The investigators evaluated local tolerability reactions at each visit, burning/stinging, induration/edema, oozing and crusting, pruritus, erythema, and scaling.

Reviewer's comment: *Few local safety issues were reported. Most were mild and moderate and resolved without treatment. On comparison to the adult studies, these local safety evaluations were similar.*

7.4.6. Safety Analyses by Demographic Subgroups

N/A

7.4.7. Specific Safety Studies/Clinical Trials

None

7.4.8. Additional Safety Explorations

No other safety explorations were conducted in this open-label study.

7.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No post-marketing safety issues have been identified since approval of the original NDA. A multidisciplinary 915 safety review was conducted in August, 2016 with no recommendations

for new safety labeling. Pediatric safety is anticipated to be similar to the adult population experience.

The applicant provided cases of adverse events reported for KERYDIN in the post marketing of this drug product for application site reactions and hypersensitivity. A review of all KERYDIN cases that reported an application site reaction in the preferred term (PT) and hypersensitivity SMQ search revealed a higher frequency of reporting for these events. (b) (4) .

Reviewer's comment: *A 915 review conducted less than two years ago by the Agency did not reveal cases of anaphylaxis or hypersensitivity events. The applicant presented an algorithm for evaluation of these events observed events. There are no clear evidence of serious hypersensitivity (anaphylaxis) by review of the cases.* (b) (4) .

Expectations on Safety in the Postmarket Setting

No safety issues are expected in the post-market setting.

7.4.10. Integrated Assessment of Safety

KERYDIN (tavaborole) topical solution, 5% for the treatment of onychomycosis appear to be well tolerated with little safety issues in pediatric subjects ages 6 years to 16 years and 11 months when treated for 52 weeks. Like the adult registration studies, this open-label study (TAV-ONYC-401) has demonstrated adequate safety and pharmacokinetics of KERYDIN for the pediatric population.

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

There are no statistical issues that would prevent approval of this supplement.

7.6. Conclusions and Recommendations

KERYDIN (tavaborole) topical solution, 5% was well tolerated at the application site and systemically. The majority AEs were assessed as unrelated to KERDIN, Events were generally self-limiting or resolved with standard medical intervention. No deaths, permanent discontinuations, temporary discontinuations, or dose reductions due to AEs were reported in

this study. No trends for laboratory abnormalities were noted. The safety of KERYDIN in this pediatric population is similar to that reported in the two Phase 3 registration studies in 795 adult subjects treated with KERYDIN for onychomycosis.

The pharmacokinetics of KERYDIN for onychomycosis was also investigated in 22 pediatric subjects 12 to 16 years of age with distal subungual onychomycosis involving at least 4 toenails (including 1 great toenail with at least 20% involvement) following once daily topical application of 5% solution of tavaborole to all ten toenails and 2 mm of skin surrounding each toenail for 29 days. The results of the PK are acceptable to determine efficacy extrapolation to pediatric subjects.

In conclusion, the applicant has provided an acceptable clinical and pharmacokinetic study in pediatric subjects 6 years to 6 years and 11 months old to satisfy the Written Request and the PMR/PMC from the Agency. Pediatric exclusivity should be granted and the applicant can be released from their PMR/PMC requirement.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X Gary Chiang -S Digitally signed by Gary Chiang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Gary Chiang -S, 0.9.2342.19200300.100.1.1=2000332370 Date: 2018.07.25 08:40:09 -04'00'	X David L. Kettl -S Digitally signed by David L. Kettl -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David L. Kettl -S, 0.9.2342.19200300.100.1.1=1300383857 Date: 2018.07.26 09:29:45 -04'00'
Primary Clinical Reviewer	Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this product.

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9 Pediatrics

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Pediatric Exclusivity Determination Template
NDA 204427 KERYDIN (tavaborole) Solution, 5%

Written Request Items	9.1. **Information Submitted/Sponsor's Response**
Types of studies/Study Design: *Open-label pharmacokinetic/safety study of tavaborole topical solution, 5% in pediatric subjects age 6 to 17 years and 11 months with onychomycosis of the toenails. The PK assessments will be performed on a subset of at least 16 subjects under maximal use conditions. The protocol for this study must be agreed upon with the FDA prior to initiation.* *The study protocol was amended for inclusion of 17 years and 11 months of age. The sponsor may have been confused and the age inclusion was 6 to 16 years and 11 months in the final study protocol dated 6-OCT-2015.*	**Types of studies:** *An Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Kerydin® (Tavaborole) Topical Solution, 5% in the Treatment of Onychomycosis of the Toenail in Pediatric Subjects Ages 6 to 16 Years and 11 Months*
Indication(s) to be studied: *For the treatment of mild to moderate onychomycosis of the toenails in pediatric subjects 6 to 16 years, 11 months of age*	**Indication(s) studied:** *For the treatment of mild to moderate onychomycosis of the toenails in pediatric subjects 6 to 16 years, 11 months of age*
Written Request Items	Information Submitted/ Sponsor's response
Age group and population in which study will be performed:	Age group and population in which study was performed:

10 ***This study investigates the potential use of tavaborole in the treatment of pediatric population 6 years to 17 years 11 months old with onychomycosis of toenail caused by Trichophyton rubrum or T. mentagrophytes.*** 11 12	*(TAV-ONYC-401) An Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Kerydin® (Tavaborole) Topical Solution, 5% in the Treatment of Onychomycosis of the Toenail in Pediatric Subjects Ages 6 years to 16 years and 11 months.* • *6 to <12 years…… 13 (24%)* • *12 to 16 years, 11 months…….. 41 (75.9%)* 13
Number of patients to be studied or power of study to be achieved: *Number of patients to be studied: At least 40 subjects 12-16 years and 11 months of age out of which at least 16 evaluable subjects meet maximal use conditions.*	**Number of patients studied or power achieved:** *Study TAV-ONYC-401: 47/55 subjects completed the study. Eight (8) subjects discontinued the study: 4 due to lost to follow-up and 4 due to subject withdrawal. 54 subjects are in the safety population (1 subject excluded- without postbaseline safety assessment). Mean age of subjects is 13.2 years, 68% male, 31.5% female, 50% are Latino, and 85% White.*
Written Request Items	Information Submitted/ Sponsor's response
Entry criteria: *Entry criteria: Subjects with distal subungual onychomycosis involving at least 20% of the total area of target great toenail accompanied by a positive potassium hydroxide (KOH) wet mount and positive fungal*	Entry criteria used: *Subjects for this study must have a clinical diagnosis of distal subungual onychomycosis (DSO) affecting either great toenail with positive KOH and T. rubrum or T. mentagrophytes culture from the target toenail (TGT)*

culture for the dermatophytes Trichophyton rubrum (T. rubrum) or Trichophyton mentagrophytes (T. mentagrophytes).	*confirmed by a central mycology laboratory during screening period. Subjects must have DSO involving at least 20% of the TGT.*
Clinical endpoints: • *Pharmacokinetic Endpoints: The PK endpoints for the study should include descriptive statistical analysis of steady state systemic concentrations of tavaborole* • *Complete Cure must be assessed as 0% clinical involvement of the target toenail and negative KOH and fungal culture at Week 52* • *Important secondary endpoints must include Complete or Almost Complete Cure at Week 52 (defined as ≤ 5% target toenail involvement), The Clinical Efficacy rate at Week 52, and the Mycological Cure rate at Week 52.* • *These assessments are intended to assess compliance with treatment for the purposes of the safety assessment* • *Safety Endpoints: adverse events, vital signs, routine clinical laboratory testing*	**Clinical endpoints used:** • *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.* • *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 ≤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.*
Timing of assessments: if appropriate *None*	**Timing of assessments:** *None*
Written Request Items	Information Submitted/ Sponsor's response
Drug specific safety concerns:	**Drug specific safety concerns evaluated:**

• *Evaluation of local safety*	• *Evaluation of local safety*
Drug information: *Cut and paste from the WR* • **Route of administration:** *Topical* • **Dosage:** *solution 5%* • **Regimen:** *once daily*	**Drug information:** • **Route of administration:** *Topical* • **Dosage:** *solution 5%* • **Regimen:** *once daily*
Statistical information (statistical analyses of the data to be performed): *The study must each assess at least 40 subjects of which at least 16 evaluable subjects meet maximal use conditions. The reports should include descriptive summary statistics for all safety, efficacy, and PK assessments as agreed with the Agency at the time of protocol submission and review prior to initiation of the study*	**Statistical information (statistical analyses of the data to be performed):** • *All subjects who received at least 1 confirmed dose of study drug and had at least 1 post-baseline safety assessment were included in the safety population. The safety population included 54 subjects. The primary and secondary efficacy endpoints were summarized for the safety population.* • *All subjects from the maximal use subgroup with available PK data on Day 15 and at least 1 collection on Day 29 were included in the PK population. The PK population included 37 subjects.*
Written Request Items	Information Submitted/ Sponsor's response
Labeling that may result from the studies: *Labeling that may result from the study(ies): You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that tavaborole is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA*	**Labeling that may result from the studies:** (b) (4)

determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).	(b) (4)
Format of reports to be submitted: *Format and types of reports to be submitted: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full*	**Format of reports submitted:** *Full study report for TAV-ONC-401 was submitted to the Agency including full analysis, assessment, and interpretation of the data was submitted. The reports included information on the representation of pediatric patients of*

analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.	*ethnic and racial minorities according to the categories and designations in the WR.*
Timeframe for submitting reports of the studies: *Report of the above study must be submitted to the Agency on or before 28-FEB-2018.*	**Timeframe for submitting reports of the studies:** 14 ***The study was submitted to the Agency on 2-FEB-2018***

10 Labeling Recommendations

10.1 Prescribing Information

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[Insert text here.]

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**

10.2 Patient Labeling

[Insert text here.]

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11 Risk Evaluation and Mitigation Strategies (REMS)

[Insert text here.]

11.1. Safety Issue(s) that Warrant Consideration of a REMS

None

11.2. Conditions of Use to Address Safety Issue(s)

None

11.3. Recommendations on REMS

None

12 Postmarketing Requirements and Commitments

The applicant has satisfied all requirements.

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13 Appendices

13.1. References

None

13.2. Financial Disclosure

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[Insert text here.]

Covered Clinical Study (Name and/or Number): TAV-ONYC-401

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 15		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1. Summary of Bioanalytical Method Validation and Performance

The concentrations of tavaborole in plasma PK samples from the clinical study TAV-ONYC-401 were measured using an adequately validated high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS) assay. The assay validation results are summarized in Table 9.

Table 9: Validation Results of the Bioanalytical Method for Measuring Plasma Tavaborole Concentrations in Study TAV-ONYC-401.

Matrix	Human plasma using sodium citrate as an anticoagulant and 6.0% citric acid as a preservative
Standard curve assay range	0.500 to 50.0 ng/mL
Intra-run precision	3.42% to 15.3% (LLOQ); 1.89% to 6.90% (QCs)
Intra-run accuracy	9.20% to 18.6% (LLOQ); -5.33% to -0.125% (QCs)
Inter-run precision	10.6% (LLOQ); 3.08% to 5.54% (QCs)
Inter-run accuracy	12.8% (LLOQ); -4.00% to 2.25% (QCs)
Long term stability	273 days at -20°C (The longest storage time from sample collection to the analysis was 163 days for study TAV-ONYC-401)
Incurred sample reanalysis (ISR)	100% of 28 ISR samples (~12% of a total of 226 samples) met the criteria of reproducibility (i.e., difference within ± 20% of average of original and repeat value).

Source: reviewer's table based on data provided by the applicant.
LLOQ=lower limit of quantification
QCs=quality controls

13.4.2. Clinical PK Assessments

Plasma samples were collected in 40 out of 55 subjects in the study TAV-ONYC-401 to evaluate the PK of KERYDIN (tavaborole) topical solution, 5%. The study drug was applied onto all 10 toenails, including up to 2 mm of the surrounding skin, once daily, during Days 1-29 in these subjects. The mean (SD) amount of drug used per dosing

day was 0.36 (0.25) grams during this period (Table 10). After Day 29 in the study, study drug was continued to be applied but only to the affected toenails.

Table 10: Summary of Treatment Exposure in the PK Subgroup During the PK Evaluation Period (Days 1-29).

	KERYDIN® (N=40)				
	n	MEAN	SD	MEDIAN	MIN to MAX
Total Amount of Drug Used (g)	35	10.45	7.27	8.60	3.0 to 33.4
Total Number of Applications	39	27.67	3.90	28.00	19.0 to 35.0
Average Drug Use (g) Per Application	35	0.38	0.24	0.31	0.1 to 1.2
Total Number of Dosing Days	39	29.97	3.14	29.00	22.0 to 36.0
Average Drug Use (g) Per Dosing Day	35	0.36	0.25	0.30	0.1 to 1.2

Source: Table 1.1.2.1 in a response submitted on 5/14/2018 by applicant upon the Agency's information request.

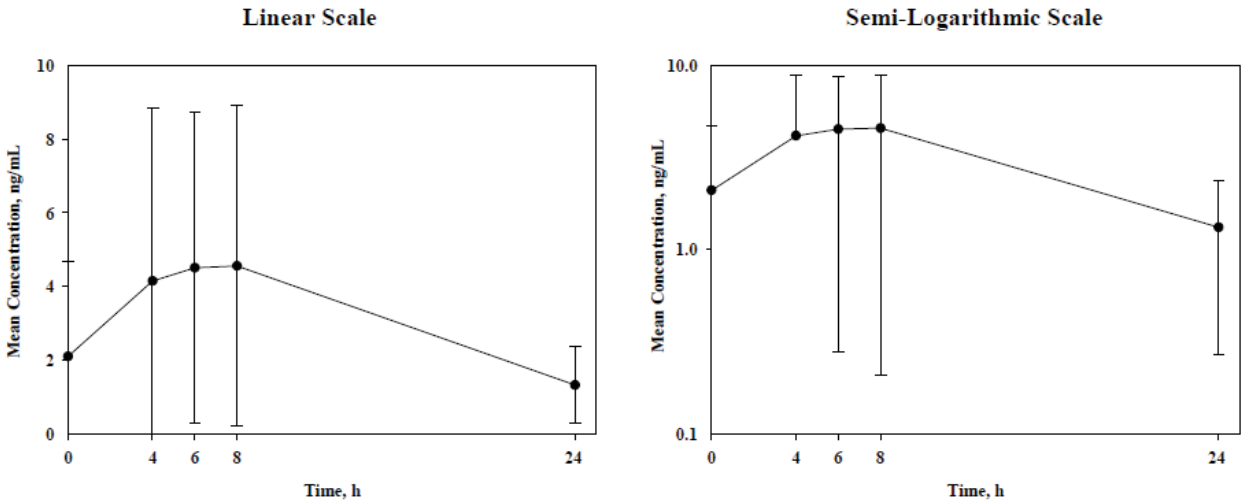
All subjects in this subgroup with available PK data on Day 15 and at least 1 collection on Day 29 were included in the PK population. The PK population included 37 subjects. Demographic and baseline characteristics for the PK population are summarized in

Table 11.

Plasma PK parameters on Day 29 are presented in Table 2. The linear and semi-logarithmic mean (±SD) plasma concentration-time profiles on Day 29 are presented in Figure 1. The mean (±SD) plasma concentrations at the pre-dose on Days 15 and 29 and the 24-hour postdose on Day 29 are presented in Figure 2. Steady state was achieved within the PK evaluation period.

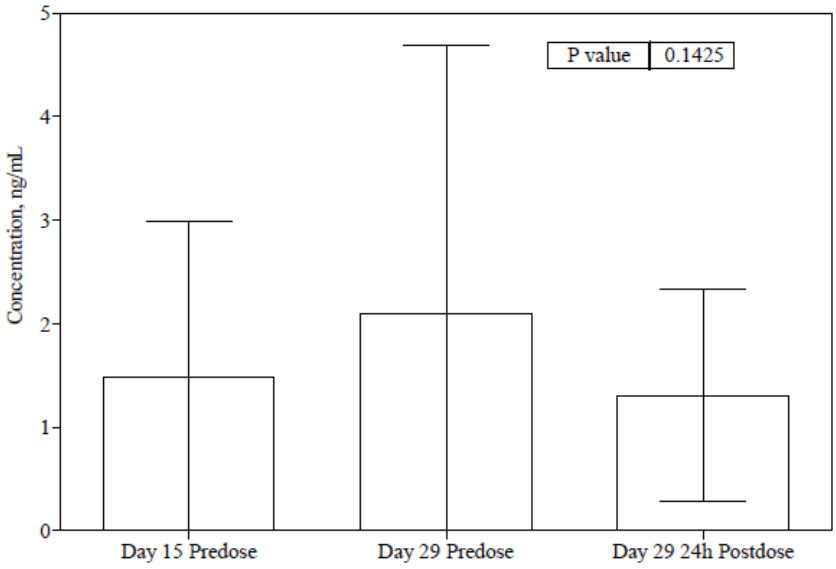
Tavaborole 5% topical solution was generally well tolerated in the study and there was no dose reduction due to adverse events. In this study, no deaths were reported and none of the subjects discontinued the study due to an adverse event. Refer to Section 7 for details of safety assessments of the drug in the study.

Figure 1: Mean (±SD) Plasma Concentration-Time Profiles of Tavaborole in Pediatric Subjects on Day 29 Following Once Daily Application of KERYDIN (tavaborole) solution, 5%.



Source: Figure 1 of PK analytical report.

Figure 2: Mean (±SD) Pre-dose Plasma Tavaborole Concentrations in Pediatric Subjects Following Once Daily Application of KERYDIN (tavaborole) solution, 5%.



Source: Figure 2 of PK analytical report.

Table 11: Summary of Subject Demographic and Baseline Characteristics (PK Population).

Parameters	Tavaborole (N=37)
Age (years)	
N	37
Mean	14.2
SD	1.62
Median	15.0
Min to max	11 to 16
6 to <12 years	1 (2.7%)
12 years to 16 years, 11 months	36 (97.3%)
Sex	
N	37
Male	21 (56.8%)
Female	16 (43.2%)
Ethnicity	
N	37
Hispanic or Latino	20 (54.1%)
Not Hispanic or Latino	17 (45.9%)
Race	
N	37
American Indian or Alaska native	0 (0.0%)
Asian	0 (0.0%)
Black or African American	4 (10.8%)
Native Hawaiian or other Pacific Islander	0 (0.0%)
White	33 (89.2%)
Clinical assessment of disease severity of target great toenail	
N	37
Completely clear nail	0 (0.0%)
Almost clear nail	0 (0.0%)
Mild onychomycosis	0 (0.0%)
Moderate onychomycosis	18 (48.6%)
Severe onychomycosis	19 (51.4%)
Percent involvement of target great toenail	
N	37
Mean	54.0
SD	18.90
Median	60.0
Min to max	21 to 90
Number of other affected toenails	
N	37
Mean	3.5
SD	2.76
Median	3.0
Min to max	0 to 8

Abbreviations: Max=maximum; Min=minimum; N=number of subjects; PK=pharmacokinetic; SD=standard deviation.

Source: Table 9 of study report.

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14 Division Director (DHOT)

X n/a

15 Division Director (OCP)

X Chandrahas G. Sahajwalla -A

Digitally signed by Chandrahas G. Sahajwalla -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300079192, cn=Chandrahas G. Sahajwalla -A
Date: 2018.07.24 12:28:18 -04'00'

16 Division Director (OB)

X n/a

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17 Division Director (Clinical)

X see signature block in DARRTS

18 Office Director (or designated signatory authority)

n/a

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CRISTINA Petruccelli Attinello
07/30/2018

JILL A LINDSTROM
07/30/2018