NDA/BLA Multidisciplinary Review and Evaluation

Application Type	Supplement NDA
Application Number(s)	203567
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Division/Office	DDD/OII
Review Completion Date	April 3, 2020
Established/Proper Name	Efinaconazole
(Proposed) Trade Name	JUBLIA®
Pharmacologic Class	Antifungal
Applicant	Bausch Health Americas, Inc.
Dosage Form	Topical solution
Applicant Proposed Dosing Regimen	Apply to affected toenails once daily for 48 weeks using the integrated flow-through brush applicator
Applicant Proposed Indication(s)/Population(s)	Indicated for topical treatment of onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes* in patients 6 years old and above
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	Onychomycosis of toenails (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for topical treatment of onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes* in patients 6 years old and above
Recommended SNOMED CT Indication Disease Term for Each Indication (if applicable)	Onychomycosis of toenails (disorder)
Recommended Dosing Regimen	Apply to affected toenails once daily for 48 weeks, using the integrated flow-through brush applicator

Table of Contents

Table of Tables 5
Table of Figures 6
Reviewers of Multidisciplinary Review and Evaluation 7
Glossary 9
1 Executive Summary 10
1.1. Product Introduction 10
1.2. Conclusions on Substantial Evidence of Effectiveness 10
1.3. Benefit-Risk Assessment 11
1.4. Patient Experience Data 14
2 Therapeutic Context 15
2.1. Analysis of Condition 15
2.2. Analysis of Current Treatment Options 15
3 Regulatory Background 17
3.1. U.S. Regulatory Actions and Marketing History 17
3.2. Summary of Presubmission/Submission Regulatory Activity 17
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 18
4.1. Office of Scientific Investigations 18
4.2. Product Quality 18
4.3. Clinical Microbiology 18
4.4. Devices and Companion Diagnostic Issues 18
5 Nonclinical Pharmacology/Toxicology 18
5.1. Executive Summary 18
5.2. Referenced NDAs, BLAs, DMFs 18
5.3. Pharmacology 18
5.4. ADME/PK 19
5.5. Toxicology 19
5.5.1. General Toxicology 19
5.5.2. Genetic Toxicology 19
5.5.3. Carcinogenicity 19
5.5.4. Reproductive and Developmental Toxicology 19
5.5.5. Other Toxicology Studies 19
6 Clinical Pharmacology 20
6.1. Executive Summary 20
6.1.1. Recommendations 20

6.2. Summary of Clinical Study V01-108A-401....21
6.2.1. Study Objective....21
6.2.2. Study Design....21
6.2.3. Pharmacokinetic Sampling....22
6.2.4. Pharmacokinetic Results....22
6.3. Question-Based Clinical Pharmacology Review....23
6.3.1. How Does the Systemic Exposure to Efinaconazole and Its Metabolite(s) in Adolescent Subjects Compare With Adults?....23
6.3.1. What Are the Study Population and Drug Usage in Study V01-108A-401?....24
6.3.2. What Are the Efficacy Results of Efinaconazole Topical Solution in Pediatric Subjects With Onychomycosis in Study V01-108A-401?....25
6.3.3. Were the Bioanalytical Methods Validated?....26
7 Sources of Clinical Data and Review Strategy....27
7.1. Table of Clinical Studies....27
7.1.1. Review Strategy....27
8 Statistical and Clinical and Evaluation....27
8.1. Review of Relevant Individual Trials Used to Support Efficacy....27
8.1.1. V01-108A-401....27
8.1.2. Study Results....29
8.1.3. Integrated Assessment of Effectiveness....32
8.2. Review of Safety....32
8.2.1. Review of Safety Database....32
8.2.2. Adequacy of Applicant's Clinical Safety Assessments....32
8.2.3. Safety Results....33
8.2.4. Integrated Assessment of Safety....34
8.3. Conclusions and Recommendations....34
9 Advisory Committee Meeting and Other External Consultations....35
10 Pediatrics....35
11 Labeling Recommendations....36
11.1. Prescription Drug Labeling....36
12 Risk Evaluation and Mitigation Strategies....43
13 Postmarketing Requirements and Commitment....43
14 Division Director (DHOT) Comments....44
15 Division Director (OCP) Comments....44
16 Division Director (OB) Comments....44

17 Division Director (Clinical) Comments 44
18 Office Director (or Designated Signatory Authority) Comments 44
19 Appendices 45
19.1. References 45
19.2. Financial Disclosure....45
19.3. Nonclinical Pharmacology/Toxicology 46
19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)....46

Table of Tables

Table 1. Distribution Data for JUBLIA (Efinaconazole) Topical Solution, 10%.....17
Table 2. Pharmacokinetics of Efinaconazole and Metabolite H3 on Day 28.....23
Table 3. Pharmacokinetics of Efinaconazole and Its Metabolites (H3 and H4) in Adults and Adolescents Following 4-Week Efinaconazole Treatment Under Maximal-Use Conditions.....23
Table 4. Demographic and Baseline Characteristics of the Safety Population 24
Table 5. Demographics and Baseline Variables of Pharmacokinetics Population 25
Table 6. Summary of Study Drug Exposure and Amount.....25
Table 7. Summary of the Key Efficacy Results 26
Table 8. Subject Disposition (All Enrolled Subjects).....30
Table 9. Demographic and Baseline Characteristics (Safety Population) 30
Table 10. Summary of Key Efficacy Results (Safety Population LOCF).....31
Table 11. Bioanalytical method validation parameters 46

Table of Figures

Figure 1. Summary of Approved Onychomycosis Therapies 16
Figure 2. Plasma Concentrations of Efinaconazole and Metabolite H3 After 4-Week Treatment 22

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OPQ=Office of Pharmaceutical Quality
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PLT=Patient Labeling Team
TL=Team Leader

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Liping Pan, PhD	Office of Clinical Pharmacology (OCP)/ Division of Clinical Pharmacology 3 (DCP 3)	Sections: Section 6, Section 11: Labeling section 12.1, 12.2 and 12.3, and Section 19.4.	Select one: _X__ Authored ___ Approved
	Signature: Signature in DARRTS			
Clinical Pharmacology Reviewer	Chinmay Shukla, PhD	OCP/DCP 3	Section: Section 6, Section 11: Labeling section 12.1, 12.2 and 12.3 Section 19.4.	Select one: ___ Authored _X__ Approved
	Signature: Signature in DARRTS			
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	Signature: Signature in DARRTS			

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AUC	area under the concentration-time curve
BLA	biologics license application
CFR	Code of Federal Regulations
DHOT	Division of Hematology Oncology Toxicology
FDA	Food and Drug Administration
KOH	microscopic potassium hydroxide
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PK	pharmacokinetics
PMR	postmarketing requirement
PRO	patient-reported outcome
SAE	serious adverse event
TEAE	treatment-emergent adverse event

1 Executive Summary

1.1. Product Introduction

Efinaconazole (JUBLIA®) 10% topical solution was approved on June 6, 2014, for the topical treatment of onychomycosis in adults. At the time of approval, the Applicant agreed to a postmarketing requirement (PMR) (2156-1) to evaluate the safety, efficacy, and pharmacokinetics (PK) of JUBLIA topical solution, 10% versus vehicle in pediatric subjects 12 to 17 years of age with onychomycosis of the toenails.

The active ingredient, efinaconazole, is an azole antifungal agent with activity against a wide range of pathogenic fungi. Efinaconazole has been shown in vitro to be effective against dermatophytes (*Trichophyton, Microsporum,* and *Epidermophyton* species) and yeasts (*Malassezia* species, *Candida albicans*, and other *Candida* species). The mechanism of action of efinaconazole, like other triazole antifungal therapeutics, is inhibition of lanosterol 14α-demethylase, resulting in blockage of ergosterol synthesis. Fungal cell membrane structure and function are compromised by the resulting ergosterol depletion and accumulation of 14-α methyl sterols.

The active ingredient is combined in a nonaqueous solution containing eight other drug substances (cyclomethicone; diisopropyl adipate; C12-15 alkyl lactate; butylated hydroxytoluene; citric acid, anhydrous; edetate disodium; purified water; and alcohol). The drug product (IDP-108) is intended to be applied directly to the nail, to the skin folds surrounding the nail, and to any accessible skin of the nail bed for the treatment of onychomycosis.

Efinaconazole solution, 10%, is packaged in a white (b) (4)-mL high-density polyethylene bottle, together with a brush applicator and a (b) (4) cap.

1.2. Conclusions on Substantial Evidence of Effectiveness

Bausch Health Americas, Inc. has submitted a supplement to the approved new drug application (NDA) 206567, JUBLIA (efinaconazole solution, 10%) with a proposed indication of once-daily topical treatment of onychomycosis (tinea unguium) down to 6 years of age. The Applicant completed study V01-108A-401 in pediatric subjects aged 6 years to less than 17 years with at least mild onychomycosis of the toenails. Included in this study is an evaluation of the PK of once-daily topically administered efinaconazole solution for 4 weeks in pediatric subjects (12 to 16 years, 11 months) with moderate to severe onychomycosis of the toenails.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Efinaconazole (JUBLIA) 10% topical solution was approved on June 6, 2014, for the topical treatment of onychomycosis in adults. At the time of approval, the Applicant agreed to a postmarketing requirement (PMR) (2156-1) to evaluate the safety, efficacy, and pharmacokinetics (PK) of JUBLIA topical solution, 10% versus vehicle in pediatric subjects 12 to 17 years of age with onychomycosis of the toenails. In addition, the Applicant also submitted a Proposal for Pediatric Studies Request for PMR 2156-1. In response, the FDA issued a Written Request (WR) on April 17, 2015, to study subjects down to 6 years of age to obtain adequate safety data for pediatric onychomycosis. The agreed phase 4 study, V01-108A-401, was reviewed by the FDA on April 7, 2016.

In Supplement 9 to NDA 203567, Bausch Health US, LLC submitted a multicenter, open-label, single-arm study evaluating the safety and PK of efinaconazole 10% topical solution in subjects with mild to severe onychomycosis of the toenails. The primary objectives of evaluating once-daily topically administered JUBLIA 10% topical solution for 48 weeks in pediatric subjects (6 years to 16 years, 11 months) with at least mild onychomycosis of the toenails has been met. The study also evaluated the PK of JUBLIA 10% topical solution in subjects 12 years to 16 years,11 months. The Applicant has met the request of the FDA for pediatric safety data in children with onychomycosis. The labeling will reflect the pediatric safety data and the approved updates to the Pregnancy and Lactation Labeling Rule.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Onychomycosis is a chronic and recurring fungal infection of the fingernails or toenails, and accounts for about half of all nail disorders. Onychomycosis is usually caused by dermatophytes, either *Trichophyton rubrum* (71%) or *Trichophyton mentagrophytes* (20%). The prevalence of onychomycosis in the United States may be as high as 13%, with the infection observed predominantly in elderly patients (60%).[1] Onychomycosis of the toenail can result in permanent toenail deformity and has a significant impact on quality of life as a result of concern with the appearance of the toenails and interference with wearing shoes, walking, and participating in various sports activities.[2]	Onychomycosis is a chronic condition that may affect children, especially in humid climates. Evaluation of the safety of long-term topical onychomycosis treatment in children is required.
Current Treatment Options	Penlac® (ciclopirox 8%) Nail Lacquer[3] was the only topical treatment for onychomycosis available in in the United States until the approval of JUBLIA and KERYDIN®. Ciclopirox is a broad-spectrum antifungal agent that exhibits fungicidal activity in vitro against dermatophytes, *Candida* species, and some nondermatophyte molds.	Topical treatment options for patients who cannot take oral antifungals were, until the approval of efinaconazole and tavaborole, limited to ciclopirox 8% nail lacquer.

[1] Elewski BE, Hay RJ. Update on the management of onychomycosis: highlights of the Third Annual International Summit on Cutaneous Antifungal Therapy. Clin Infect Dis 1996; 23: 305-13.

[2] Levy LA. Epidemiology of onychomycosis in special-risk populations. J Am Podiatr Med Assoc 1997; 87: 546-50

[3] Penlac nail lacquer (ciclopirox) topical solution, 8% prescribing information. Dermik Laboratories, Inc., 2000.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Topical treatment for onychomycosis presents few risks. Oral treatment is typically used for onychomycosis, but its efficacy may be limited in some patients by drug-drug interactions (especially in the elderly, who have a high rate of concomitant medications), other safety concerns (e.g., liver toxicity), and by the potential need for laboratory monitoring. Only itraconazole (Sporanox®) and terbinafine (Lamisil®) have been approved in the United States, and have respective cure rates of 14% and 38%. Hepatotoxicity is associated with systemic exposure to oral antifungal medications.	Safety of topical onychomycosis treatment presents few risks. It is imperative to have options for the treatment of onychomycosis in both adults and children.
Risk and Risk Management	Since its approval for topical treatment of onychomycosis, few safety issues have been related to use of JUBLIA. The benefits outweigh the risk of extending the age limit for topical treatment down to 6 years of age.	No special risk management is required. The Applicant has complied with the PMR and PMR has been fulfilled.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient-reported outcome (PRO)	
		☐	Observer-reported outcome (ObsRO)	
		☐	Clinician-reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data were not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Onychomycosis refers to a nail infection caused by any fungus, including yeasts and nondermatophyte molds. It is characterized by hyperkeratosis (hypertrophy of the skin/nail) of the nail bed, yellow to brownish discoloration of the nail plate, onycholysis (separation of the nail from the nail bed along the lateral margins), and paronychial inflammation (inflammation caused by infection of the skin fold at the nail margin).[4] Dermatophytic onychomycosis (tinea unguium) occurs in three distinct forms: distal subungual (most common), proximal subungual, and white superficial. One or several toenails or fingernails may be involved, seldom all. The majority of cases of toenail onychomycosis is caused by dermatophytes; however, many cases of fingernail onychomycosis are caused by yeast.

Multiple factors may contribute to the prevalence of onychomycosis. The prevalence has been increasing especially in diabetic, immunologically challenged, and elderly patient populations.[5] Multiple environmental factors may play a role in this increase, including the rise in the use of broad-spectrum antibiotics.[6] Numerous other factors that may predispose the nail to fungal infection; include geography, ethnicity, social class, occupation, genetics, vascular disease, obesity, atrophy, participation in sports, trauma, acrylic nails, ill-fitting shoes, nutritional status, nondermatophyte exposure, and poor nail grooming.[7]

The most common presentation of this disease is distal subungual onychomycosis, typically caused by the dermatophyte *Trichophyton rubrum*. Proximal subungual onychomycosis is generally caused by the same organism as distal subungual onychomycosis. White superficial onychomycosis is usually caused by *T. mentagrophytes*, although *T. rubrum* has also been implicated. Yeast onychomycosis is most commonly due to *Candida albicans*. Because other nail diseases—including psoriasis, eczema, and lichen planus—may have a similar clinical presentation, confirmation of onychomycosis by direct-microscopic examination, nail clip biopsy, and fungal culture is necessary prior to initiating therapy.[8]

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

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[4] Elewski BE, Hay RJ. Update on the management of onychomycosis: highlights of the Third Annual International Summit on Cutaneous Antifungal Therapy. Clin Infect Dis 1996; 23: 305-13

[5] Weschler WP, Smith SA, Bondar GL. Treatment of onychomycosis in the elderly. Clin Geriatr 2002; 10: 19-24, 29-30

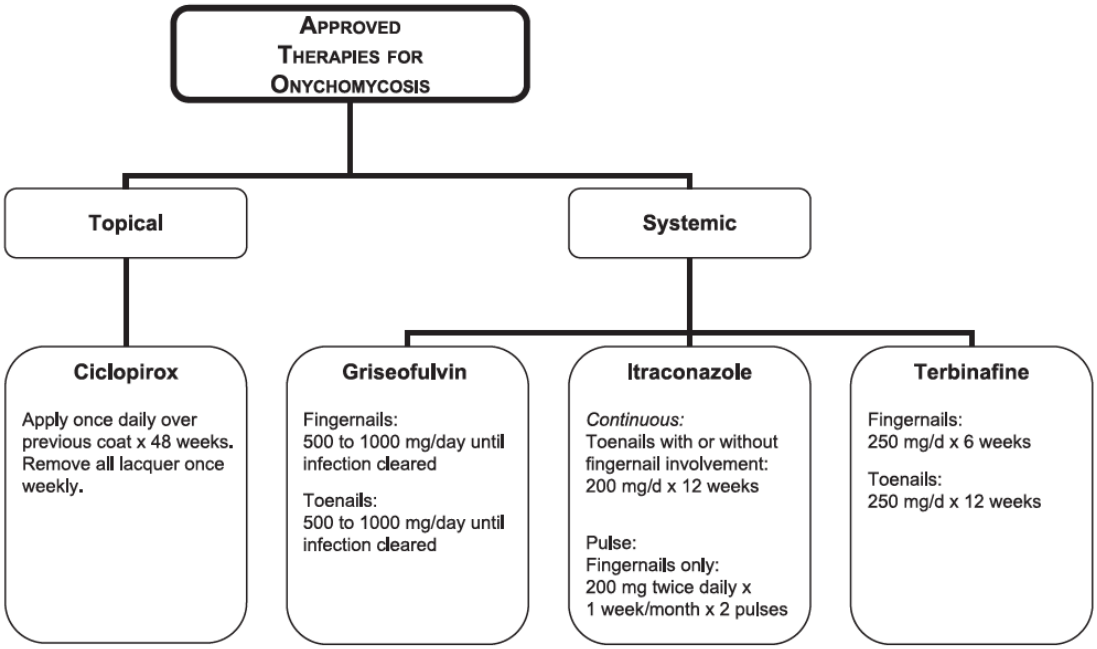
[6] Levy LA. Epidemiology of onychomycosis in special-risk populations. J Am Podiatr Med Assoc 1997; 87: 546-50

[7] Haneke E, Roseeuw D. The scope of onychomycosis: epidemiology and clinical features. Int J Dermatol 1999; 38 Suppl. 2: 7-12

[8] Weinberg JM, Koestenblatt EK. Comparison of diagnostic methods in the evaluation of onychomycosis. Dermatol Online J 2001; 7: 236

modalities (Figure 1). Factors that influence the choice of therapy include the presentation and severity of the disease, medications the patient is taking, previous therapies for onychomycosis and the patient's response to them, physician and patient preference, and cost of therapy.

Figure 1. Summary of Approved Onychomycosis Therapies



Source: Uptodate review on onychomycosis.

Penlac® (ciclopirox) nail lacquer topical solution, 8%, was the only topical product approved (1999) in the United States for the treatment of onychomycosis until the approval in 2014 of JUBLIA (efinaconazole) and KERYDIN (tavaborole). Ciclopirox lacquer, approved in 1999, has demonstrated modest efficacy in treating mild to moderate onychomycosis not involving the lunula, with a reported complete cure rate of 8.5%; frequent nail debridement is required when using this product.

Oral treatment has been generally used for onychomycosis, but its efficacy may be limited in some patients by drug-drug interactions (especially in the elderly, who have a high frequency of concomitant medications), other safety concerns (e.g., liver toxicity), and by the potential need for laboratory monitoring. Only itraconazole (Sporanox®) and terbinafine (Lamisil®) have been approved in the United States, and have cure rates of 14% and 38%, respectively. Hepatotoxicity is associated with systemic exposure to most oral antifungal medications.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

JUBLIA was approved on June 6, 2014, for the topical treatment of onychomycosis in adults. Based on the annual report for NDA 203567 submission August 5, 2019, for JUBLIA (efinaconazole) topical solution, 10%, covering the period of June 6, 2018 to June 5, 2019, the quantities of JUBLIA distributed during the reporting period are presented in Table 1.

Table 1. Distribution Data for JUBLIA (Efinaconazole) Topical Solution, 10%

NDC Number	Description / Size	Domestic Units	Domestic Units (PUERTO RICO)	Domestic Units (VIR)	Non-US Units	Total Packages
	Topical Solution, 10%					
0187-5400-04	4mL	(b) (4)				
0187-5400-08	8mL					
0187-5400-10	4mL (SAMPLE)					
0187-5400-02	2mL (SAMPLE)					
	Topical Solution, 10%					
060752-0015-40	8mL	(b) (4)				

Source: Annual Report 5, NDA 203567

3.2. Summary of Presubmission/Submission Regulatory Activity

Postmarketing experience is taken from the annual Periodic Adverse Drug Experience Report for JUBLIA. The most recent report was submitted to the FDA on July 31, 2019. No new action was taken and no new safety issue was found.

No other regulatory action was taken for JUBLIA prior to the submission of this supplement.

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

4.1. Office of Scientific Investigations

OSI inspections of clinical study sites were not requested for this supplement.

4.2. Product Quality

No new product quality information was submitted for this approved drug product.

4.3. Clinical Microbiology

No new clinical microbiology information was submitted in this supplement.

4.4. Devices and Companion Diagnostic Issues

Not applicable for this supplement.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

N/A

5.2. Referenced NDAs, BLAs, DMFs

N/A

5.3. 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

6 Clinical Pharmacology

6.1. Executive Summary

JUBLIA (efinaconazole topical solution, 10%), an azole antifungal, was approved in 2014 for the topical treatment of onychomycosis of the toenails caused by *Trichophyton rubrum* and *Trichophyton mentagrophytes* in patients 17 years or older.

At the time of the original approval, there was a Pediatric Research Equity Act PMR to evaluate JUBLIA in adolescents (2156-1), as shown below.

PMR 2156-1

A multicenter, randomized, double-blind study evaluating the safety, efficacy and pharmacokinetics of JUBLIA (efinaconazole) topical solution, 10% versus vehicle in pediatric subjects aged 12 to less than 17 years with onychomycosis of the toenails.

In April 2015, the FDA issued a written request for pediatric studies for JUBLIA. That written request was modified in July 2015 to include a request for the study described below (see communication in DARRTS dated July 10, 2015).

Study 1

An open-label pharmacokinetics and safety study of once-daily topical application of efinaconazole solution, 10%, for 48 weeks in subjects aged 6 years to 16 years, 11 months with mild to moderate 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 Food and Drug Administration (FDA) prior to initiation.

It should be noted that PK assessment under maximal-use conditions was requested only in subjects down to 12 years old, not down to 6 years old, because of the low prevalence of the disease in subjects below the age of 12 years.

In the current supplemental NDA, the Applicant submitted the final study report to fulfill the aforementioned PMR (2156-1). Labeling revisions to reflect the results of the PMR study have been submitted as part of this application.

6.1.1. Recommendations

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology, has reviewed the final study report of the PMR (2156-1) and concluded that the Applicant has fulfilled this PMR.

6.2. Summary of Clinical Study V01-108A-401

A multicenter, open-label, single-arm study evaluating the safety and pharmacokinetics of efinaconazole 10% topical solution in subjects with mild to severe onychomycosis of the toenails

6.2.1. Study Objective

The primary objectives of this study were to evaluate the following:

- Safety of once-daily topical administration of efinaconazole 10% solution (efinaconazole solution) for 48 weeks in pediatric subjects (6 years to 16 years, 11 months) with at least mild onychomycosis of the toenails
- Pharmacokinetics of once-daily topical administration of efinaconazole solution for 4 weeks in pediatric subjects (12 years to 16 years, 11 months) with moderate to severe onychomycosis of the toenails

6.2.2. Study Design

This was an open-label, single-arm study designed to evaluate the safety of once-daily topical application of efinaconazole solution in the treatment of pediatric subjects 6 to 16 years of age with mild to severe onychomycosis of the toenails. A total of 60 subjects aged 6 to 16 years was assigned to treatment, of whom 18 subjects aged 12 to 16 years were treated under maximal use conditions (PK subset). The duration of the study is up to 56 weeks, consisting of 4-week screening, 48-week treatment, and 4-week follow-up periods.

- Subjects aged 6 to 16 years not participating in the PK subset must have had onychomycosis involving at least 20% of one affected great toenail; onychomycosis could be present in up to six other toenails.

- Subjects aged 12 to 16 years in the PK subset must have had onychomycosis involving at least 50% each of both affected great toenails and at least four toenails other than the great toenails should have onychomycosis.

Dosing Regimen

- Subjects aged 6 to 16 years not participating in the PK subset (n=42): once-daily topical application to affected toenails for up to 48 weeks
- Subjects aged 12 to 16 years in the PK subset (n=18): once-daily topical application to all 10 toenails for 4 weeks (i.e., maximal use), then once-daily topical application to the affected toenails from Day 29 for up to 44 additional weeks (a total of 48 weeks of treatment)

Reviewer's comments: The dosing regimen used in pediatric patients is the same as the approved dosing regimen for adults. For the maximal-use PK studies, both adolescent and adult patients received the same dose regimen—once-daily topical application to all 10 toenails for 4 weeks.

6.2.3. Pharmacokinetic Sampling

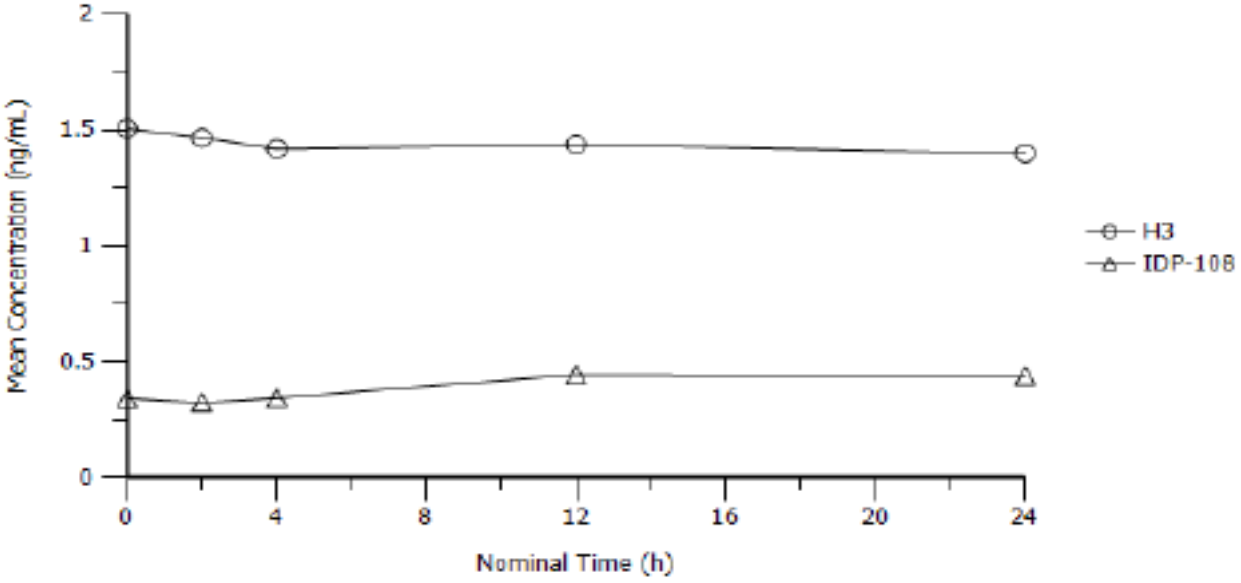
In the PK subset, blood samples were collected for PK analysis of efinaconazole and its metabolites (H3 and H4) on Day 28: predose and at 2, 4, 12, and 24 hours postdose.

Reviewer's comments: In the maximal-use PK study in adults, blood samples were collected on Days 1, 14, and 28 predose and at 1, 2, 4, 6, 8, 10, 12, 16, and 24 hours postdose for PK analysis.

6.2.4. Pharmacokinetic Results

The systemic exposure, expressed as the observed maximum concentration (C_{max}) and area under the concentration-time curve $(AUC)_{0-24}$ to efinaconazole and its metabolites (H3 and H4), in the adolescent patients of the study were generally low. Exposure to the inactive metabolite H3 was approximately five-fold higher than that to the parent drug, efinaconazole (Figure 2). For most of the samples, the plasma concentration of the active metabolite H4 was not detectable or below the lower limit of quantification of 0.100 ng/mL. The PK parameters of efinaconazole and of metabolite H3 in the adolescent patients following once-daily topical application of efinaconazole 10% solution for 4 weeks are summarized in Table 2.

Figure 2. Plasma Concentrations of Efinaconazole and Metabolite H3 After 4-Week Treatment



The lower limit of quantification for each analyte was 0.100 ng/mL
Source of data: Clinical Study Report V01-108A-401, Figure 1
Abbreviations: H3, metabolite of efinaconazole; IDP-108, efinaconazole

Table 2. Pharmacokinetics of Efinaconazole and Metabolite H3 on Day 28

	Efinaconazole				H3			
	N	Mean	SD	CV%	N	Mean	SD	CV%
T_{max} (h)[a]	15	12.0 (0.00 – 24.5)			15	4.05 (0.00 – 24.5)		
C_{max} (ng/mL)	15	0.549	0.375	68.32	15	1.65	1.31	79.48
C_{min} (ng/mL)	15	0.263	0.260	99.16	15	1.21	1.22	100.10
AUC_{0-24} (h•ng/mL)	11	11.4	7.68	67.57	13	38.1	30.4	79.74
AUC_{0-24} (h•nmol/mL)		0.0327[b]				0.169[b]		
AUC_{0-t} (h•ng/mL)	12	11.6	7.47	64.64	14	36.1	30.4	84.03
T_{last} (h)	15	23.3	3.12	13.37	15	23.3	3.12	13.37
C_{last} (ng/mL)	15	0.456	0.287	63.02	15	1.48	1.11	75.13

[a], T_{max} reported as median (min-max)
[b], Mean AUC_{0-24} in molar amounts (h*nmol/mL), adjusted for a molecular weight of 348.39 g/mol for efinaconazole and 225.19 g/mol for H3
Source of data: Clinical Study Report V01-108A-401, Table 8
Abbreviation: AUC, area under the concentration-time curve; C_{max}, observed maximum observed concentration

6.3. Question-Based Clinical Pharmacology Review

6.3.1. How Does the Systemic Exposure to Efinaconazole and Its Metabolite(s) in Adolescent Subjects Compare With Adults?

The PK data of efinaconazole and its metabolites (H3 and H4) in adults and adolescents following once-daily topical application of efinaconazole solution for 4 weeks or under maximal-use conditions are summarized in Table 3 (adult PK data were obtained from the review of the original NDA, Study DPSI-IDP-108-P1-03). The PK results suggest that under maximal-use conditions, systemic exposure to efinaconazole and its metabolites in adolescent patients is comparable to that observed in adult patients. Of note, the plasma concentration of the inactive metabolite H3 was approximately five-fold higher than that of efinaconazole in both adolescent and adult patients under maximal-use conditions (Table 3). Metabolite H4 is pharmacologically active and was not quantifiable in any of the adolescent subjects.

Table 3. Pharmacokinetics of Efinaconazole and Its Metabolites (H3 and H4) in Adults and Adolescents Following 4-Week Efinaconazole Treatment Under Maximal-Use Conditions

	Adults (n=19)[1] (Mean±SD)			Adolescents (n=17)[2] (Mean±SD)		
Analyte	n	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	n	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)
Efinaconazole	18	0.67±0.37	12.15±6.91	15	0.55±0.38	11.4±7.68
Metabolite H3	18	2.26±1.64	45.80±31.85	15	1.65±1.31	38.1±30.4
Metabolite H4	5	0.05±0.08	1.85±1.01	15	ND	ND

Source of data: Reviewer's summary based on the data from the CSRs of DPSI-IDP-108-P1-03 and V01-108A-401)
[1] Subjects must have onychomycosis involving at least 80% of each great toenail and at least 4 toenails other than the great toenails with onychomycosis; once-daily application to all 10 toenails for 4 weeks (maximal-use conditions)
[2] Subjects must have had onychomycosis involving at least 50% each of both affected great toenails and at least four toenails other than the great toenails with onychomycosis; once-daily application to all 10 toenails for 4 weeks (maximal-use conditions)
Lower limit of quantification, 0.100 ng/mL for each analyte
Abbreviations: n, number of subjects; ND, not detectable; AUC, area under the concentration-time curve, C_{max}, observed maximum concentration

6.3.1. What Are the Study Population and Drug Usage in Study V01-108A-401?

A total of 60 subjects who received once-daily topical application of efinaconazole solution for 4 weeks were included in the safety population. A subset of 18 subjects was treated under maximal-use conditions; of those 18 subjects, 17 were included in the PK population. The demographic and baseline characteristics, and the total amount of drug used over the treatment period, are summarized in Table 4, Table 5, and Table 6, respectively. Of note, there were no meaningful differences in demographics between the safety and PK analysis populations.

Table 4. Demographic and Baseline Characteristics of the Safety Population

	Efinaconazole Solution (N = 60)
Age (years)	
Mean (SD)	13.4 (2.29)
Median	14.0
Min, Max	6, 16
Sex, n (%)	
Male	40 (66.7%)
Female	20 (33.3%)
If Female, is the Subject of Childbearing Potential? n (%)[a]	
Yes	17 (85.0%)
No	3 (15.0%)
Ethnicity, n (%)	
Hispanic or Latino	46 (76.7%)
Not Hispanic or Latino	14 (23.3%)
Race, n (%)[b]	
White	53 (88.3)
Black or African American	6 (10.0)
Other	1 (1.7)
Target Great Toenail, n (%)	
Left	32 (53.3%)
Right	28 (46.7%)

Source of data: CSR V01-108A-401, Table 5

Reviewer's comment: On evaluation of the demographics, the mean age was 13.4 years. There were seven subjects aged under 12 years (6 years [1], 8 years [3], and 10 years [3]). The other subjects were aged above 12 years and were included in the PK subset (12 years [10], 13 years [12], 14 years [8], 15 years [11], and 16 years [12]).

Table 5. Demographics and Baseline Variables of Pharmacokinetics Population

	PK Subjects (N=17)
Age (years)	
n	17
Mean (SD)	14.1 (1.48)
Median	14.0
Min, Max	12, 16
Sex	
Male	11 (64.7%)
Female	6 (35.3%)
If Female, is the Subject of Childbearing Potential?[1]	
Yes	6 (100.0%)
No	0
Ethnicity	
Hispanic or Latino	16 (94.1%)
Not Hispanic or Latino	1 (5.9%)
Race	
American Indian or Alaska Native	0
Asian	0
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
White	17 (100.0%)
Multi-Racial	0
Other	0
Target Great Toenail	
Left	13 (76.5%)
Right	4 (23.5%)
Missing	0

Source of data: CSR V01-108A-401, Table 14.1.2.2
Abbreviations: PK, pharmacokinetics; SD, standard deviation

Table 6. Summary of Study Drug Exposure and Amount

		Mean ± SD	
Population	**Number of Subjects**	**Study Drug Exposure (Days)**	**Total Amount of Study Drug (Grams)**
Safety population	60	315.6 ± 78.9	32.5 ± 20.4
PK population	17	339.6 ± 9.6	51.1 ± 21.9
Non-PK population	42	313.3 ± 79.2	25.4 ± 14.3

Source of data: Reviewer's summary based on CSR V01-108A-401, Tables 14.1.5.3, 14.1.5.4, and 14.1.5.5

6.3.2. What Are the Efficacy Results of Efinaconazole Topical Solution in Pediatric Subjects With Onychomycosis in Study V01-108A-401?

Efficacy was assessed through Week 52 to evaluate compliance with treatment as part of the safety assessment. The efficacy variables evaluated in this study included the outcomes of microscopic potassium hydroxide (KOH) examination and of mycological culture of the target toenail(s), the percentage involvement of the target toenail(s), growth of the target toenail(s), and assessment of nontarget toenail(s). The key efficacy results are summarized in (Table 7Error! Reference source not found.).

Overall, 40% of the subjects achieved complete cure and 65% achieved mycologic cure by Week 52.

Reviewer's comment: The efficacy outcomes in pediatric patients 6 to 16 years of age are slightly better than those in the two pivotal phase 3 studies of the original NDA, in which approximately 17% and 55% of adult patients (18 to 70 years of age) achieved complete cure and mycologic cure, respectively. See Clinical review for additional details.

Table 7. Summary of the Key Efficacy Results

Parameter Study Visit	N	Success n (%)	Failure n (%)
Complete Cure[a]			
Screening	60	0 (0.0)	60 (100.0)
Week 12	60	0 (0.0)	60 (100.0)
Week 24	60	0 (0.0)	60 (100.0)
Week 36	60	5 (8.3)	55 (91.7)
Week 48	60	21 (35.0)	39 (65.0)
Week 52	60	24 (40.0)	36 (60.0)
Complete or Almost Complete Cure[b]			
Screening	60	0 (0.0)	60 (100.0)
Week 12	60	0 (0.0)	60 (100.0)
Week 24	60	3 (5.0)	57 (95.0)
Week 36	60	9 (15.0)	51 (85.0)
Week 48	60	22 (36.7)	38 (63.3)
Week 52	60	25 (41.7)	35 (58.3)
Clinical Efficacy[c]			
Screening	60	0 (0.0)	60 (100.0)
Week 12	60	0 (0.0)	60 (100.0)
Week 24	60	5 (8.3)	55 (91.7)
Week 36	60	11 (18.3)	49 (81.7)
Week 48	60	26 (43.3)	34 (56.7)
Week 52	60	30 (50.0)	30 (50.0)
Mycologic Cure[d]			
Screening	60	0 (0.0)	60 (100.0)
Week 12	60	22 (36.7)	38 (63.3)
Week 24	60	32 (53.3)	28 (46.7)
Week 36	60	42 (70.0)	18 (30.0)
Week 48	60	42 (70.0)	18 (30.0)
Week 52	60	39 (65.0)	21 (35.0)

[a] Complete cure: 0% clinical involvement of the target toenail plus negative KOH and fungal culture
[b] Complete or almost-complete cure: ≤5% target toenail area affected plus negative KOH and fungal culture
[c] Clinical efficacy: <10% target great toenail area affected
[d] Mycologic cure: negative KOH and fungal culture
Source of data: CSR V01-108A-401, Table 6
Abbreviation: KOH, microscopic potassium hydroxide

6.3.3. Were the Bioanalytical Methods Validated?

The bioanalytical methods were well validated. See Section 19.4 for further information.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

A single PMR clinical study is submitted (V01-108A-401): A multicenter, open-label, single-arm study evaluating the safety and pharmacokinetics of efinaconazole 10% topical solution in subjects with mild to severe onychomycosis of the toenails

7.1.1. Review Strategy

The safety and efficacy studies in the single clinical study V01-108A-401 are reviewed.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. V01-108A-401

A multicenter, open-label, single-arm study evaluating the safety and pharmacokinetics of efinaconazole 10% topical solution in subjects with mild to severe onychomycosis of the toenails

Trial Design

This was an open-label, single-arm study designed to evaluate the safety of a once-daily topical application of efinaconazole solution in the treatment of pediatric subjects 6 to 16 years of age (inclusive) with mild to severe onychomycosis of the toenails. In addition, the PK of efinaconazole solution was determined after once-daily topical application of efinaconazole solution in pediatric subjects 12 to 16 years of age with moderate to severe onychomycosis of the toenails (PK subset). Approximately 60 subjects with at least mild onychomycosis were planned to be enrolled in the study.

V01-108A-401 included male and female subjects 6 to 16 years of age (inclusive) with a clinical diagnosis of distal lateral subungual onychomycosis. Subjects not participating in the PK subset must have had onychomycosis involving at least 20% of one affected great toenail with onychomycosis in up to six other toenails. Subjects in the PK subset (12 to 16 years of age, inclusive) must have had onychomycosis involving at least 50% each of both affected great toenails and at least four toenails other than the great toenails with onychomycosis.

Study Endpoints

Safety

Safety was evaluated by monitoring adverse events (AEs) and serious adverse events (SAEs), local skin reaction scores (redness, swelling, burning, itching, and vesiculation), clinical laboratory findings (hematology, chemistry, and urinalysis), and vital signs (sitting blood pressure, respiration, pulse, and temperature).

Efficacy

Efficacy was assessed to evaluate compliance with treatment for the purpose of assessing safety. The efficacy variables evaluated in this study included microscopic potassium hydroxide (KOH) examination and mycological culture outcomes of the target great toenail, percentage involvement of the target great toenail, growth of the target great toenail, and results of assessments of the nontarget toenails.

Statistical Analysis Plan

The objective of this study was to assess the safety and PK of the study drug in a pediatric population. Descriptive statistics for the efficacy endpoints were used to evaluate compliance with treatment for the purpose of assessing safety. The efficacy endpoints included the following:

- Complete cure, defined as 0% clinical involvement of the target toenail and negative KOH examination and fungal culture at Week 52
- Complete or almost-complete cure at Week 52, defined as ≤5% toenail involvement, negative KOH examination, and negative fungal culture of the target great toenail
- Clinical efficacy rate at Week 52, defined as involvement of <10% of the target great toenail
- Mycologic cure rate at Week 52, defined as negative KOH examination and negative fungal culture of the target great toenail

Efficacy endpoints for the safety, PK, and non-PK populations were analyzed using descriptive statistics (sample size, frequency counts, and percentages).

The change from baseline in the percentage affected toenail area was summarized at Weeks 12, 24, 36, 48, and 52 (4-week post-treatment follow-up). In addition, the growth of the target great toenail at each study visit and the change from baseline in the number of affected nontarget toenails were summarized descriptively (sample size n, mean, SD, median, Q1, Q3, maximum, and minimum) at the corresponding visits for the safety, PK, and non-PK populations.

A last observation carried forward imputation was performed to impute missing values for the efficacy variables in each of the analysis populations. No sensitivity analysis was planned or conducted.

All AEs occurring during the study were recorded and classified using the Medical Dictionary for Regulatory Activities (version 19.0). Events that occurred or worsened on or after the date of the first application of the

study drug were considered treatment-emergent adverse events (TEAEs). All TEAEs were summarized by the number of subjects reporting the events, the associated system organ class and preferred term, severity, seriousness, and relationship to the study drug for the safety, PK, and non-PK populations. Each subject was counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category.

The plasma concentrations of efinaconazole and its metabolites (H3 and H4) at each scheduled sampling time point and the PK parameters were summarized for the PK analysis set using descriptive statistics (n, number of quantifiable concentrations, mean, SD, standard error of the mean, percentage coefficient of variation, median, minimum, and maximum). Geometric means were also used to summarize the observed maximum drug concentration (C_{max}) and observed minimum drug concentration (C_{min}) following multiple dosing, AUC from time 0 to the sampling time corresponding to the last quantifiable concentration (AUC_{0-t}), and the AUC from time 0 to 24 hours (AUC_{0-24}). The individual plasma concentrations for each subject were recorded.

8.1.2. Study Results

Compliance With Good Clinical Practices

This study was in compliance with Good Clinical Practices as established by guidelines of the International Council for Harmonisation.

Financial Disclosure

In compliance with 21 CFR 54—Financial Disclosure by Clinical Investigators (final rule published on February 2, 1998 [63 FR 5233] and subsequently revised on December 31, 1998 [63 FR 72171]; hereafter collectively referred to as “the rule”), financial interest information is provided for clinical investigators participating in studies covered by the rule.

The disclosure certification shows no financial agreements by the investigators.

Patient Disposition

Overall, 163 pediatric subjects were screened and 62 were enrolled in the study. Of the 62 enrolled subjects, 60 (96.8%) administered at least one application of the study drug; 18 of those subjects were in the PK subset and 42 were in the non-PK subset. A total of 50 subjects (80.6%) completed the study and 12 subjects (19.4%) discontinued. The subjects who discontinued were withdrawn by a parent/legal guardian (six subjects), were lost to follow-up (five subjects), or withdrew consent (one subject).

Table 8. Subject Disposition (All Enrolled Subjects)

	Efinaconazole Solution (N = 62) n (%)
Treatment Completion	
Completed	54 (87.1)
Discontinued	6 (9.7)
Primary Reason for Treatment Discontinuation[a]	
Lost to Follow-Up	4 (66.7)
Withdrawal by Parent/Guardian	2 (33.3)
Study Completion	
Completed	50 (80.6)
Discontinued	12 (19.4)
Primary Reason for Study Discontinuation[a]	
Lost to Follow-Up	5 (41.7)
Withdrawal by Parent/Guardian	6 (50.0)
Subject Request	1 (8.3%)

Source: Applicant's submission study report V01-108A-401.
The N in the header represents the total number of subjects enrolled; percentages are based on this total unless otherwise noted
[a] Percentages are based on the total number of subject discontinuations

Of the 62 subjects enrolled in the study, 2 (3.2%) did not apply the study drug and were excluded from all analysis populations; 17 (27.4%) administered at least one application of the study drug, were in the PK subset, had PK data for Days 28/29, and were included in the PK population. Also, 42 subjects (67.7%) administered at least one application of the study drug, were not in the PK subset, and therefore were included in the non-PK population.

Table of Demographic Characteristics

The 60 subjects in the safety population had a mean age of 13.4 years (range, 6 to 16 years), were primarily male (66.7%), primarily white (88.3%), and primarily Hispanic or Latino (76.7%) (Table 9). The target great toenail was on the left foot of 53.3% of the subjects and on the right foot of 46.7% of the subjects.

Table 9. Demographic and Baseline Characteristics (Safety Population)

Demographic Parameters	JUBLIA Solution (N=60) n (%)
Sex	
Male	40 (66.7%)
Female	20 (33.3%)
Age	
Mean years (SD)	13.4 (2.29)
Median (years)	14.0
Min, max (years)	6, 16
Race	
White	53 (88.3%)
Black or African American	6 (10.0%)

Other	1 (1.7%)
Ethnicity	
Hispanic or Latino	46 (76.7%)
Not Hispanic or Latino	14 (23.3%)
Target great toenail, n (%)	
Left	32 (53.3%)
Right	28 (46.7%)

Abbreviation: SD, standard deviation
Race is presented only for those races that accounted for at least one subject

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

No remarkable medical condition was reported at baseline. The historical conditions reported at the highest frequency in each population were seasonal allergy (18.3% of the subjects in the safety population and 21.4% in the non-PK population) and dysmenorrhea and tinea pedis (11.8% of the subjects in the PK population reported each condition).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There were no remarkable concomitant medications reported. The individual concomitant medication reported at the highest frequency in all three populations was paracetamol (21.7% in the safety population, 41.2% in the PK population, and 14.3% in the non-PK population).

Efficacy Results: Primary Endpoint

Efficacy was evaluated using the descriptive statistics for the safety population. No hypothesis testing was conducted.

The primary endpoints for this study mirror those in the adult approval studies. Complete cure was defined as 0% clinical involvement of the target toenail and negative KOH examination and negative fungal culture of the target great toenail. The complete cure rate was 40% in this study.

Table 10. Summary of Key Efficacy Results (Safety Population LOCF)

Week 52	N	Success n (%)	Failure n (%)
Complete cure[1]	60	24 (40)	36 (60)
Complete or almost complete cure[2]	60	25 (41.7)	35 (58.3)
Clinical efficacy[3]	60	30 (50)	30 (50)
Mycological cure[4]	60	39 (65)	21 (35)

[1] Complete cure was defined as 0% clinical involvement of the target toenail, a negative KOH examination, and a negative fungal culture of the target great toenail
[2] Complete or almost-complete cure was defined as ≤5% great toenail involvement, a negative KOH examination, and a negative fungal culture of the target great toenail
[3] Clinical efficacy was defined as <10% of the target great toenail affected
[4] Mycological cure was defined as a negative KOH examination and a negative fungal culture of the target great toenail
Abbreviations: LOCF, last observation carried forward; KOH, microscopic potassium hydroxide

Reviewer's comment: The findings in this clinical study are similar to those in the adult studies for approval, although no hypothesis testing can be performed nor proper comparisons can be made.

Persistence of Effect

The clinical study evaluated primary and secondary efficacy endpoints at Weeks 12, 24, 36, and 48 to the conclusion of Week 52. A trend of efficacy is seen but no statistical evaluation was conducted.

8.1.3. Integrated Assessment of Effectiveness

This was an open-label safety study with efficacy assessment to evaluate compliance with treatment as part of the safety assessment. No hypothesis testing was completed for the efficacy variables. No comparison of this open-label study can be performed.

8.2. Review of Safety

8.2.1. Review of Safety Database

A brief summary of the safety data is presented. Of the 60 subjects included in the safety population, 38 (63.3%) experienced a total of 99 TEAEs. No subject died or discontinued the study as a result of a TEAE. One subject experienced a serious TEAE (pneumonia); the SAE was not considered by the investigator to be treatment related. All of the subjects who experienced TEAEs reported events of mild (31 subjects) or moderate (seven subjects) severity. Overall, two subjects experienced a total of eight TEAEs that were considered by the investigator to be treatment related; all eight TEAEs were evaluated as ingrowing nail.

Overall Exposure

In the safety population, subjects applied an average of 32.452 g of the study drug over an average of 315.6 days. In the PK population, subjects applied an average of 51.087 g of the study drug over an average of 339.6 days. Finally, in the non-PK population, subjects applied an average of 25.394 g of the study drug over an average of 313.3 days.

Adequacy of Safety Database

The safety database is adequate for the evaluation of pediatric safety for the purpose of labeling.

8.2.2. Adequacy of Applicant's Clinical Safety Assessments

Standard safety evaluations were used in this pediatric trial for onychomycosis. The protocol was discussed with and agreed upon by the FDA.

8.2.3. Safety Results

Serious Adverse Events

No subject died. A total of two nonfatal SAEs occurred during the study (ankle fracture and pneumonia). No subject discontinued the study because of an AE.

Significant Adverse Events

Most of the individual TEAEs were experienced by one or two subjects each (i.e., 1.7 to %-3.3% of the subjects). The only events occurring in more than two subjects each, regardless of severity or relationship to the study drug, were as follows:

- Nasopharyngitis (18 subjects [30.0%])
- Headache (six subjects [10.0%])
- Influenza (five subjects [8.3%])
- Contusion, ingrowing nail, nail injury, and tinea pedis (four subjects [6.7%] each)
- Food poisoning (three subjects [5.0%])

Treatment-Emergent Adverse Events and Adverse Reactions

All of the TEAEs were of mild or moderate severity; no subject experienced a severe TEAE. A total of eight TEAEs was reported by two subjects; all eight TEAEs were coded as ingrowing nail.

Laboratory Findings

No observed changes in laboratory findings were noteworthy.

Vital Signs

No significant changes in vital signs were measured.

Local Skin Reactions

Local skin reactions of redness, swelling, burning, itching, and vesiculation were evaluated throughout the study. Note that redness and swelling were reported as none, mild, moderate, or severe; burning, itching, and vesiculation were reported only as absent or present.

No subject experienced itching or vesiculation at any study visit. Overall, one subject ((b) (6)) experienced both mild redness and mild swelling at Week 28, one subject (b) (6) experienced mild swelling at Weeks 36 and 48, one subject experienced burning at Week 24 ((b) (6)), and one subject experienced burning at Week

36 (b) (6)). No other instance of redness, swelling, or burning was reported during the study and no safety signal or trend associated with local skin reactions was observed.

8.2.4. Integrated Assessment of Safety

No safety signal or trend was evident based on a review of the safety database for this study. No new safety issue was discovered in this pediatric study. Labeling should mirror that for adults.

8.3. Conclusions and Recommendations

Based on the PMR study V01-108A-401, the pediatric safety data provided are acceptable for labeling. Supplement -009 is acceptable for approval.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee was not required for this supplement.

10 Pediatrics

The Pediatric Review Committee reviewed the submitted supplement and agreed that the Applicant can be released from the PMR for this pediatric study.

11 Labeling Recommendations

6 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a draft of the label. The final labeling will be attached to the approval letter.

12 Risk Evaluation and Mitigation Strategies

N/A

13 Postmarketing Requirements and Commitment

N/A

14 Division Director (DHOT) Comments

N/A

15 Division Director (OCP) Comments

N/A

16 Division Director (OB) Comments

N/A

17 Division Director (Clinical) Comments

N/A

18 Office Director (or Designated Signatory Authority) Comments

N/A

19 Appendices

19.1. References

See footnotes

19.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): V01-108A-401 entitled "A Multicenter, Open Label, Single-arm Study Evaluating the Safety and Pharmacokinetics of Efinaconazole 10% Topical Solution in Subjects with Mild to Severe Onychomycosis of the Toenails"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 12		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
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: 2 Significant payments of other sorts: none Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in study: none Sponsor of covered study: none		
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) none		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

N/A

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

Method: Liquid chromatography/mass spectrometry/mass spectrometry
Matrix: Human plasma

Table 11. Bioanalytical method validation parameters

Analyte	Linear Range (ng/mL)	LLOQ (ng/mL)	Intra-Day Accuracy (%)	Intra-Day Precision (%)	Study Identifier
IDP-108	0.1 - 100	0.1	99.7 - 107.2	1.4 – 3.8	
H3	0.1 - 100	0.1	97.7 - 102.0	1.9 – 3.5	DCN4003594[1]
H4	0.1 - 100	0.1	100.3 – 105.6	5.3 – 16.6	

[1] The bioanalytical methods applied in Study V01-108A-401 are the same validated methods used in the original NDA (ATM-1824, validation revision to ATM-1824, original revision) with minor changes in the high-performance liquid chromatography system (such as changes in pump flow rate and injection volume).
Abbreviations: H3, metabolite H3; H4, metabolite H4; IDP-108, efinaconazole; LLOQ, lower limit of quantification

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