

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204427Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Application Number 204,427
Priority or Standard Standard

Submit Date July 29, 2013
Received Date July 29, 2013
PDUFA Goal Date July 29, 2014
Division / Office DDDP

Reviewer Name Milena Lolic, M.D., M.S.
Review Completion Date March 11, 2014

Established Name Tavaborole solution 5%
Trade Name Kerydin
Therapeutic Class Oxaborole antifungal
Applicant Anacor Pharmaceuticals Inc.

Formulation Solution
Dosing Regimen Daily for 48 weeks
Indication Onychomycosis
Intended Population Adults

Template Version: [March 6, 2009](#)

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	7
1.1	Recommendation on Regulatory Action	7
1.2	Risk Benefit Assessment	7
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies	8
1.4	Recommendations for Postmarket Requirements and Commitments	8
2	INTRODUCTION AND REGULATORY BACKGROUND	9
2.1	Product Information	9
2.2	Currently Available Treatments for Proposed Indication	10
2.3	Availability of Proposed Active Ingredient in the United States	12
2.4	Important Safety Issues with Consideration to Related Drugs	12
2.5	Summary of Presubmission Regulatory Activity Related to Submission	12
2.6	Other Relevant Background Information	13
3	ETHICS AND GOOD CLINICAL PRACTICES	13
3.1	Submission Quality and Integrity	13
3.2	Compliance with Good Clinical Practices	13
3.3	Financial Disclosures	27
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	28
4.1	Chemistry Manufacturing and Controls	28
4.2	Clinical Microbiology	29
4.3	Preclinical Pharmacology/Toxicology	33
4.4	Clinical Pharmacology	34
4.4.2	Pharmacodynamics	35
4.4.3	Pharmacokinetics	35
5	SOURCES OF CLINICAL DATA	38
5.1	Tables of Studies/Clinical Trials	38
5.2	Review Strategy	39
5.3	Discussion of Individual Studies/Clinical Trials	40
6	REVIEW OF EFFICACY	48
	Efficacy Summary	48
6.1	Indication	49
6.1.1	Methods	49
6.1.2	Demographics	50
6.1.3	Subject Disposition	51
6.1.4	Analysis of Primary Endpoint	52
6.1.5	Analysis of Secondary Endpoints(s)	53
6.1.6	Other Endpoints	55

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

6.1.7	Subpopulations	55
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	56
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	56
6.1.10	Additional Efficacy Issues/Analyses	57
7	REVIEW OF SAFETY.....	59
	Safety Summary	59
7.1	Methods.....	60
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	60
7.1.2	Categorization of Adverse Events.....	63
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	63
7.2	Adequacy of Safety Assessments	63
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	63
7.2.2	Explorations for Dose Response.....	65
	Study AN2690-ONYC-200/200A	68
7.2.3	Special Animal and/or In Vitro Testing	70
7.2.4	Routine Clinical Testing	70
7.2.5	Metabolic, Clearance, and Interaction Workup	71
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	71
7.3	Major Safety Results	71
7.3.1	Deaths.....	71
7.3.2	Nonfatal Serious Adverse Events	72
7.3.3	Dropouts and/or Discontinuations	75
7.3.4	Significant Adverse Events	77
7.3.5	Submission Specific Primary Safety Concerns	78
7.4	Supportive Safety Results	80
7.4.1	Common Adverse Events	80
7.4.2	Laboratory Findings	82
7.4.3	Vital Signs.....	83
7.4.4	Electrocardiograms (ECGs)	83
7.4.5	Special Safety Studies/Clinical Trials.....	84
7.4.6	Immunogenicity.....	87
7.5	Other Safety Explorations.....	87
7.5.1	Dose Dependency for Adverse Events	87
7.5.2	Time Dependency for Adverse Events.....	88
7.5.3	Drug-Demographic Interactions	89
7.5.4	Drug-Disease Interactions.....	91
7.5.5	Drug-Drug Interactions.....	91
7.6	Additional Safety Evaluations	92
7.6.1	Human Carcinogenicity	92
7.6.2	Human Reproduction and Pregnancy Data.....	92
7.6.3	Pediatrics and Assessment of Effects on Growth	93

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	95
7.7	Additional Submissions / Safety Issues	95
8	POSTMARKET EXPERIENCE.....	95
9	APPENDICES	96
9.1	Literature Review/References	96
9.2	Labeling Recommendations	96
9.3	Advisory Committee Meeting.....	96
9.4.	Clinical Investigator Financial Disclosure	96

Table of Tables

Table 1	List of Investigators for Trial 301	14
Table 2	List of Investigators for Trial 302	20
Table 3	Minimum Inhibitory Concentration for AN2690, and Comparator Drugs Against 19 Test Strains of Fungi	30
Table 4	MIC and MFC (in µg/mL) of AN2690 in Clinical Isolates	30
Table 5	Summary of Mycology Results for Phase 3 Trials.....	31
Table 6	Tavaborole Susceptibility against Screening Isolates	32
Table 7	Tavaborole Susceptibility from Last Isolates	32
Table 8	Pharmacokinetic Parameters for Tavaborole Solution 5%.....	36
Table 9	Tavaborole Clinical Studies	38
Table 10	Phase 3 Trial Schedule.....	43
Table 11	IGA Scale from Phase 3 Trials.....	45
Table 12	Local Tolerability Scale from Phase 3 Trials.....	47
Table 13	Analysis Sets	49
Table 14	Baseline Demographics-ITT	50
Table 15	Baseline Disease Characteristics-ITT	50
Table 16	Disposition of Subjects-ITT	51
Table 17	Primary Endpoint Analysis	52
Table 18	Complete Cure Rates under Missing Data Sensitivity Analyses	53
Table 19	Secondary Endpoints Analysis.....	53
Table 20	Trials Used for Safety Assessment.....	61
Table 21	Demographics-Safety Population.....	63
Table 22	Summary of AEs-Trial 201	66
Table 23	Summary of AEs-Trial 203.....	68
Table 24	Summary of AEs-Trial 200/200A.....	69
Table 25	SAE in Tavaborole Solution 5% Arm-Phase 3	72
Table 26	SAE in Vehicle Arm-Phase 3	73
Table 27	SAEs from Phase 2 Trials	74
Table 28	Subject Discontinuations.....	75
Table 29	Summary of AEs Leading to Subject Discontinuation from the Trials	76
Table 30	Treatment Discontinuations.....	76
Table 31	Severe Adverse Reactions	77
Table 32	Application Site Reactions	78
Table 33	Number of Subjects with Local Signs and Symptoms.....	79
Table 34	Distribution of Severe Local Signs and Symptoms	79
Table 35	Most Common AEs Occurring in >1% of Subjects.....	80
Table 36	Adverse Events Occurring in >2% of Tavaborole –Treated Subjects and at the Greater Frequency that Vehicle	81
Table 37	Laboratory Findings Occurring in >2 Tavaborole –Treated Subjects and at the Greater Frequency that Vehicle	83
Table 38	Summary of Mean Cumulative Data (Irritation Phase).....	85

Table of Figures

Figure 1	Approved Drugs for Onychomycosis Treatment.....	11
Figure 2	Trial Flow	41
Figure 3	Complete Cure Rates over Time.....	57
Figure 4	Efficacy by Analysis Center (Trial 301)	58
Figure 5	Efficacy by Analysis Center (Trial 302)	58
Figure 6	Number of Subjects Exposed to Tavaborole.....	65
Figure 7	Subjects Disposition.....	75

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that NDA 204,427 Kerydin (tavaborole solution, 5%) be approved for the treatment of onychomycosis of the toenail caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.

Two phase 3 trials (AN2690-ONYC-301 and AN2690-ONYC-302) demonstrated the efficacy and safety of tavaborole solution, 5% for adult patients with toenail onychomycosis caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.

This reviewer's recommended indication differs from the (b) (4) that the applicant proposes. The recommended indication is based on the population which was studied and for whom the safety and effectiveness has been demonstrated:

1. Safety and efficacy of Kerydin was studied in subjects with onychomycosis of toenails (b) (4)
2. The submission characterized the mycology and susceptibility of strains of *Trichophyton rubrum* and *Trichophyton mentagrophytes* obtained from clinical isolates of subjects treated with Kerydin. (b) (4)

1.2 Risk Benefit Assessment

The risk to benefit assessment for this application is based on the clinical trial results.

The primary efficacy endpoint, defined as the proportion of subjects with complete cure of toenail onychomycosis at Week 52, was achieved by 7% of subjects treated with Kerydin in trial 301 and by 9% in trial 302. Complete cure for vehicle-treated subjects was 1% and 2% for respective trials ($p \leq 0.001$). The analysis of secondary endpoints (mycological cure and treatment success) supported the primary endpoint. While modest, the observed treatment effect is comparable to the only other approved topical product in USA for the treatment of toenail onychomycosis (Penlac® (ciclopirox) topical solution 8%).

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

In two pivotal phase 3 clinical trials, the most common adverse reactions were application site reactions (rate occurrence 7%) and ingrown toenail (3%), and the vast majority of which were mild to moderate in intensity and resolved spontaneously. Severe reactions were rare and did not differ between the groups (0.6% and 0.5% for active and vehicle). The incidence of serious adverse events (SAE) was similar between subjects treated with Kerydin and vehicle (2.5% versus 2.4%, respectively). None of the SAEs appear to be related to the treatment. The safety review of supportive trials from phase 2 was comparable to pivotal trials.

In conclusion, benefits outweigh the risks for the recommended indication. If approved, Kerydin could offer an additional therapeutic option for toenail onychomycosis. Topical tavaborole 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 topical treatment required for Penlac® use. The adverse events associated with the drug product can be adequately informed by labeling. The label also provides adequate information for instructions for use.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for a specific postmarketing risk management plan beyond labeling. Routine risk minimization measures such as professional labeling, prescription status, and spontaneous adverse event reporting, comprise an adequate risk management plan for this application.

1.4 Recommendations for Postmarket Requirements and Commitments

Kerydin was studied in the adult population only. [REDACTED] (b) (4)
[REDACTED] (7.6.3 Pediatrics
and Assessment of Effects on Growth).

The request [REDACTED] (b) (4) was presented to Pediatric Review Committee (PeRC) on February 5, 2014. The Committee agreed with the Division [REDACTED] (b) (4)
[REDACTED] recommended a partial waiver for subjects less than 6 years of age.

It is my recommendation that partial waiver be granted for pediatric subjects less than 12 years of age. The decision is based on section 505B (a)(4)(B)(iii) of the Pediatric Research Equity Act where the Agency may grant the partial waiver if the drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and (2) is not likely to be used by a substantial number of pediatric patients in that age group). The cut off age of 12 years is

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

based on literature review. For full discussion on the selected age recommended for partial waiver see Section 7.6.3.

Given that adult studies are complete and ready for approval, I recommend that a deferral to conduct studies in pediatric subjects 12-18 years is warranted. Due to similar clinical presentation of toenail onychomycosis in adults and adolescents, drug effectiveness can be extrapolated from adults; however a safety study is needed to address potential differences in systemic bioavailability and local tolerability. Thus, my recommendation is that the following PMR be attached to this NDA approval:

1. Pharmacokinetic/safety/tolerability trial in pediatric subjects with toenail onychomycosis ages 12 years to 17 years 11 months.

2 Introduction and Regulatory Background

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 onychomycosis¹. Older age, tinea pedis, and immunodeficiency are some of the risk factors for acquiring onychomycosis.

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*².

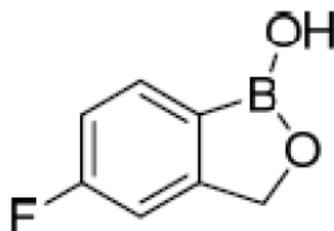
The clinical manifestations of onychomycosis include separation of the nail plate from the nail bed (onycholysis), subungual hyperkeratosis, and changes in the nail plate that make it thicker, brittle, and discolored. Symptoms include toenail discomfort when walking including pain and social embarrassment.

Treatment may be indicated from both medical and psychosocial perspectives. Without treatment, the disease can cause 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).

2.1 Product Information

Tavaborole is a (b) (4) boronic acid complex (5-fluoro-1, 3-dihydro-1-hydroxy-2,1-benzoxaborole) with molecular weight of 151.93 Da. Its structural formula is:

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%



The composition of tavaborole topical solution, 5% is presented below:

Components	Quality Standard	Function	Concentration (% w/w)
Tavaborole	In-house	Active	5.00
Alcohol	USP	[REDACTED]	(b) (4)
Propylene Glycol	USP		
Edetate Calcium Disodium	USP		

Source: Applicant's Table 1 from 3.2.P1

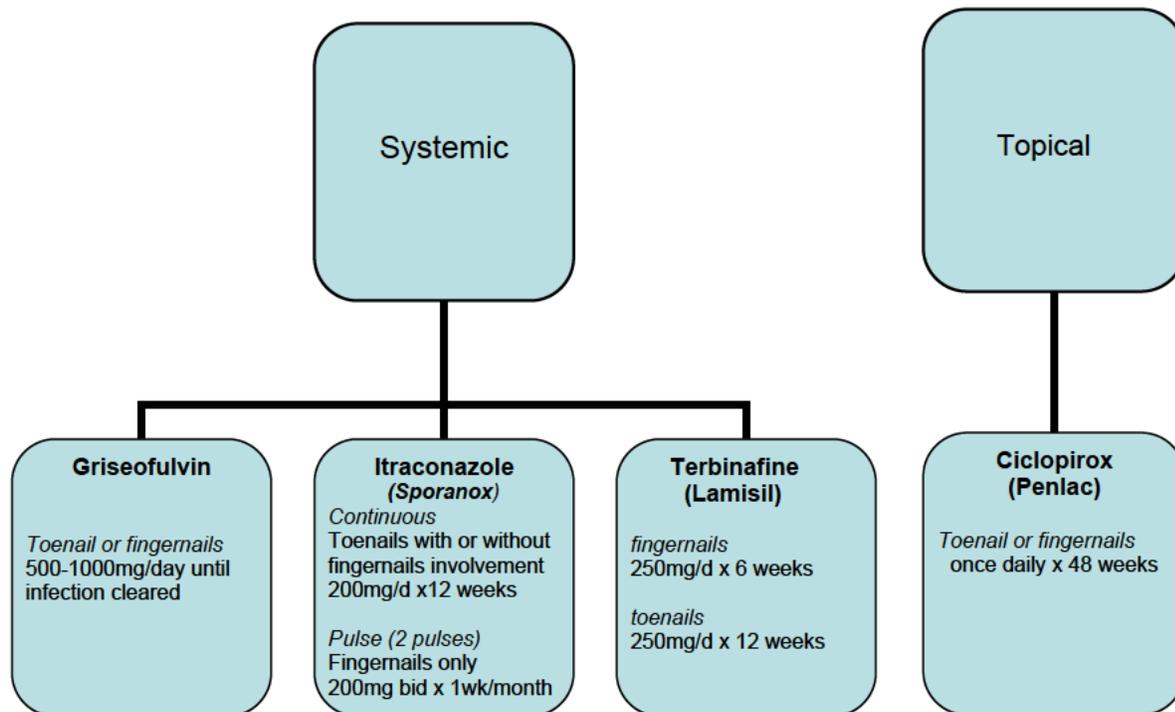
There are no novel excipients used in the drug product.

τ

2.2 Currently Available Treatments for Proposed Indication

The treatment duration of onychomycosis is often long as the disease is difficult to eradicate and has a tendency to recur³. Current therapeutic approaches include mechanical or chemical nail avulsion, topical therapy, oral therapy, or a combination of these treatment modalities⁴. 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.

Figure 1 Approved Drugs for Onychomycosis Treatment



Systemic therapy includes oral agents (e.g., Lamisil®, Sporanox®) which have efficacy rates of 14%-38 %. There is only one topical agent -Penlac®, approved in USA in 1999 for onychomycosis. However, Penlac® has lower efficacy than oral agents (about 8%) and it's labeling requires regular debridement of the nail by a health professional as adjunctive therapy.

The major efficacy issue with development of topical treatments for onychomycosis to date is achievement of sufficient drug concentrations at the nail bed due to poor nail permeability.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

2.3 Availability of Proposed Active Ingredient in the United States

Tavaborole is a new molecular entity thus not available in the United States and has not been marketed in any other country.

2.4 Important Safety Issues with Consideration to Related Drugs

There are no related drugs to tavaborole as it belongs to a new therapeutic class of oxaborols. There are safety issues related to all other approved drugs for onychomycosis treatment.

Major concerns with griseofulvin are hypersensitivity and numerous drug-drug interactions. Itriconazole and terbinafine may induce hepatotoxicity and require that liver function tests be monitored during the treatment. Additionally, itraconazole has a boxed warning for multiple drug interactions and CHF.

The only topical agent, ciclopirox may cause irritation of the periungual area, observed in 5% of patients.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relevant pre-submission regulatory activity for tavaborole (AN2690) was notable for the following:

- Pre-IND Meeting October 3, 2005
- Guidance Meeting June 11, 2007
 - The population studied will be reflected in labeling.
- Guidance Meeting August 13, 2008
- End-of-Phase 2 Meeting October 8, 2009. Division comments included:
 - Evaluation of the primary endpoints at Week 52 after 48 weeks of treatment appears acceptable
 - The proposed primary endpoint, complete cure of the target great toenail is acceptable
- SPA received August 4, 2010 and the Agreement Letter sent on September 13, 2010
- Guidance Meeting November 14, 2012
 - The Division will consider a partial waiver from pediatric studies that is supported by evidence
- Pre-NDA Meeting May 13, 2013

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

Comment: The content of this NDA is consistent with the prior agreements with the Division.

2.6 Other Relevant Background Information

Tavaborole solution 5% was developed by Anacor Pharmaceuticals. The code name was designated as AN2690. Schering Plough was also involved with part of the clinical development and the code name for that phase was SCH 900340.

Throughout the clinical review, the terms tavaborole, tavaborole solution 5 %, and AN2690 reflect the same product and are used interchangeably.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission was acceptable.

3.2 Compliance with Good Clinical Practices

The applicant affirmed that the studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) harmonized tripartite guidelines for Good Clinical Practice and the compliance with local and FDA regulatory requirements. The protocol and Informed Consent Forms were reviewed by the Investigations Review Board (IRB) associated with the trial sites or by consulting central IRB. Written informed consents were obtained from subjects at the first (baseline) visit.

The Division of Scientific Investigators (DSI) was consulted to review the conduct of both clinical trials, and included the inspections of site 301-122 in Baltimore, MD and site 302-325 in Evansville, IN. Both sites were selected by the Division based on high number of patients enrolled and the high number of treatment responders.

DSI inspections of the trial sites have been completed but the review is pending.

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Table 1 List of Investigators for Trial 301

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
101	Primary Investigator: Terry M. Jones	J & S Studies, Inc. 1710 Crescent Pointe Parkway College Station, TX 77845 USA Telephone: (979) 776-7546
102	Primary Investigator: Phoebe Rich	Oregon Dermatology & Research Center 2565 NW Lovejoy Street, Suite 200 Portland, OR 97210 USA Telephone: (503) 226-3376
103	Primary Investigator: Richard A. Pollak	Endeavor Clinical Trials, PA 8042 Wurzbach Road, Suite 420 San Antonio, TX 78229 USA Telephone: (210) 949-0807
104	Primary Investigator: Howard Sofen	Dermatology Research Associates 8930 S. Sepulveda Blvd #114 Los Angeles, CA 90045 USA Telephone: (310) 337-7171
105	Primary Investigator: Steven E. Kempers	University of Minnesota Minnesota Clinical Study Center 7205 University Avenue, NE Fridley, MN 55432 USA Telephone: (763) 571-4200

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
106	Primary Investigator: Raza Aly	University of California San Francisco Department of Dermatology Mount Zion Medical Center 1701 Divisadero Street, 3rd Floor San Francisco, CA 94115 USA Telephone: (415) 353-9684
108	Primary Investigator: Steven R. Feldman	Department of Dermatology Wake Forest University Health Sciences 4618 Country Club Road Winston-Salem, NC 27104 USA Telephone: (336) 716-3775
110	Primary Investigator: Michael T. Jarratt	DermResearch, Inc. 8140 North Mopac Bldg. 3, Suite 120 Austin, TX 78759 USA Telephone: (512) 502-9324
111	Primary Investigator: Robert J. Kaylor	Deaconess Clinic 421 Chestnut Street Evansville, IN 47713 USA Telephone: (812) 426-6697
112	Primary Investigator: Michael J. Noss	Radiant Research, Inc. 11500 Northlake Drive, Suite 320 Cincinnati, OH 45249 USA Telephone: (513) 247-5588
113	Primary Investigator: Carlos Petit	Radiant Research 6300 Glenwood Street, Bldg 10, Suite 100 Overland Park, KS 66202 USA Telephone: (913) 599-3333

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
114	Primary Investigator: Joel Schlessinger	Advanced Skin Research Center 2802 Oak View Mall Drive Omaha, NE 68144 USA Telephone: (402) 334-7546
115	Primary Investigator: George J. Schmieder	Park Avenue Dermatology, PA 906 Park Avenue Orange Park, FL 32073 USA Telephone: (904) 541-0315
116	Primary Investigator: Michael A. Schneider	Dermatology East 1335 Cordova Cove Germantown, TN 38138 USA Telephone: (901) 756-8763
117	Primary Investigator: Teresa S. Sligh	Translational Research Group, Inc. (dba Providence Clinical Research) 6400 Laurel Canyon Boulevard, Suite 300A North Hollywood, CA 91606 USA Telephone: (818) 558-7555
119	Primary Investigator: Dowling B. Stough, IV	Burke Pharmaceutical Research 3633 Central Avenue, Suite 1 Hot Springs, AR 71913 USA Telephone: (501) 620-4449
120	Primary Investigator: James M. Swinehart	Colorado Dermatology Center 950 East Harvard Avenue, Suite 630 Denver, CO 80210 USA Telephone: (303) 744-1202
121	Primary Investigator: John H. Tu	Skin Search of Rochester, Inc 100 White Spruce Boulevard Rochester, NY 14623 USA Telephone: (585) 697-1818

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
122	Primary Investigator: Max Weisfeld	Mid Atlantic Research Center for Health (MARCH) Hamilton Foot Care 5508 Harford Road Baltimore, MD 21214 USA Telephone: (410) 426-5508
123	Primary Investigator: William P. Werschler	Premier Clinical Research 104 W 5th Avenue #320 Spokane, WA 99204 USA Telephone: (509) 343-3710
124	Primary Investigator: David C. Wilson	The Education & Research Foundation, Inc. (ERF) 2095 Langhorne Road Lynchburg, VA 24501 USA Telephone: (434) 847-8400
125	Primary Investigator: Fran E. Cook-Bolden	Skin Specialty Dermatology 150 E 58th Street, 3rd Floor Annex New York, NY 10155 USA Telephone: (212) 223-6599
126/526	Primary Investigator: Diane McConnehey	Northwest Clinical Trials 7373 W. Emerald Street Boise, ID 83704 USA Telephone: (208) 577-5380
127	Primary Investigator: Jennie J. Muglia	Rhode Island Hospital 593 Eddy Street Jane Brown South 1, Room 115 Providence, RI 02903 USA Telephone: (401) 444-7853

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
129	Primary Investigator: Dale M. Levinsky	Genova Clinical Research 1925 W. Orange Grove Road, Suite 303 Tucson, AZ 85704 USA Telephone: (520) 219-6394
131	Primary Investigator: Robert S. Haber	Haber Dermatology & Cosmetic Surgery, Inc. 14077 Cedar Road, Suite 200 South Euclid, OH 44118 USA Telephone: (216) 932-5200
132	Primary Investigator: Francisco Flores	FXM Research Miramar 3000 SW 148th Avenue, Suite 216 Miramar, FL 33027 USA Telephone: (954) 430-1097
200	Primary Investigator: Mirna E. Toledo Bahena	IMIC Durango No. 216, Col. Roma Mexico, D.F. 6700 Mexico Telephone: 52-55331566
202	Primary Investigator: Remigio F. Gonzalez Soto	Centro de Dermatologia de Monterrey Paseo de los Leones No. 603-D esquina Oguinaga Monterrey, Nuevo Leon 64460 Mexico Telephone: 52-81-8347-1977
203	Primary Investigator: Jorge de Jesus Ocampo Candiani	Hospital Universitario "Dr José Eleuterio. González" Av. Francisco I. Madero Pte s/n y Av. Gonzalitos Col. Mitras Centro, Monterrey, Nuevo Leon C.P. 64460, México Mexico Telephone: 52-81-8348-1465

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
204	Primary Investigator: Benjamin Moncada Gonzalez	Hospital Central "Dr. Ignacio Morones Prieto" Av. Venustiano Carranza No. 2395 Zona Universitaria Col. Los Filtros, San Luis Potosi, S.P.L.P.C. 78240 Mexico Telephone: 52-444-834-2795
206	Primary Investigator: Carlos A. Mena-Cedillos	Clinical Research Institute S.C. Boulevard Manuel Avila Camacho #1994 Depto 1103 Col. San Lucas Tepetlaco, Tlalnepantla, Edo. De Mexico C.P. 54055 Mexico Telephone: 52-55-5362-7780
207	Primary Investigator: Luis Hernandez-Batalla	Hospital de Jesús Av. 20 de Noviembre #82, Col. Centro Ala Mesones 2º Piso, Cardiología C.P. 06090, Mexico, D.F. Mexico Telephone: 52-55-5542-6501

Source: Applicant's Table 30 from 5.2

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Table 2 List of Investigators for Trial 302

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
301	Primary Investigator: Scott Ashton	Ashton Podiatry Assoc. PA 11613 N. Central Expressway, Suite 121 Dallas, TX 75243 USA Telephone: (214) 691-0790
302	Primary Investigator: Steven A. Davis	Dermatology Clinical Research Center of San Antonio 7810 Louis Pasteur, Suite 200 San Antonio, TX 78229 USA Telephone (210) 614-3355
304	Primary Investigator: Boni E. Elewski	Department of Dermatology at Birmingham University of Alabama 2000 6th Avenue, South, 3rd Floor Birmingham, AL 35233 USA Telephone: (205) 502-9960
305	Primary Investigator: David P. Fivenson	David Fivenson, MD, PLC 3001 Miller Road Ann Arbor, MI 48103 USA Telephone: (734) 222-9630
306	Primary Investigator: Kimberly K. Grande	The Skin Wellness Center 10215 Kingston Pike #200 Knoxville, TN 37922 USA Telephone: (865) 251-9963

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
308	Primary Investigator: John Humeniuk	Radiant Research, Inc. 5-22A Memorial Drive Ext. Greer, SC 29650 USA Telephone: (864) 877-9239
309	Primary Investigator: Craig L. Leonardi	Central Dermatology, PC 1034 S Brentwood Blvd, Suite 600 St. Louis, MO 63117 USA Telephone: (314) 721-5565
310	Primary Investigator: Verlan T. Marshall	HOPE Research Institute 3900 E. Camelback Road, Suite 185 Phoenix, AZ 85018 USA Telephone: (602) 288-4673
311	Primary Investigator: Robert T. Matheson	Oregon Medical Research Center PC 9495 SW Locust Street, Suite G Portland, OR 97223-6683 USA Telephone: (503) 245-1525
312	Primary Investigator: Walter K. Nahm	Cabrillo Medical Center 7695 Cardinal Court, Suite 200 San Diego, CA 92123 USA Telephone: (858) 361-7300
313	Primary Investigator: Adnan Nasir	Wake Research Associates 3100 Duraleigh Road, Suite 304 Raleigh, NC 27612 USA Telephone: (919) 781-2514

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
314	Primary Investigator: Robert Nossa	The Dermatology Group P.C. 60 Pompton Avenue Verona, NJ 07044 USA Telephone: (973) 571-2121
315	Primary Investigator: Elyse S. Rafal	Derm Research Center of New York 2500 Route 347 Building 22A Stony Brook, NY 11790 USA Telephone: (631) 689-0300
316	Primary Investigator: Robert Shouey	Harrisonburg Foot & Ankle Clinic 401 University Blvd, Lower Level Harrisonburg, VA 22801 USA Telephone: (540) 434-2949
317	Primary Investigator: Kenneth Stein	Kenneth M. Stein Inc 1221 Farmers Lane, Suite 500 Santa Rosa, CA 95405 USA Telephone: (707) 542-1469
318	Primary Investigator: Leonard J. Swinyer	Dermatology Research Center Inc. 1548 East 4500 South, Suite 201 Salt Lake City, UT 84117 USA Telephone: (801) 269-0135
319	Primary Investigator: Eduardo H. Tschen	Academic Dermatology Associates 1203 Coal S.E., Suite B Albuquerque, NM 87106 USA Telephone: (505) 247-4220

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
320	Primary Investigator: Darryl S. Wong	Dermatology Specialists Inc. 3629 Vista Way Oceanside, CA 92056 USA Telephone: (760) 757-7546
321	Primary Investigator: Fred D. Youngswick	San Francisco Foot and Ankle Center 165 Rowland Way Suite 206 Novato, CA 94945 USA Telephone: (415) 898-9818
322	Primary Investigator: Javier Alonso-Llamazares	International Dermatology Research, Inc. 8370 W Flagler St., Suite 200 Miami, FL 33144 USA Telephone: (305) 225-0400
324	Primary Investigator: Douglas R. Schumacher	Radiant Research, Inc. 1275 Olentangy River Road, Suite 202 Columbus, OH 43212 USA Telephone: (614) 294-3854
325	Primary Investigator: Charles P. Hudson	Hudson Dermatology 3501 Washington Ave Evansville, IN 47714 USA Telephone: (812) 474-1234
326	Primary Investigator: Michael D. Tharp	Rush University Medical Center 1725 W. Harrison Street, Suite 264 Chicago, IL 60612 USA Telephone: (312) 563-4001

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
327	Primary Investigator: George J. Murakawa	Somerset Skin Centre 255 Kirts Boulevard, Suite 100 Troy, MI 48084 USA Telephone (248) 244-8448
328	Primary Investigator: Alexander Reyzelman	California School of Podiatric Medicine 2299 Post St. Suite 205 San Francisco, CA 94115 USA Telephone: (415) 292-0638
329	Primary Investigator: Mark Turner	Advanced Clinical Research 2950 E. Magic View Dr. Suite 182 Meridian, ID 83642 USA Telephone: (208) 377-8653
330	Primary Investigator: David M. Pariser	Virginia Clinical Research Inc. 601 Medical Tower Norfolk, VA 23507 USA Telephone: (757) 625-0151
331	Primary Investigator: Lawrence C. Parish	Parish Dermatology 1760 Market Street, Suite 301 Philadelphia, PA 19103 USA Telephone: (215) 563-8333
332	Primary Investigator: Daniel J. Piacquadio	Therapeutics Clinical Research 9025 Balboa Avenue, Suite 105 San Diego, CA 92123 USA Telephone (858) 571-6800

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
333	Primary Investigator: Othon H. Wiltz	FMX Research Corporation 11760 Bird Road, Suite 452 Miami, FL 33175 USA Telephone: (305) 220-5222
334	Primary Investigator: Harry Penny	Blair Medical Associates, Inc. Station Medical Center 1414 Ninth Avenue Altoona, PA 16602 USA Telephone: (814) 946-7569
335	Primary Investigator: Jonathan S. Weiss	Gwinnett Clinical Research Center Gwinnett Dermatology 2383 Pate Street Snellville, GA 30078 USA Telephone: (770) 972-2214
336	Primary Investigator: James A. Solomon	Advanced Dermatology & Cosmetic Surgery 725 West Granada Boulevard, Suite 44 Ormond Beach, FL 32174 USA Telephone: (386) 898-0547
401	Primary Investigator: Kirk A. Barber	Kirk Barber Research 1100 1 st Street SE, Suite #510 Calgary, AB T2G 1B1 Canada Telephone: (403) 299-5807
403	Primary Investigator: Rodion A. Kunyetz	Ultranova Skincare 125 Bell Farm Road, Suite 104 Barrie, ON L4M 6L2 Canada Telephone: (705) 722-4930

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
404	Primary Investigator: Charles W. Lynde	Lynderma Research Inc. 5762 Highway 7, Suite 201 Markham, ON L3P 1A8 Canada Telephone: (905) 471-8011
405	Primary Investigator: Simon Nigen	Innovaderm Research Inc. 1851 Sherbrooke St. East, Suite 502 Montreal, QC H2K 4L5 Canada Telephone: (514) 521-4285
406	Primary Investigator: Kim A. Papp	K. Papp Clinical Research Inc. 135 Union Street East Waterloo, ON N2J 1C4 Canada Telephone: (519) 579-9535
407	Primary Investigator: Yves Poulin	Centre de Recherche Dermatologique Centre de Dermatologique du Quebec Metropolitain 2880 Chemin des Quatre-Bourgeois, Suite 105 Quebec, QC G1V 4X7 Canada Telephone: (418) 650-3555
408	Primary Investigator: Les Rosoph	North Bay Dermatology Centre Site Ontario Medical School 500 Cassells Street North Bay, ON P1B 3Z7 Canada Telephone: (707) 476-3376
409	Primary Investigator: Norman Wasel	Stratica Medical 10140-117 Street Northwest, Suite 200 Edmonton, AB T5K 1X3 Canada Telephone (780) 428-5554

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Investigational Site Number	Primary Investigators	Investigational Site Name, Address, and Telephone Number
410	Primary Investigator: Alain Y Martel One subject enrolled that was transferred to investigational site 407 (Poulin)	Recherche Clinique CMC 2880 Quatre-Bourgeois, Suite 115 Quebec, QC G1V 4X7 Canada Telephone: (418) 563-2603
411	Primary Investigator: Christina Morin	Centre Podiatrique 550 de Mortagne Blvd., Suite 280 Boucherville, QC J4B 5E4 Canada Telephone: (450) 655-7155

Source: Applicant's table 31 from 5.2.

3.3 Financial Disclosures

Financial disclosure forms were reviewed, and all investigators reported no financial interests. The applicant certified in Form 3454 that they had not entered into any financial arrangements with any of the clinical investigators. It was also affirmed that none of the clinical investigators disclosed any proprietary interest in the product, or significant equity interest in the sponsor company. Certification was made that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f). See 9.4. Clinical Investigator Financial Disclosure.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Tavaborole is a white to off-white powder. Tavaborole topical solution, 5% is an alcohol/propylene glycol-based solution containing 5% tavaborole (w/w) or 43.5 mg/mL. All excipients are below approved levels listed in the FDA's database of inactive ingredients in approved drug products for topical administration. CMC review notes in Section 3 Characterization that "none of the potential impurities possess any of the structural alerts for mutagenicity, and no genotoxic impurities have been identified."

The solution is contained in a 12 mL amber glass bottle with a conventional dropper that is used to dispense the product on and around the affected nail. The proposed fill of solution is 10ml. The compatibility, suitability, functionality, and safety of the in-use container closure system with the drug product have been established.

Stability data support the proposed expiration period of 24 months when stored at 20-25 °C (68-77 °F). After insertion of the dropper upon initial use, the product should be discarded within 3 months.

Microbial limits testing for product release and stability was waived as the product is inherently antimicrobial and the applicant has performed suitable microbiological testing during development.

The Office of Compliance found that the compliance to the cGMP involving all facilities pertaining to the drug substance manufacturing and testing operations was acceptable.

In the Executive Summary of NDA 204427, the CMC reviewers Bogdan Kurtyka Ph.D, Nina Ni, Ph.D., and Gene W. Holbert, Ph.D. concluded:

"The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product."

Comment: The only outstanding review issues from the CMC perspective is agreed upon labeling.

(b) (4)

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

4.2 Clinical Microbiology

Diagnosis of onychomycosis is made by physical examination and confirmed by microscopic examination with KOH (potassium hydroxide) and culture. Most commonly toenail onychomycosis is caused by dermatophytes (60%) but it can also be caused by non-dermatophytes (20%), and yeast (20%)¹.

(b) (4)
[REDACTED], the microbiology reviewer, Dr. Grande-Roche, has determined that for labeling purposes tavaborole has been shown to be active against isolates of only *T. rubrum* and *T. mentagrophytes*.

In vitro testing of antimicrobial spectrum of tavaborole

The antimicrobial spectrum of activity was tested using the microbroth dilution method and the culture collection. In study 002-NCL PP-002-01 the *in vitro* activity of AN2690 against 19 test strains of fungi was tested in microbroth. The *in vitro* activity of tavaborole against clinical isolates of *Trichophyton rubrum* and *Trichophyton mentagrophytes* obtained from the culture collection was assessed in study 002-NCL PP-003-02.

The results of both studies are presented in the tables below. The MIC₉₀ (minimum inhibitory concentration) was defined as the lowest concentration that resulted in over 90% reduction of growth, as compared to a drug-free control. The MFC₉₀ (minimal fungicidal concentration) was defined as the lowest concentration that killed over 90% of the fungi, as compared to a drug-free control.

Table 3 Minimum Inhibitory Concentration for AN2690, and Comparator Drugs Against 19 Test Strains of Fungi.

Fungus	Broth used	MIC (µg/mL)				
		AN2690	Ciclopirox	Terbinafine	Fluconazole	Itraconazole
<i>A. fumigatus</i> ATCC 13073	RPMI	0.25	nt	nt	>64	0.25
<i>C. albicans</i> ATCC 90028	RPMI	1	0.5	nt	0.25	≤ 0.12
<i>C. albicans</i> F56	RPMI	0.5	nt	nt	>64	0.25
<i>C. glabrata</i> ATCC 90030	RPMI + MOPs	≤ 0.5	≤ 0.5	64	nt	≤ 0.5
<i>C. krusei</i> ATCC 44507	RPMI + MOPs	1	≤ 0.5	64	nt	≤ 0.5
<i>C. neoformans</i> F285	RPMI	0.25	nt	nt	2	≤ 0.12
<i>C. parapsilosis</i> ATCC 22019	RPMI + MOPs	≤ 0.5	≤ 0.5	≤ 0.5	nt	≤ 0.5
<i>C. tropicalis</i> ATCC 13803	RPMI + MOPs	≤ 0.5	≤ 0.5	256	nt	1
<i>E. floccosum</i> ATCC 52066	RPMI + MOPs	≤ 0.5	≤ 0.5	≤ 0.5	nt	≤ 0.5
<i>F. solani</i> ATCC 36031	RPMI + MOPs	≤ 0.5	4	64	nt	>256
<i>M. furfur</i> ATCC 44344	Urea	1	≤ 0.5	2	nt	≤ 0.5
<i>M. pachydermatis</i> ATCC 96746	Urea	1	≤ 0.5	≤ 0.5	nt	≤ 0.5
<i>M. sympodialis</i> ATCC 44031	Urea	1	≤ 0.5	≤ 0.5	nt	≤ 0.5
<i>M. audouinii</i> ATCC 42558	RPMI + MOPs	2	1	≤ 0.5	nt	≤ 0.5
<i>M. canis</i> ATCC 10214	RPMI + MOPs	2	≤ 0.5	≤ 0.5	nt	≤ 0.5
<i>M. gypseum</i> ATCC 24103	RPMI + MOPs	2	≤ 0.5	≤ 0.5	nt	≤ 0.5
<i>T. mentagrophytes</i> F311	RPMI + MOPs	1	0.5	≤ 0.5	32	≤ 0.12
<i>T. rubrum</i> F296	RPMI + MOPs	1	1	≤ 0.5	1	≤ 0.12
<i>T. rubrum</i> F296	RPMI + MOPs + 5% keratin powder	2	1	nt	1	nt
<i>T. tonsurans</i> ATCC 28942	RPMI + MOPs	2	≤ 0.5	≤ 0.5	nt	≤ 0.5

nt = not tested

Source: Study report 002-NCL PP-002-01 section 5.3.5.

Table 4 MIC and MFC (in µg/mL) of AN2690 in Clinical Isolates

Isolate	AN2690					
	MIC	MIC ₅₀	MIC ₉₀	MFC	MFC ₅₀	MFC ₉₀
	Range			Range		
<i>T. rubrum</i>	1.0-8.0	4.0	8.0	8.0-128	64	64
<i>T. mentagrophytes</i>	4.0-8.0	4.0	8.0	16->128	64	128

Source: Study report 002-NCL PP-003-02 section 5.3.5.

Comment: Although the applicant has obtained test results on (b) (4) (MFC₉₀), I agree with the Dr. Roche's recommendation that, claims of (b) (4)

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

might be misleading. In general, Division of Anti-Infective Products recommends against specific labeling of the terms (b) (4) for the two reasons:

a) (b) (4)

In separate study (report 002-NCL PP-010-01) the vehicle was tested against *Trichophyton rubrum* in a microdilution assay and was found not to exhibit antifungal activity against *T. rubrum* at concentrations below 6.25% by volume.

Antifungal activity evaluated in Phase 3 trials

Subungual samples obtained from the targeted toe nail (TGT) of all subject in the Phase 3 trials were sent to a central mycology laboratory for KOH wet mount and culture evaluations. Summary of mycology results for pooled subjects is presented below:

Table 5 Summary of Mycology Results for Phase 3 Trials

	<u>Week 12</u>	<u>Week 24</u>	<u>Week 30</u>	<u>Week 36</u>	<u>Week 48</u>	<u>Week 52</u>
<u>Culture Negative</u>						
Active (N=795)						
Success	720 (90.6%)	750 (94.3%)	748 (94.1%)	741 (93.2%)	741 (93.2%)	685 (86.2%)
Failure	75 (9.4%)	45 (5.7%)	47 (5.9%)	54 (6.8%)	54 (6.8%)	110 (13.8%)
Vehicle (N=399)						
Success	283 (70.9%)	308 (77.2%)	306 (76.7%)	299 (74.9%)	294 (73.7%)	198 (49.6%)
Failure	116 (29.1%)	91 (22.8%)	93 (23.3%)	100 (25.1%)	105 (26.3%)	201 (50.4%)
<u>KOH Negative</u>						
Active (N=795)						
Success	85 (10.7%)	163 (20.5%)	166 (20.9%)	209 (26.3%)	286 (36.0%)	275 (34.6%)
Failure	710 (89.3%)	632 (79.5%)	629 (79.1%)	586 (73.7%)	509 (64.0%)	520 (65.4%)
Vehicle (N=399)						
Success	19 (4.8%)	22 (5.5%)	24 (6.0%)	31 (7.8%)	36 (9.0%)	52 (13.0%)
Failure	380 (95.2%)	377 (94.5%)	375 (94.0%)	368 (92.2%)	363 (91.0%)	347 (87.0%)
<u>Negative Mycology*</u>						
Active (N=795)						
Success	84 (10.6%)	162 (20.4%)	165 (20.8%)	208 (26.2%)	284 (35.7%)	266 (33.5%)
Failure	711 (89.4%)	633 (79.6%)	630 (79.2%)	587 (73.8%)	511 (64.3%)	529 (66.5%)
Vehicle (N=399)						
Success	17 (4.3%)	21 (5.3%)	23 (5.8%)	28 (7.0%)	33 (8.3%)	39 (9.8%)
Failure	382 (95.7%)	378 (94.7%)	376 (94.2%)	371 (93.0%)	366 (91.7%)	360 (90.2%)

Source: Applicant's ISE Table 14.2.1.1

A susceptibility testing was conducted in central mycology laboratory on 1543 isolates from *T. rubrum* and *T. mentagrophytes* recovered from randomized subjects in the two phase 3 clinical studies (each viable isolate collected at screening and from the last viable mycology-positive visit). The results are presented below:

Table 6 Tavaborole Susceptibility against Screening Isolates

Species	Tavaborole Topical Solution, 5%				Vehicle			
	No. of Isolates	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	No. of Isolates	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)
<i>Trichophyton rubrum</i>								
Study AN2690-ONYC-301	366	0.5–8	2	4	176	0.5–8	2	4
Study AN2690-ONYC-302	355	0.5–8	4	4	179	1–8	4	4
<i>Trichophyton mentagrophytes</i>								
Study AN2690-ONYC-301	14	1–8	2	4	6	2–4	ND	ND
Study AN2690-ONYC-302	15	2–8	4	8	11	2–4	4	4
All dermatophytes								
Study AN2690-ONYC-301	380	0.5–8	2	4	182	0.5–8	2	4
Study AN2690-ONYC-302	370	0.5–8	4	4	190	1–8	4	4

Source: Agency Microbiology Review, Table 21

The overall MIC range values for tavaborole tested against the viable last culture-positive samples collected from subjects enrolled in the phase 3 studies is presented below:

Table 7 Tavaborole Susceptibility from Last Isolates

Species	Tavaborole Topical Solution, 5%				Vehicle			
	No. of Isolates	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	No. of Isolates	MIC Range (µg/mL)	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)
<i>Trichophyton rubrum</i>								
Study AN2690-ONYC-301	64	0.5-8	2	4	115	1-8	2	4
StudyAN2690-ONYC-302	65	1-4	4	4	115	1-4	4	4
<i>Trichophyton mentagrophytes</i>								
Study AN2690-ONYC-301	3	1-4	ND	ND	3	2-4	ND	ND
StudyAN2690-ONYC-302	1	4 ^a	ND	ND	6	4 ^a	ND	ND
All dermatophytes								
Study AN2690-ONYC-301	67	0.5-8	2	4	118	1-8	2	4
StudyAN2690-ONYC-302	66	1-4	4	4	121	1-4	4	4

Source: Agency Microbiology Review, Table 26

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

The microbiology reviewer concluded that “tavaborole topical solution 5% was shown to be active against *T. rubrum* and *T. mentagrophytes* when compared to vehicle in subjects with onychomycosis. No susceptibility testing interpretive criteria for tavaborole are recommended.”

Comment: I agree with Dr. Roche's recommendations. [REDACTED] (b) (4) as proposed by the applicant is not supported by the data. Therefore I recommend that indication, in regard to [REDACTED] (b) (4), reads (deletion is strikethrough, additions are double underlined):

KERYDIN (tavaborole) Topical Solution, 5% is indicated for the [REDACTED] (b) (4) [REDACTED] (b) (4) Trichophyton rubrum or Trichophyton mentagrophytes.

4.3 Preclinical Pharmacology/Toxicology

All appropriate nonclinical studies were conducted and reviewed by Pharmacology/Toxicology Review Barbara Hill, Ph.D. Presented below is the summary of nonclinical studies:

- Oral repeat dose toxicology studies conducted in rats for up to 6 months demonstrated epithelial hyperplasia and hyperkeratosis of nonglandular stomach. Given that humans do not have nonglandular stomach Dr. Hill noted in her review that the “clinical significance of this finding is unclear.” The effect was reversible after stopping the treatment.
- Dermal toxicology studies with tavaborole solution conducted in minipigs for up to 9 months demonstrated a dose dependent increase in the incidence and severity of dermal irritation. The effect was reversible after stopping the treatment.
- In genetic toxicology studies tavaborole was negative in a bacterial mutagenicity test, an *in vitro* chromosome aberration test, and an *in vivo* micronucleus test.
- Carcinogenicity studies: An oral rat and a dermal mouse carcinogenicity study have been conducted with tavaborole solution. The Executive Carcinogenicity Assessment Committee (ECAC) reviewed results from these two carcinogenicity studies on December 10, 2013 and concluded that no signals for carcinogenicity were noted in either study.
- Reproductive toxicology studies include an oral fertility study in rats, oral embryofetal development studies in rats, dermal embryofetal development study in rabbits, and an oral pre- and post-natal development study in rats.
 - No treatment related effects on fertility were noted in rats at oral doses up to 300 mg/kg/day tavaborole.

Clinical Review

Milena Lolic, MD, MS

NDA 204,427

Kerydin (tavaborole) Topical Solution, 5%

- At oral dose of 300 mg/kg/day in rats drug related skeletal malformations were noted in fetuses as well as lower fetal body weights and a maternal body weight decrease.
 - An increase in mortality and significant body weight loss was noted at 150 mg/kg/day tavaborole in the oral embryofetal development study in rabbits. The NOAEL for drug related malformations was 150 mg/kg/day.
 - No treatment related effects on pre- and post-natal development were noted in rats at doses up to 100 mg/kg/day tavaborole.
 - No treatment related effects on fetal evaluations were detected in dermal embryofetal development study in rabbits.
- Special toxicology studies: Tavaborole solution was tested in a primary skin irritation study in rabbits and was found to be slightly irritating after a single 24 hour topical application under occlusion. An eye irritation study in rabbits was positive, and a dermal sensitization study in guinea pigs was negative.
 - Safety pharmacology studies have been conducted to evaluate the effects of tavaborole on the cardiovascular system (hERG assay and in vivo oral dog study) and CNS (in vivo oral rat study). As for CV system, tavaborole was classified as low-potency HERG-channel blocker and did not elicit any cardiovascular effects in dogs at the 30 mg/kg dose (NOEL). Similarly, there were no observed neurological effects at doses up to 200 mg/kg in rats.

Pharmacology/Toxicology Review Barbara Hill, Ph.D. recommended approval for this NDA from a pharmacological/toxicological perspective without nonclinical postmarketing requirements.

Comment: I agree with Dr. Hill that, based on nonclinical data, there are no significant safety concerns for tavaborole solution at the proposed clinical dose. I also agree with her recommendation that product should be labeled as pregnancy category C. I also concur with the recommended edits and additions to the nonclinical sections of Kerydin labeling.

4.4 Clinical Pharmacology

The following studies comprise the clinical pharmacology development of tavaborole 5% solution:

- a. Maximal use PK trial
- b. PK portion of Thorough QTc Trial
- c. Absorption, Metabolism, and Excretion of ¹⁴C-tavaborole study
- d. In vitro inhibition and induction studies

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

4.4.1 Mechanism of Action

Per applicant, tavaborole inhibits fungal protein synthesis by inhibition of an aminoacyl-tRNA synthetase (AARS) via an oxaborole-tRNA.

4.4.2 Pharmacodynamics

The effect of a suprathreshold dose of tavaborole 5% solution on ventricular repolarization (QT/QTc interval duration) was assessed in study AN2690-ONYC-102 ([see Section 7.4.4 Electrocardiograms (ECGs)]).

C_{max} obtained from suprathreshold dose of this TQT study was 4-times higher than the one from maximal use PK study P06118, thus sufficient for the assessment. The study did not find any significant QTc prolongation effects of tavaborole.

4.4.3 Pharmacokinetics

The pharmacokinetics of tavaborole was investigated in maximal use PK study P06118 and study P0557.

Study P06118 was an open-label, single center, pharmacokinetic study designed to quantify the PK profile of tavaborole solution 5% following single and repeated once daily dosing. Total number of days with dosing was 15. Population consisted of 24 adult subjects with at least 4 toenails (including targeted great toenail) affected with onychomycosis on one or both feet. Treatment consisted of a single 200µL dose of tavaborole solution 5% to all toenails and 2 mm skin surrounding followed by daily treatment from Day 5-18. PK parameters for tavaborole and its metabolites were calculated from the plasma samples collected on Days 1 and 18.

The plasma concentrations of tavaborole solution 5% were relatively low. After a single dose C_{max} of tavaborole was 3.54 ± 2.26 ng/mL and the mean AUC_{last} was 44.4 ± 25.5 ng*hr/mL. After 2-week daily dosing C_{max} was 5.17±3.47 ng/mL and the mean AUC_τ was 75.8 ± 44.5 ng*hr/mL. The steady state was reached after 6 days of dosing.

Tabular presentation of the pharmacokinetic parameters is presented below:

Table 8 Pharmacokinetic Parameters for Tavaborole Solution 5%

Parameter	Day 1 (n=21) ^e	Day 18 (n=24)
Tmax ^a (hr)	12.0 (4.03-23.9)	8.03 (0.467-24.0)
Cmax (ng/mL)	3.54 (64) ^f	5.17 (67)
Cmin ^b (ng/mL)	NA	0.942 (65)
AUClast ^c (ng*hr/mL)	44.4 (57) ^{g, h}	148 (63)
AUC _τ (ng*hr/mL)	NA	75.8 (59)
t _{1/2} (hr)	7.68 (27) ⁱ	28.5 (37) ^j
RA ^d	NA	2.22 (64) ^k

AUC24 = area under the concentration-time curve from time 0 to 24 hours; AUClast = area under the concentration-time curve from time 0 to the time of the final measurable sample; AUC_τ = area under the concentration-time curve during a dosing interval at steady state; Cmax = maximum observed plasma concentration; Cmin = minimum observed plasma concentration; NA: not applicable; RA = accumulation ratio (index); t_{1/2} = terminal phase half-life; Tmax = time to maximum observed plasma concentration.

a: Median (range) reported

b: Cmin was calculated over a dosing interval of 24 hours

c: Plasma samples were collected until 24 hours postdose on Day 1 and until 96 hours postdose on Day 18

d: Ratio of AUC_τ to AUClast on Day 1; both the AUCs were calculated over 24 hr interval

e: Three subjects had all plasma SCH 900340 below lower limit of quantification (0.500 ng/ml) on Day 1

f: Inclusion of 3 subjects with Cmax of 0.00 resulted in mean (CV, %) Cmax values of 3.10

g: The last measurable time point was within 10% of 24 hour for all but one subject, thus AUClast also represents AUC24 on Day 1

h: One subject had the last measurable concentration at 16 hr and was included in the summary statistics

i: n=4, t_{1/2} could be determined only in 4 subjects

j: n=10, t_{1/2} could be determined only in 10 subjects

k: n=21

Source: Clinical Pharmacology Review, Table 1

Two metabolites, a sulfate conjugate (M5) and a benzoic acid metabolite (M6a) were detected at trace levels of on Day 18 in the pooled plasma and pooled urine samples.

Study P0557 titled Absorption, Metabolism, and Excretion of ¹⁴C-SCH 900340 when Administered as a 5% Topical Solution in Healthy Adult Male Subjects investigated pharmacokinetics of tavaborole in 6 healthy men following a single application of 5% ¹⁴C-tavaborole. Tavaborole conjugates and metabolites were shown to be excreted primarily in the urine. Dr. Lu concluded in her review:

“The ratio of C_{max} for plasma tavaborole/plasma total radioactivity was approximately 0.146, indicating extensive metabolism and that the systemic exposure to tavaborole was approximately 15% of the exposure to plasma total radioactivity... Tavaborole derived radioactivity was primarily excreted in the urine... A sulfate-conjugate (M5) of a benzyl alcohol metabolite (M6) was the only metabolite identified in human urine.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

The amount of M5 excreted during 0-120 hr post-dose represented 14.6% of the nominal dose applied topically. “

In vitro inhibition and induction studies are presented in Section 7.2.3 Special Animal and/or In Vitro Testing. In summary, studies demonstrated that is unlikely for tavaborole to either inhibit or induce cytochrome P450 enzymes.

Comment: I agree with the conclusion of An-Chi Lu, M.S., Pharm.D that NDA 204427 is approvable from a Clinical Pharmacology perspective. Considering the lack of pediatric assessments, I agree with recommendation for a PMR-PK/safety trial in at least 16 evaluable subjects age 12-17 years and 11 months.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

During the tavaborole development program, a total of 1966 subjects were enrolled in 12 trials: 377 healthy volunteers and 1589 subjects with onychomycosis. See Table 9 for a listing and summary of these trials.

Table 9 Tavaborole Clinical Studies

Study Identifier (Protocol/ Report Number)	Study Description	No. of Subjects
Clinical Pharmacology		
AN2690-ONYC-101/ 002-CLN CL 004-01	21 day cumulative irritation test	37
AN2690-ONYC-103/ 002-CLN CL-007-01	Definitive repeat insult patch test (RIPT) and cumulative irritation study of Tavaborole Topical Solution, 5% in healthy volunteers	279
P05577/ 002-CLN PK 005-01	Absorption, metabolism, and excretion of ¹⁴ C-tavaborole as a topical solution in adult males	6
P06118/ 002-CLN PK 003-01	Maximal use systemic exposure (MUSE) safety and PK evaluation of Tavaborole Topical Solution, 5% in subjects with onychomycosis (14 days of dosing)	24
AN2690-ONYC-102/ 002-CLN CL 006-01	Thorough QT/QTc safety and PK study of Tavaborole Topical Solution, 5% in healthy subjects (14 days of dosing)	55
AN2690-ONYC-202/ 002-CLN PK 001-01	Open-label multiple-dose study of safety and PK of tavaborole solution 7.5% (29 days of dosing)	15
AN2690-ONYC-205/ 002-CLN PK 004-01	Open-label multiple-dose study of safety and PK of tavaborole solution 7.5% (29 days of dosing)	20
Phase 2 Uncontrolled Trials		
AN2690-ONYC-201/ 002-CLN CL 005-01	Open-label rising multiple-dose multi-center study to evaluate safety and efficacy of tavaborole solutions 5% and 7.5% in subjects with onychomycosis (180 or 360 days of dosing)	89
AN2690-ONYC-203/ 002-CLN CL 003-02	Open-label rising multiple-dose multi-center study to evaluate safety and efficacy of tavaborole solutions 1% and 5% in subjects with onychomycosis (180 days of dosing)	60
Phase 2 Controlled Trial		
AN2690-ONYC- 200/200A/ 002-CLN CL-001-03	Randomized, double-blind, vehicle-controlled, multi-center study to evaluate the safety and efficacy of topically applied tavaborole 2.5%, 5% and 7.5% solution vs. vehicle for the treatment of adult subjects with onychomycosis of the great toenail (180 days of dosing)	187
Phase 3		
AN2690-ONYC-301/ 002-CLN CL-008-01	Randomized, double-blind, vehicle-controlled, multi-center study to evaluate the efficacy and safety of Tavaborole Topical Solution, 5%, vs. vehicle in the treatment of onychomycosis of the toenail in adults (48 weeks of dosing)	594
AN2690-ONYC-302/ 002-CLN CL-009-01	Randomized, double-blind, vehicle-controlled, multi-center study to evaluate the efficacy and safety of Tavaborole Topical Solution, 5%, vs. vehicle in the treatment of onychomycosis of the toenail in adults (48 weeks of dosing)	604

Source: Sponsor's Table 1 from Clinical section 2.5

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

Comment: It should be noted that studies AN2690-ONYC-101, AN2690-ONYC-205, AN2690-ONYC-202, and P05577 were conducted with different tavaborole formulation than the final-to-be-marketed formulation. Reliance on these studies is not intended by the applicant, and the clinical trial experience with to-be -marketed formulation is adequate to demonstrate safety and efficacy of tavaborole for the labeled indication.

5.2 Review Strategy

Only studies conducted with final-to-be-marketed formulation will be reviewed and those include two phase 3 trials, three phase 2 trials, and three phase 1 trials.

A brief review of the protocol for pivotal trials will be presented in this section.

Efficacy evaluation for tavaborole solution 5% based on intent-to-treat (ITT) population from phase 3 trials is presented in section 6 Review of Efficacy. Relevant Phase 2 efficacy data will be presented in section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.

Safety evaluation is presented in section

7 Review of Safety. Safety was primarily based on the pivotal trials. Raw datasets were reviewed in conjunction with the Applicant's clinical study reports (CSRs) and the Integrated Summary of Safety (ISS). Data from the other trials in the development program were used as supporting evidence. Phase 2 data are presented separately from pooled Phase 3 data in section 7.2.2 Explorations for Dose Response due to different dosing regimens.

Review of the pharmacokinetic trial was deferred to Clinical Pharmacology. The key review points and safety data from maximal use PK study are presented in section 7.2.5 Metabolic, Clearance, and Interaction Workup.

The review of the dermal safety trial is provided in section 7.4.5 Special Safety Studies/Clinical Trials.

A summary of thorough QT study is provided in the section 7.4.4 Electrocardiograms (ECGs).

Published literature, internal FDA data, and Clinical Review of NDA 21-022 were used for reference.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

5.3 Discussion of Individual Studies/Clinical Trials

Identical phase 3 protocols AN2690-ONYC-301 and AN2690-ONYC-302 were submitted under IND 71, 206.

Protocol 301 was submitted as a Special Protocol Assessment (SPA) on 8/14/2010, and an agreement letter was issued on 9/13/2010. The Agency and applicant reached agreement on the study design and endpoints.

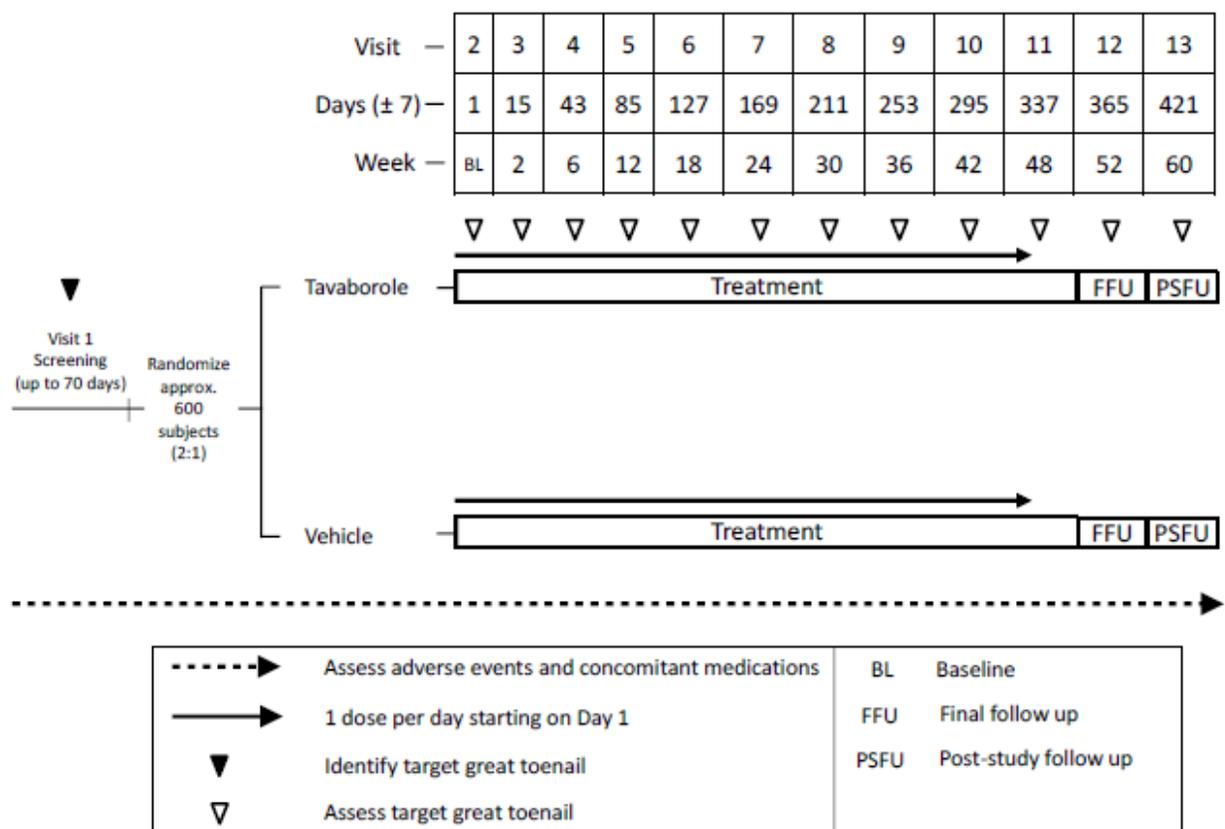
The protocols were amended two times, in November 2010 and in September 2012. The first amendment addressed issues such as providing additional details regarding missing data and sensitivity analyses. The second amendment added an additional 8-week follow-up for subjects with completely clear or almost clear nails. As this amendment was added during the study, only a portion of eligible subjects had the additional follow-up.

Trials were conducted from December 2010 to February 2013 at 61 sites in USA, 6 in Mexico and 9 in Canada.

Trial design(s)

The design of the trials was identical: randomized, vehicle controlled, double blind, 2 arm parallel trial of approximately 60 weeks duration. Treatment period was for 48 weeks and primary efficacy assessment was at 52 weeks (4 weeks post treatment) as presented in Figure 2 below:

Figure 2 Trial Flow



Note: PSFU visit was conducted only for subjects who participated in the PSFU period.
 The TGT was also assessed at the time of early termination, as applicable.

Source: Applicant's Figure 1 from section 5.3.5.1

Major inclusion criteria:

- Male or female subjects ≥ 18 years of age at the time of Screening
- A clinical diagnosis of distal subungual onychomycosis affecting at least one great toenail confirmed by a central mycology laboratory to be positive for KOH

Clinical Review
Milena Lolic, MD, MS
NDA 204,427

Kerydin (tavaborole) Topical Solution, 5%

wet mount and fungal culture for a dermatophyte, obtained from the TGT sample during the screening period

- Onychomycosis involving 20% to 60% of the TGT after the nail had been trimmed, with at least 3 mm clear nail measured from the proximal nail fold to the most proximal visible mycotic border at the Screening visit (had to be confirmed by independent review of Screening photograph prior to randomization)

Major exclusion criteria:

- Proximal subungual onychomycosis
- Superficial white onychomycosis, dermatophytoma, exclusively lateral disease, or yellow/brown spikes
- Screening culture results that demonstrated infection or co-infection with a non-dermatophyte fungus (e.g., *Candida* spp., *Scopulariopsis* spp.)
- Current or past history of chronic moccasin-type tinea pedis (involving the sides or dorsum of the foot)
- Active interdigital tinea pedis or exclusively plantar tinea pedis (which did not involve the sides or dorsum of the foot) at the Screening and/or Baseline visits
- History of any known immunodeficiency

Prohibited medications:

- Topical antifungals applied to the toenails: 4 weeks
- Topical antifungals applied to the feet and/or toes (not to the toenails): 2 weeks
- Topical anti-inflammatory, corticosteroid, or immunomodulatory agents applied to the toes or toenails: 2 weeks
- Systemic corticosteroids (including intramuscular injections): 4 weeks
- Systemic immunomodulatory agents: 4 weeks
- Systemic antifungals for treatment of onychomycosis or with known activity against dermatophyte: 24 weeks

Treatment

Treatment was applied by the subject topically once daily for 48 weeks. Subjects were instructed to apply a sufficient amount of the investigational product to cover the infected TGT and infected non-target toenails with a thin and even layer. The investigational product had to be applied on, under, and around each nail being treated. Subjects were instructed to remove the excess medication on the surrounding skin using a tissue. Subjects were encouraged not to trim their TGT between visits. Proper nail trimming was to be done within approximately 1 mm distal of the hyponychium or distal groove and performed by investigator on the scheduled visits. Toenail debridement (i.e., partial or complete removal of the toenail) was not permitted.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427

Kerydin (tavaborole) Topical Solution, 5%

If a persistent Grade 2 or greater burning/stinging or pruritus and/or Grade 2 or greater erythema occurred to the target great toe or if another AE that the Investigator determined required temporary discontinuation of the investigational product occurred, treatment was temporarily interrupted and a drug holiday was started for a minimum of 2 weeks and a maximum of 6 weeks. Following the complete resolution of the signs and symptoms, the frequency of treatment was reduced to 3×/week. For

subjects who experienced signs and symptoms of irritation at the reduced application frequency of 3×/week, the treatment was completely discontinued.

Trial schedule was as follows:

Table 10 Phase 3 Trial Schedule

Visit	Treatment Phase											Final Follow-Up	Post-study Follow-Up ^j	
	1	2	3	4	5	6	7	8	9	10	11			
Days (±7 days)	Up to 70 days	1	15	43	85	127	169	211	253	295	337		365	421
Week	Screening	Baseline	2	6	12	18	24	30	36	42	48	Early Termination	52	60
Informed consent ^a	x													
Obtain subject number from IWRS	x													
Demographics	x													
Review study entry criteria	x	x												
Medical and medication history ^b	x													
Concomitant medications ^b	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AEs	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x ^c	x	x	x	x	x	x	x	x	x	x	x ^d	x ^e	x
Identify TGT ^d	x													
Randomization via IWRS		x												
Trim TGT ^e	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Assess TGT ^f		x	x	x	x	x	x	x	x	x	x	x	x	x
Assess other toenails ^g		x	x	x	x	x	x	x	x	x	x	x	x	
Safety laboratory tests	x	x	x	x	x		x		x		x	x	x	
Pregnancy test	x ^h	x ^h	x	x	x	x	x	x	x	x	x	x	x	

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

12 lead ECG ^a	x	x (triplicate)	x		x		x			x	x	x	
Vital signs ^b	x	x	x	x	x		x		x	x	x	x	x
Photographs ^c	x	x		x	x	x	x	x	x	x	x	x	x
Mark the TGT ^d	x	x	x	x	x	x	x	x	x	x	x	x	x
KOH wet mount and fungal culture	x ^e		(x) ^f	(x) ^f	x	x	x						
Dispense investigational product ^g		x	x	x	x	x	x	x	x	x			
Investigational product collection/accountsability			x	x	x	x	x	x	x	x	x		
Dispense dosing diary ^h		x	x	x	x	x	x	x	x	x			
Collect dosing diary ⁱ			x	x	x	x	x	x	x	x	x		
Supervise investigational product self-administration		x	x	x	x	x	x	x	x	x			
Identify subjects for PSFU											x		
Schedule visits	x	x	x	x	x	x	x	x	x	x	x		x ^j
Telephone call ^k	x												

^a Performed prior to any study-specific evaluations or procedures.
^b Significant medical history included prior treatment of onychomycosis, all systemic antifungals used within 24 weeks, and all medications used within 30 days prior to Screening.
^c Performed a **complete** physical examination, including height (at Screening only) and weight at Screening, and Final Follow-Up (Week 52) or Early Termination visits only. At all other visits, performed a disease-focused physical examination. Also assessed ASRs at all visits except Screening (Visit 1).
^d Requirements for clinical eligibility; 20% to 60% involvement with at least 3 mm CN measured from the proximal nail fold to most proximal visible mycotic border and ≤ 3 mm distal nail plate thickness.
^e Proper nail trimming was to be to within approximately 1 mm distal of the hyponychium or distal groove.
^f Assessment was to include, but not be limited to extent of involvement, clinical cure, and ASR.
^g Determined the total number of other toenails (other than TGT) that were completely clear (0% involvement), almost clear (disease present but ≤ 10% involvement) or more than 10% affected, based on the presence of onycholysis and subungual hyperkeratosis.
^h A serum and urine pregnancy test was performed at Screening (all women) and Baseline (women of childbearing potential only). A serum pregnancy test was obtained thereafter at Weeks 2, 6, 12, 18, 24, 30, 36, 42, 48, and 52, and the Early Termination visit, if applicable (women of childbearing potential only).
ⁱ Obtained ECG after the subject had been in the supine position for at least 5 minutes and before blood collection, or at least 15 minutes after. Final Screening ECG report from central ECG laboratory was used for eligibility. Single ECGs were obtained at all visits except at Baseline, when three ECGs were obtained within 15 minutes.
^j The protocol was amended to include an examination of the durability of clinical benefit in a subset of subjects with a completely CN or almost CN at Week 48 (the end of treatment) (see section 8.8.1). These subjects were scheduled to visit the investigational site at Week 60 and followed for an additional 8 weeks post-study for a total off-treatment follow-up period of 12 weeks.
^k Included temperature, pulse rate, respiratory rate, and blood pressure taken in the sitting position after the subject had been sitting calmly for at least 5 minutes.
^l Digital photographs (taken prior to sample collection) were obtained by the Investigator or a qualified designee prior to nail trimming and following nail trimming/nail marking. If clinically significant ASRs were present, photographs were taken of local area(s) affected.
^m Marked the TGT (distal groove and the proximal mycotic border).
ⁿ Took samples after nail trimming, marking and photography. Both big toes may have been sampled if they met clinical criteria. A subject may have been retested once in the case of either a negative initial KOH or fungal culture result.
^o Only obtained samples for KOH wet mount and fungal culture at Week 2, 6, 18, 30, or 42 if the TGT was observed for the *first time* to have ≤ 10% nail involvement (completely CN or almost CN).
^p Dispensed IWRS-assigned investigational product kit at Visit 2 and registered visit in the IWRS to obtain another investigational product kit assignment at Visits 3 through 10.
^q Subjects were instructed to complete the diary daily. Diary procedures were reviewed at the Baseline visit.
^r Diaries were reviewed for any missed doses and completeness.
^s Investigational site personnel informed subject of eligibility status (to have occurred sometime between Screening and Baseline visits).
 IWRS = Integrated web response system; AE = Adverse event; TGT = Target great toenail; ECG = Electrocardiogram; PSFU = Post-study follow-up

Source: Applicant's Table 4 from section 5.3.5.1

Efficacy assessment

Efficacy assessment included clinical evaluation and mycological evaluation. Clinical evaluation was performed on the TGT (using the IGA grading scale below) at Weeks 2, 6, every 6 weeks thereafter through Week 48, and Week 52.

Table 11 IGA Scale from Phase 3 Trials

Terminology	Definition
Investigator's Static Global Assessment (ISGA) Ratings	
1= Clear (Stated as Completely Clear in Phase 3 studies)	No clinical evidence of onychomycosis as evidenced by normal toenail plate, no onycholysis, and no subungual hyperkeratosis
2= Almost clear	No more than minimal evidence of onychomycosis as evidenced by toenail plate dystrophic or discolored over $\leq 10\%$ of the distal aspect, with minimally evident onycholysis and subungual hyperkeratosis
3=Mild onychomycosis	Onychomycosis as evidenced by toenail plate dystrophic or discolored over $>10\%$ to $\leq 20\%$ of the distal aspect, with clearly evident onycholysis and subungual hyperkeratosis
4=Moderate onychomycosis	Onychomycosis as evidenced by toenail plate dystrophic or discolored over $>20\%$ to $\leq 60\%$ of the distal aspect, with clearly evident onycholysis and subungual hyperkeratosis
5=Severe onychomycosis	Onychomycosis as evidenced by a toenail plate dystrophic or discolored over $>60\%$ of the distal aspect, with pronounced onycholysis and subungual hyperkeratosis

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%
Source: Applicant's Table 4 from 2.7.3

For assessment of clear nail, nail discoloration and nail dystrophy *per se* were not considered to be necessarily indicative of disease. Clinical assessments of non-target toenails also were performed.

Samples for KOH wet mount and fungal culture were obtained at Screening, at Weeks 12, 24, 36, 48 and 52.

Primary endpoint:

- Complete Cure defined as
 - no clinical evidence of onychomycosis of the TGT and
 - negative mycology (negative KOH and negative fungal culture) of the TGT

Secondary endpoints:

- Completely clear nail or almost clear nail ($\leq 10\%$ involvement of the nail) of the TGT
- Treatment Success (defined as clear or almost clear nail and negative mycology) of the TGT
- Negative Mycology (defined as negative KOH and negative fungal culture) of the TGT

Statistical analysis plan

Analysis sets were:

- Safety population

All subjects who were randomized, received at least one confirmed dose of investigational product, and had at least one post-baseline assessment.

- Intent-to-treat (ITT) population

All subjects who were randomized and dispensed study drug.

- Per-protocol (PP) population

All subjects in the ITT without major protocol deviations.

The primary efficacy assessment on the TGT was performed at Week 52, 4 weeks following the end of treatment (Week 48). Efficacy analyses were performed for the ITT and PP populations. The treatment group differences for the primary efficacy endpoint were compared using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. To adjust for multiplicity within the efficacy analyses, interpretation of the secondary endpoints was performed in a sequential manner beginning with a test for the proportion of subjects with completely or almost clear TGT at Week 52, followed by the proportion of subjects with treatment success, and then followed by the proportion of subjects with negative mycology for the TGT at Week 52. The primary method of

Clinical Review

Milena Lolic, MD, MS

NDA 204,427

Kerydin (tavaborole) Topical Solution, 5%

handling missing data for the primary efficacy analysis was last observation carried forward (LOCF). As a sensitivity analysis, subjects with missing Week 52 complete cure assessments were imputed as failures.

Safety assessment

Safety assessment included adverse events (AEs), application site reactions (ASRs), clinical safety laboratory tests, physical examinations, vital signs, digital 12-lead electrocardiograms (ECGs), and pregnancy tests for women of childbearing potential.

Local tolerability was actively assessed by investigator at every visit and was not reported as AE unless it resulted in treatment with a medication or a drug holiday. Local tolerability was assessed using the following scale:

Table 12 Local Tolerability Scale from Phase 3 Trials

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

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

Source: Applicant's Table 5 from 2.7.3

6 Review of Efficacy

Efficacy Summary

To establish tavaborole efficacy, the applicant submitted data from two randomized, double-blind, vehicle-controlled phase 3 trials (301 and 302). The efficacy population consisted of all randomized subjects 18 years and older who had a clinical diagnosis of onychomycosis of the toenails, 20-60% involvement of target nail, \geq 3mm of clear nail from proximal fold, positive KOH, and positive culture.

The treatment was applied once daily to all affected nails for 48 weeks. Primary endpoint defined as Complete cure (no clinical evidence of onychomycosis, negative KOH, and negative culture) was assessed at Week 52. Three secondary endpoints (Completely or Almost Clear Nail, Treatment Success, and Negative Mycology) were assessed at the same time point.

Success at the primary endpoint was achieved by 7% of subjects treated with tavaborole solution 5% in trial 301 and by 9% in trial 302. Complete cure for vehicle-treated subjects was 1% and 2% for respective trials ($p \leq 0.001$).

Statistical superiority of the three pre-specified secondary endpoints was achieved in both trials.

As per agreed SPA protocol, the analysis of endpoints was performed on the targeted great toenail, thus indication should be limited to “onychomycosis of the toenails.” The efficacy for onychomycosis of fingernails was not studied and can not be assumed as the demographics for these two conditions may be different.

In summary, this reviewer concludes that efficacy of tavaborole solution 5% was demonstrated for onychomycosis of the toenails in subjects 18 years of age and older when applied daily for 48 weeks.

6.1 Indication

The applicant proposes that tavaborole topical solution, 5% receive the following indication: for the treatment of onychomycosis (b) (4)

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427

Kerydin (tavaborole) Topical Solution, 5%

Comment: As noted below, the conclusion of this efficacy review is that only the indication of onychomycosis of the toenails is supported by substantial evidence.

Discussion on causative (b) (4) pertinent to indication is included in section 4.2 Clinical Microbiology. It is my recommendation that Section 1 Indications and Usage reads (deletions are ~~strikethrough~~, additions are double underlined):

KERYDIN (Tavaborole) Topical Solution, 5% is indicated for the treatment of onychomycosis of the toenails due to (b) (4) Trichophyton rubrum or Trichophyton mentagrophytes.

6.1.1 Methods

The primary population for the efficacy analysis of pivotal trials 301 and 302 was the intent to treat (ITT) and included all subjects randomized and dispensed study drug (1194). Per-protocol population consisted of subjects who did not have any protocol deviation.

Table 13 Analysis Sets

	Tavaborole topical solution 5%		Vehicle	
	Trial 301	Trial 302	Trial 301	Trial 302
	N		N	
Randomized	400	399	194	205
ITT analysis set*	399	396	194	205
Per-protocol set	312	299	156	157

*Four subjects in the Tavaborole topical solution, 5% group were excluded from the ITT population because they were not dispensed study drug.

Source: Data sets adcomp.xpt., adeff.xpt, adex.xpt and adsl.xpt and reviewer's analysis

6.1.2 Demographics

There were no notable differences in demographic characteristics between either arms or trials. Similarly, there were no notable differences in regard to baseline disease characteristics (Table 15).

Table 14 Baseline Demographics-ITT

	Trial 301		Trial 302	
	Tavaborole 5%	Vehicle	Tavaborole 5%	Vehicle
ITT Subjects	399	194	396	205
Age (median)	55	55	56	57
≥65 years	71 (18%)	37 (19%)	80 (20%)	43 (21%)
Sex				
Female	75(19%)	36 (19%)	73 (18%)	31(15%)
Male	394 (81%)	158 (81%)	323 (82%)	174(85%)
Race				
White	316(79%)	152 (78%)	355 (90%)	183(89%)
Black	19 (5%)	12 (6%)	21 (5%)	14 (7%)
Asian	2 (<1%)	0	11 (3%)	2(1%)
Other	62(16%)	30(16%)	9 (2%)	6(3%)

Source: Data sets adcomp.xpt., adeff.xpt, adex.xpt and reviewer's analysis

Table 15 Baseline Disease Characteristics-ITT

	Trial 301		Trial 302	
	Tavaborole N=399	Vehicle N=194	Tavaborole N=396	Vehicle N=205
Target Toenail Involvement Classification				
Mild (>10% to ≤ 20%)	8 (2%)	3 (2%)	5 (1%)	3 (1%)
Moderate (>20% to ≤60%)	391 (98%)	191 (98%)	390 (98%)	202(99%)
Severe (>60%)	--	--	1 (0.3%)	--
Mean number (SD) of affected non-target toenails	3.4 (2.8)	3.8 (2.7)	3.3 (2.8)	3.3 (2.6)
Screening Culture				
<i>T. rubrum</i>	379 (95%)	184 (95%)	376 (95%)	188(92%)
<i>T. mentagrophytes</i>	8 (2%)	5 (3%)	14 (4%)	12 (6%)
<i>E. floccosum</i>	0	0	0	2 (1%)
Multiple	3 (0.7%)	4 (2%)	4 (1%)	2 (1%)
No dermatophyte	4 (1%)	1 (0.5%)	2 (0.5%)	1 (0.5%)

Source: Agency Statistical review Table 6

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Comment: Vast majority of enrolled subjects had baseline target toenails characteristics according to the inclusion criteria. About 1.6% (19) subjects had TGT with <20% involvement, however, distribution between arms was similar.

6.1.3 Subject Disposition

Similar rates of subjects discontinued on both, the tavaborole and vehicle arms (13-15%) in each study. The most common reasons for discontinuation were subject request – unrelated to study treatment and lost to follow-up.

Table 16 Disposition of Subjects-ITT

	Trial 301		Trial 302	
	Tavaborole	Vehicle	Tavaborole	Vehicle
<i>Subjects Randomized</i>	400	194	399	205
Not Dispensed Treatment	1 (0.3%)	0 (0%)	3 (0.8%) ^a	0 (0%)
Discontinued Treatment and Discontinued Study	50 (12.5%)	23 (11.9%)	45 (11.3%) ^a	27 (13.2%)
Discontinued Treatment but Completed Study	9 (2.3%) ^b	1 (0.5%) ^b	1 (0.3%) ^b	1 (0.5%) ^c
Completed Treatment but Discontinued Study	1 (0.3%) ^d	0 (0%)	2 (0.5%) ^{d,e}	1 (0.5%) ^d
Completed Treatment and Completed Study	339 (84.8%)	170 (87.6%)	348 (87.2%)	176 (85.9%)
<i>Reason for Treatment Discontinuation</i>				
Adverse event	10 (2.5%)	3 (1.5%)	3 (0.8%)	1 (0.5%)
Lost to Follow-up	18 (4.5%)	5 (2.6%)	10 (2.5%)	4 (2.0%)
Subject request – Unrelated to study treatment	19 (4.8%)	8 (4.1%)	25 (6.3%)	14 (6.8%)
Subject request – Related to study treatment	4 (1.0%)	3 (1.5%)	2 (0.5%)	5 (2.4%)
Non-compliance	2 (0.5%)	2 (1.0%)	4 (1.0%)	3 (1.5%)
Other	6 (1.5%)	3 (1.5%)	3 (0.8%) ^f	1 (0.5%)
<i>Reason for Study Discontinuation</i>				
Adverse event	1 (0.3%)	2 (1.0%)	2 (0.5%)	1 (0.5%)
Lost to Follow-up	18 (4.5%)	5 (2.6%)	10 (2.5%)	4 (2.0%)
Subject request – Unrelated to study treatment	20 (5.0%)	8 (4.1%)	27 (6.8%)	15 (7.3%)

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

	Trial 301		Trial 302	
	Tavaborole	Vehicle	Tavaborole	Vehicle
<i>Subjects Randomized</i>	400	194	399	205
Subject request – Related to study treatment	4 (1.0%)	3 (1.5%)	3 (0.8%)	5 (2.4%)
Non-compliance	2 (0.5%)	2 (1.0%)	4 (1.0%)	2 (1.0%)
Other	7 (1.8%)	3 (1.5%)	4 (1.0%)	1 (0.5%)

Source: Agency Statistical review, Table 4

6.1.4 Analysis of Primary Endpoint

The primary endpoint was proportion of subjects with complete cure of the target toenail, defined as both, a clinical cure (completely clear nail) and mycological cure (negative KOH and culture) at Week 52 (4 weeks after the last treatment). LOCF was used to impute missing data.

Efficacy of tavaborole solution 5% versus vehicle was demonstrated in both trials ($p \leq 0.001$ from a one-sided Cochran-Mantel-Haenszel test, stratified by trial site).

Table 17 Primary Endpoint Analysis

Trial	Tavaborole 5%	Vehicle
301	26/399 (7%)	1/194 (1%)
302	36/396 (9%)	3/205 (2%)

Source: Adapted from Agency Statistical review Table 7

Comment: The efficacy treatment is smaller than observed in trials with approved oral drugs for onychomycosis, but comparable to the rates of topical ciclopirox. Unlike ciclopirox, treatment protocols with tavaborole did not require adjunctive nail debridement.

The sensitivity analyses for handling missing data showed consistent treatment efficacy rates.

Table 18 Complete Cure Rates under Missing Data Sensitivity Analyses

	Trial 301		Trial 302	
	Tavaborole N=299	Vehicle N=194	Tavaborole N=396	Vehicle N=205

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

	Trial 301		Trial 302	
	Tavaborole N=299	Vehicle N=194	Tavaborole N=396	Vehicle N=205
Missing as Failure	26 (6.5%)	1 (0.5%)	34 (8.6%)	3 (1.5%)
	p=0.001		p=0.001	
Missing as Success	77 (19.3%)	24 (12.4%)	81 (20.5%)	31 (15.1%)
	p=0.026		p=0.128	
Multiple Imputation	7.4%	0.6%	9.8%	1.7%
	p=0.012		p=0.003	

Source: Adapted from Agency Statistical review Table 8

6.1.5 Analysis of Secondary Endpoints(s)

To adjust for multiplicity within the efficacy analyses, interpretation of the secondary endpoints was performed in a sequential manner starting with Clear nail as presented below. Efficacy of tavaborole solution 5% versus vehicle was demonstrated in both trials for all three secondary endpoints ($p < 0.001$). Results are presented in Table 19.

Table 19 Secondary Endpoints Analysis

Trial	Endpoints	Tavaborole	Vehicle
301	Clear nail	104/399 (26%)	18/194 (9%)
	Treatment success	61/399 (15%)	3/194 (2%)
	Negative mycology	124/399 (31%)	14/194 (7%)
302	Clear nail*	109/396 (28%)	30/205 (15%)
	Treatment success	71/396 (18%)	8/205 (4%)
	Negative mycology	142/396 (36%)	25/205 (12%)

Clear nail/almost clear nail: $\leq 10\%$ involvement of the nail

Treatment success: $\leq 10\%$ involvement of the nail AND negative mycology

Negative mycology: negative KOH and culture

Source: Adapted from Agency Statistical review Table 9

Comment: Treatment effects for each of the secondary points are higher than for primary endpoint and that could be explained by the more stringent criteria for the primary endpoint. The largest treatment effect was observed for Negative mycology and that could be explained by the virtue of less that desirable sensitivity associated with

mycological cultures.

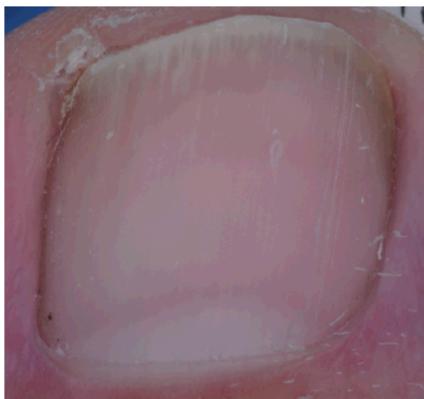
(b) (4)

Clinical Review
Milena Lolic, MD, MS
NDA 204,427

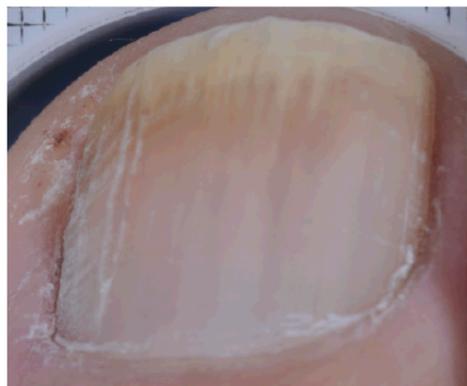
Kerydin (tavaborole) Topical Solution, 5%

The only single variable secondary endpoint was Clear /almost clear nail defined as nail with $\leq 10\%$ disease involvement. Information request for photographs of “completely clear nail” and “almost clear nail” was sent and response was received on 12/27/13.

Below are randomly selected images of completely clear nail (A) and almost clear nail (B) for demonstration purpose only.



A: Subject 113-072 (301)



B: Subject 132-017 (301)

When interpreting this secondary endpoint (Clear /almost clear nail) from clinical perspective one needs to consider that for some patients that outcome may be satisfactory (regardless of the culture results) and that diseased toenail is completely replaced with new nail in 12–18 months. However “Clear nail” is already part of primary endpoint and “Almost clear nail “is included in “Treatment success” endpoint .

(b) (4)

(b) (4)

In conclusion, my recommendation for presenting the efficacy outcomes in labeling is as follows (deletions are ~~striketrough~~):

Table 2: (b) (4) Efficacy Outcomes

Efficacy Variable	(b) (4) Trial (b) (4) 1		(b) (4) Trial (b) (4) 2	
	(b) (4) KERYDIN (N=399)	Vehicle (N=194)	(b) (4) KERYDIN (N=396)	Vehicle (N=205)
<u>Complete Cure^a</u>	<u>26 (6.5%)</u>	<u>1 (0.5%)</u>	<u>36 (9.1%)</u>	<u>3 (1.5%)</u>
<u>Treatment Success^b</u>	<u>61 (15.3%)</u>	<u>3 (1.5%)</u>	<u>71 (17.9%)</u>	<u>8 (3.9%)</u>
<u>Negative Mycology^c</u>	124 (31.1%)	14 (7.2%)	142 (35.9%)	25 (12.2%)

6.1.6 Other Endpoints

Other endpoints will be presented for descriptive and exploratory purposes given that the protocol did not include plans to adjust for the Type I error.

The mean number of affected (>10% affected) non-target toenails was 3.4 The proportion of completely clear or almost clear toenails (excluding TGT) was 0.6.

Discussion of follow up extension data is presented in 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects.

6.1.7 Subpopulations

The trials were not designed and powered to detect treatment differences in subgroups (age, gender, and race). According to descriptive analysis the treatment effects were generally consistent across subgroups.

Comment: Examination of treatment effect in by gender, race, and age did not identify clinically relevant differences

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%
Section 14 Clinical studies:

(b) (4)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In Study 200/200A, the treatment regimen was once daily for 90 days followed by three times weekly for 90 days. Treatment response was defined as complete absence of signs and symptoms, negative KOH and culture. The results are presented below:

Study	Vehicle	Tavaborole 2.5%	Tavaborole 5%	Tavaborole 7.5%
200/200A	2/63 (3%)	2/33 (6%)	4/31 (13%)	4/60 (7%)

In two open-label phase 2 studies (201 and 203) success rates for tavaborole 5% solution were 2/29 (7%) and 4/30 (13%) respectively. In study 201 the treatment regimen was once daily for 360 days. Treatment response was defined as clear nail and negative culture. In Study 203 the treatment regimen was once daily for 30 days followed by three times weekly for 150 days. Treatment response was clear nail or at least 5 mm of clear nail growth and negative KOH and culture.

Comment: Based on these efficacy results coupled with similar safety profiles of 5% and 7% solutions, the applicant appropriately selected tavaborole solution 5% for phase 3 program.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The applicant attempted to characterize the duration of effect by extending the follow up period from week 52 to week 60. This late protocol amendment was received in September 2012, thus at the time when phase 3 trials were ongoing.

The sample size was small (49 tavaborole 5%, 13 vehicle) even more so when considering subjects who actually achieved complete cure at week 52 (13 subjects in the tavaborole 5% arm).

Comment:

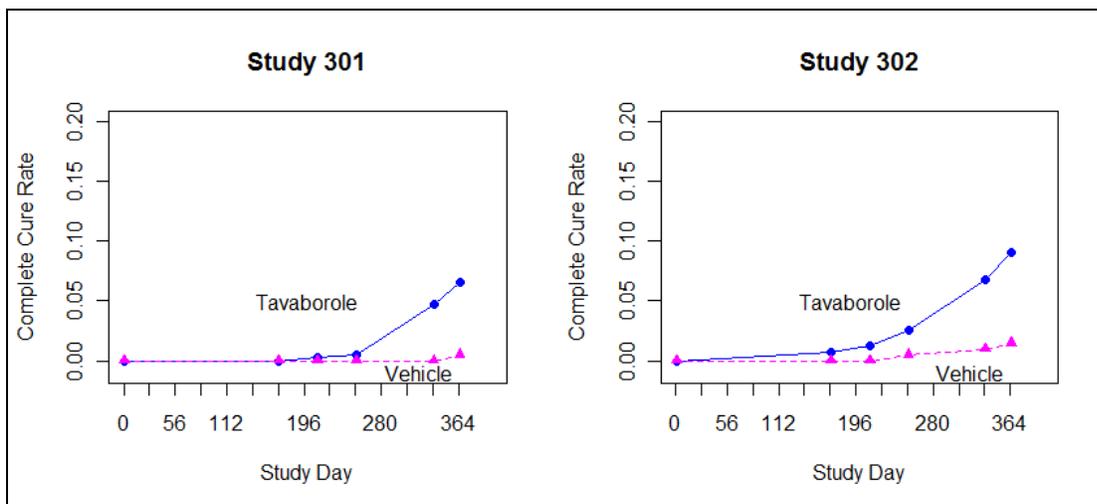
(b) (4)

(b) (4)

6.1.10 Additional Efficacy Issues/Analyses

Response over time for both trials showed improvement over 52 weeks, however, the curves begin to separate after 6 months.

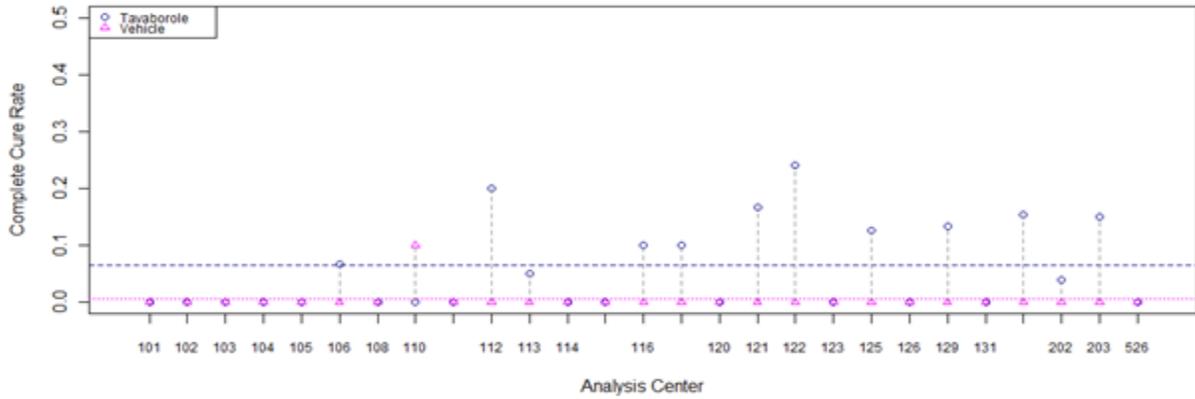
Figure 3 Complete Cure Rates over Time



Source: Agency Statistical review Figure 1

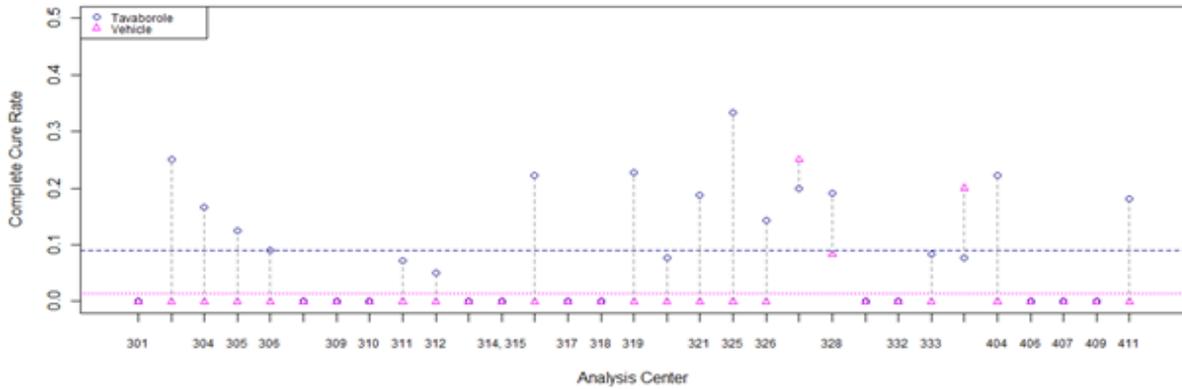
Efficacy by center was analyzed by the Agency statistical reviewer Kathleen Fritsch, PhD. For detailed analysis please see Statistical review. In brief Dr. Fritsch concluded: “Because of the large number of centers and the low overall response rate on the vehicle arm no center is overly influential on the overall results... The p-values from the Breslow-Day test for homogeneity were 0.008 for Study 301 and 0.706 in Study 302. Note that the Breslow-Day test requires a large sample size within each center, and thus the assumptions are not met. In Study 301, only 1 vehicle subject in the whole study had a complete cure. Thus the significant result for the Breslow-Day test in Study 301 is not meaningful. “

Figure 4 Efficacy by Analysis Center (Trial 301)



Source: Agency Statistical review Fig.5

Figure 5 Efficacy by Analysis Center (Trial 302)



Source: Agency Statistical review, Fig.6

7 Review of Safety

Safety Summary

The clinical program consists of 12 clinical trials/studies in which a total of 1500 subjects received at least 1 dose of tavaborole.

There was one death reported in a phase 2 dose ranging trial. The cause was head trauma secondary to a fall. This was judged by the applicant and this reviewer to be unrelated to the drug treatment.

The rest of the safety assessments from phase 1 and phase 2 clinical trials demonstrated results that were similar to those from phase 3 trials.

Safety assessment was based primarily on two adequate phase 3 vehicle-controlled trials conducted in the United States, Mexico and Canada and comprised of 1186 subjects (791 randomized to tavaborole and 295 subjects randomized to vehicle).

The drop-out rate from safety population was about 13% and similar for both arms. The exposure to the drug was adequate to assess safety issues and define language appropriate for labeling.

The safety evaluation consisted of reported adverse events, local tolerability assessments, vital signs, laboratory tests, and EKG data.

The incidence of SAEs was similar between subjects treated with tavaborole solution, 5% and vehicle (2.5% versus 2.4%, respectively). None of the SAEs appear to be related to the drug.

The most common adverse reactions were application site reactions (7%) and ingrown toenail (3%).

- Application site reactions were described by the applicant as mild to moderate and resolved spontaneously. The most common were application site exfoliation (3%) and application site erythema (2%). Number of subjects with severe reactions did not differ between the groups (0.6% and 0.5% for active and vehicle, respectively).

Clinical Review
Milena Lolic, MD, MS
NDA 204,427

Kerydin (tavaborole) Topical Solution, 5%

- Ingrown toenail was described as severe in one out of 20 subjects who developed ingrown toenails while exposed to tavaborole

Systemic exposure of tavaborole solution 5% is low and no systemic toxicities have been identified. There were no clinically meaningful changes observed in vital signs, laboratory values, or EKGs. TQT study was negative.

Dermal irritancy study showed potential of tavaborole to cause irritation.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from the trials that utilized to-be-marketed formulation: two pivotal trials AN2690-ONYC-301 and AN2690-ONYC-302 (referred as 301 and 302 trials), three phase 2 trials (AN2690-ONYC-200/200A, AN2690-ONYC-201 and AN2690-ONYC-203), one pharmacokinetic trial (P06118), one dermal safety trial AN2690-ONYC-103 (referred as trial 103), and one QT trial AN2690-ONYC-102 (referred as 102 trial).

The two pivotal randomized, double-blind, multicenter, placebo-controlled trials utilized 48 weeks of daily treatment with AN2690. The emphasis of the safety review was on the pooled data from these trials (safety population data set).

Safety data from dose ranging Phase 2 trials utilized several different dosing regimens therefore are presented separately from phase 3 trials data.

The pharmacokinetic trial P06118 was an open label trial, utilizing AN2690 daily for two weeks under maximal use conditions and, therefore, safety data is presented separately.

One dermal safety study was conducted in healthy volunteers according to typically used dermal safety protocols for dermal irritation and sensitization.

The thorough QT study was an open-label, randomized, 4-arm crossover study with a topical therapeutic and supratherapeutic tavaborole 5% dosing, vehicle control and a positive control (oral 400 mg moxifloxacin) conducted in healthy subjects.

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Table 20 Trials Used for Safety Assessment

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK (MUSE)	P06118	5.3.3.2	To determine the pharmacokinetics of Tavaborole Topical Solution, 5% in subjects with toenail onychomycosis following topical administration. The secondary objective was to evaluate the safety and tolerability of Tavaborole Topical Solution, 5%.	Open-label NA	Tavaborole Topical Solution, 5% 200 µL to all 10 toenails Topical (applied by rubber bulb dropper)	24	Distal subungual onychomycosis	15 days	Completed; Full
Safety (RIPT)	AN2690-ONYC-103	5.3.4.1	To determine the potential of Tavaborole Topical Solution, 5% to induce sensitization or to cause irritation by repeated topical application to the healthy skin of humans under controlled conditions. Safety will be assessed by evaluation of local tolerability reactions, any reported AEs and use of concomitant medications.	Single-center, randomized, controlled, within-subject comparison study. Controls for Cohort 1: Tavaborole Vehicle and 0.1% SLS Controls for Cohort 2: Tavaborole Vehicle and 0.5% SLS	Tavaborole Topical Solution, 5% Tavaborole Topical Solution, Vehicle 0.5% SLS Cohort 1: 0.2 mL 3 × weekly for a total of 3 weeks during Induction Phase, and once at Challenge Cohort 2: 0.2 mL once daily for 21 consecutive days over 3 weeks Topical	234 (Cohort 1) 45 (Cohort 2)	Healthy subjects	Cohort 1: 3-week induction and a single 48-hour challenge after a rest period of 10-14 days. Cohort 2: 21 days.	Completed; Full
Safety and PK (QT/QTc)	AN2690-ONYC-102	5.3.4.1	To assess the ECG effects of tavaborole following multiple-dose administration of Tavaborole Topical Solution 5%. Secondary objective is to assess the safety and tolerability of therapeutic and supratherapeutic doses of Tavaborole Topical Solution 5% when administered for 14 days.	Single center, open-label randomized, crossover study. Tavaborole Vehicle and moxifloxacin positive control	Tavaborole Topical Solution, 5% Tavaborole Topical Solution, Vehicle Tavaborole Topical Solution, 5% QD on all 10 toenails for 14 days Tavaborole Topical Solution, 5% BID on all 10 toenails, 10 fingernails, and ~ 5 mm of surrounding skin for 14 days. Vehicle QD on all 10 toenails for 14 days Vehicle QD on all 10 toenails for 14 days plus single dose of unblinded moxifloxacin 400 mg orally on Day 14 Topical	55	Healthy subjects	4 treatment periods of 14 days each separated by 3 washout periods of at least 7 days.	Completed; Full

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Safety and Efficacy	AN2690-ONYC-201 Cohorts 1 and 2	5.3.5.2	To evaluate the safety and efficacy of tavaborole solution 5% and tavaborole solution 7.5% administered for 180 days in the treatment of distal subungual onychomycosis of the great toenail.	Open-label NA	tavaborole solution 5% tavaborole solution 7.5% Once daily for 180 days Topical	30 30	Distal subungual onychomycosis	180 days	Completed; Full
Safety and Efficacy	AN2690-ONYC-201 Cohort 3	5.3.5.2	To determine the safety and efficacy of tavaborole solution 5% when applied daily for 360 days in the treatment of distal subungual onychomycosis of the great toenail.	Open-label NA	tavaborole solution 5% Once daily for 360 days Topical	29	Distal subungual onychomycosis	360 days	Completed; Full
Safety and Efficacy	AN2690-ONYC-203	5.3.5.2	To evaluate the safety and efficacy of tavaborole solution 1% and tavaborole solution 5% in the treatment of distal subungual onychomycosis of the great toenail.	Open-label NA	tavaborole solution 1%, once daily for 180 days tavaborole solution 5%, once daily for 30 days, 3x weekly for 150 days Topical	30 30	Distal subungual onychomycosis	180 days	Completed; Full
Safety and Efficacy	AN2690-ONYC-200/200A	5.3.5.1	To determine the safety and efficacy of tavaborole solution 2.5%, tavaborole solution 5%, and tavaborole solution 7.5% compared to the solution Vehicle alone in the treatment of distal subungual onychomycosis of the great toenail.	Randomized, double-blind Vehicle	Vehicle tavaborole solution 2.5% tavaborole solution 5% tavaborole solution 7.5% Once daily for 90 days, 3x weekly for 90 days Topical	63 33 31 60	Distal subungual onychomycosis	180 days	Completed; Full
Safety and Efficacy (Phase 3)	AN2690-ONYC-301	5.3.5.1	To determine the efficacy and safety of Tavaborole Topical Solution, 5% applied once daily as compared to Tavaborole Topical Solution, Vehicle.	Randomized, double-blind Vehicle	Tavaborole Topical Solution, 5% Tavaborole Topical Solution, Vehicle Once daily for 336 days Topical	194 399	Distal subungual onychomycosis	336 days	Completed; Full
Safety and Efficacy (Phase 3)	AN2690-ONYC-302	5.3.5.1	To determine the efficacy and safety of Tavaborole Topical Solution, 5% applied once daily as compared to Tavaborole Topical Solution, Vehicle.	Randomized, double-blind Vehicle	Tavaborole Topical Solution, 5% Tavaborole Topical Solution, Vehicle Once daily for 336 days Topical	205 396	Distal subungual onychomycosis	336 days	Completed; Full

Source: Adapted from applicant's Table 5.2

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

7.1.2 Categorization of Adverse Events

In the opinion of this reviewer, the sponsor adequately categorized the adverse events using MedDRA classification Version 13.1 terminology.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data across two pivotal trials was done by the applicant. All analysis was done on safety population.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 1198 subjects were randomized in phase 3 trials (799 to tavaborole and 399 to vehicle). However, safety population comprises of 1186 subjects due to 4 subjects (all from tavaborole arm) who did not have documentation of drug applications and 8 subjects (4 from tavaborole and 4 from vehicle arm) who did not have at least one post-baseline visit.

Target population demographics were similar between treatment arms and reflective of typical population affected with toenail onychomycosis.

Table 21 Demographics-Safety Population

Characteristics	Tavaborole (N= 791) n (%)	Vehicle (N=395) n (%)	Total (N=1186) n (%)
Male	643 (81)	329 (83)	972 (82)
Female	148 (19)	66 (17)	214 (18)
Age (mean)	55	55	55

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

≥18 to <65 years	641 (81)	316 (80)	957 (81)
≥65 years	150 (19)	79 (20)	229 (19)
Race			
White	667 (84)	333 (84)	1000 (82)
African American	40 (5)	24 (6)	64 (5)
Asian	13 (2)	2 (1)	15(2)
Other	71 (9)	36 (9)	107 (11)
Geographic region			
US	652 (82)	325 (82)	977 (82)
Mexico	59 (8)	30 (8)	89 (8)
Canada	80 (10)	40 (10)	120 (10)

Source: Data set adsl.xpt and reviewers analysis

Comment: Demographic characteristics between the groups and trials are comparable and reflective of prevalence of this condition in general population. Slight numeric differences between Table 21 and Table 5 from Statistical review are the result of using safety population v. ITT population for analysis in respected tables.

It should be noted that over 80% of all enrolled subjects were from US. The applicant submitted an acceptable rationale for assuming the applicability of foreign data to the U.S. population/practice of medicine in the amendment dated October 18, 2013. The rationale was based on 1) the overall similarity in subject demographics and the species of dermatophytes causing disease 2) standards of care, medical practice, and compliance across the countries represented, 3) the standardized diagnostic criteria and methodology applied to all enrolled subjects, and 4) the results of sensitivity analyses demonstrating similar phase 3 results irrespective of the data contributed by foreign sites.

Overall exposure in these trials was affected by several factors including variable number of treated toes, drop-out rate and missed doses, however the degree of variability did not have significant impact. For example, the total number of expected doses during the treatment period was 336 doses and reported median number of applications was 330.5 and 331 (tavaborole and vehicle arms, respectively). Also, the median amount of product used in both arms was 94 grams (range 1 to 342 grams).

Comment: Usage and dosing for the vehicle treatment group were similar to those for the tavaborole treatment group. Considering a small difference in number of expected and applied doses as well as comparable amounts of solution used in active and control groups, the exposure was adequate to analyze the safety of tavaborole solution 5%.

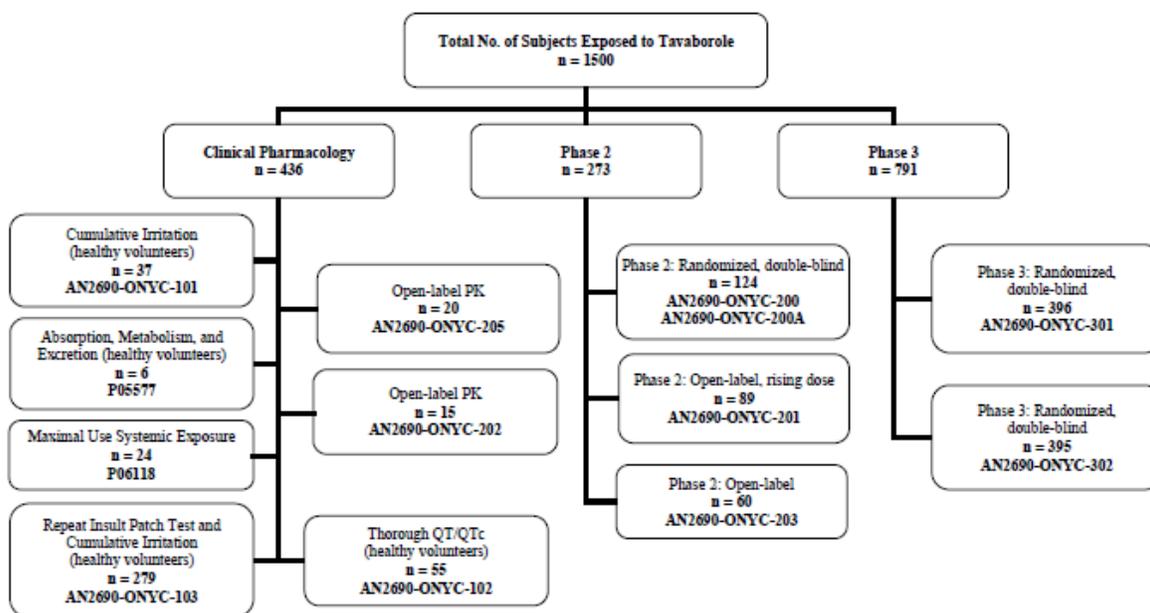
Treatment compliance was documented using subject dosing diaries and not by using investigational product accountability due to the fact that usage per subject could vary significantly (subjects may have treated multiple toes and not just the TGT). Subjects were required to have applied at least 80% and not more than 120% of expected doses, and not to have missed more than 14 consecutive doses to be considered compliant with dosing requirements.

Comment: It should be noted that compliance based on not validated subjects' assessment is unreliable. It is somewhat reassuring that despite limitations, the applicant's data show comparable compliance between treatment arms.

7.2.2 Explorations for Dose Response

During development, 1500 subjects were exposed to tavaborole solution in various concentrations and dosing regimens (of note 78 subjects used not-to-be-marketed formulation in early trials).

Figure 6 Number of Subjects Exposed to Tavaborole



Source: Figure 3 from applicants Section 2.5. Clinical Overview

Comment: Overall exposure in both subject exposure and in total numbers of exposed subjects to tavaborole is adequate for a safety assessment.

The applicant conducted three dose ranging phase 2 studies that explored tavaborole solutions of 1%, 2.5%, 5%, and 7.5% applied topically once daily or three times per week for total of 180 to 360 days. These studies are: AN2690-ONYC-201, AN2690-

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%
 ONYC-203, and AN2690-ONYC-200/200A and safety assessments will be presented for each of them separately.

Study AN2690-ONYC-201

This was an open-label, dose-rising, multicenter study of subjects with distal, subungual onychomycosis of one great toenail. Total of 89 subjects were treated as follows:

- Cohort 1.....tavaborole solution 5% daily for 180 days
- Cohort 2.....tavaborole solution 7.5% daily for 180 days
- Cohort 3.....tavaborole solution 5% daily for 360 days

There were no deaths in the study.

There were 3 SAEs: cholecystitis and hernia surgery in Cohort 2 and uterine hemorrhage reported in Cohort 3, all assessed by the applicant and this reviewer as not related.

Seven subjects had 9 severe reactions, 4 of which were application site reactions [and other five were onychomadesis, local reaction, and contact dermatitis (3)]. All were considered by applicant and this reviewer as related to the treatment.

Summary of all AEs in this dose-ranging trial is presented below.

Table 22 Summary of AEs-Trial 201

	Cohort 1 Tavaborole 5.0% QD 180 Days (N = 30)	Cohort 2 Tavaborole 7.5% QD 180 Days (N = 30)	Cohort 3 Tavaborole 5.0% QD 360 Days (N = 29)
No. of Subjects Who Reported ≥1 AE	25 (83.3%)	20 (66.7%)	16 (55.2%)
No. of Events	64	52	32
Serious ^a			
No	64 (100.0%)	50 (96.2%)	31(96.9%)
Yes	0	2 (3.8%)	1 (3.1%)
Severity ^a			
Mild	42 (65.6%)	28 (53.8%)	27 (84.4%)
Moderate	15 (23.4%)	22 (42.3%)	5 (15.6%)
Severe	7 (10.9%)	2 (3.8%)	0
Relationship ^a			
Unrelated	55 (85.9%)	39 (75.0%)	31 (96.9%)
Unlikely	0	3 (5.8%)	0
Possible	0	0	1 (3.1%)
Probable	0	1 (1.9%)	0
Related	9 (14.1%)	9 (17.3%)	0
AE Leading to Study Discontinuation ^b	1 (3.3%)	1 (3.3%)	0

Source: Applicant's Table 23 from Section 2.7.4

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

Study AN2690-ONYC-203

This was an open-label, multi-center study of subjects with distal subungual onychomycosis of at least one great toenail. Total of 60 subjects were treated as follows:

Cohort 1.....tavaborole solution 1.0%, daily for 180 days

Cohort 2.....tavaborole solution 5.0%, daily for 30 days followed by 3× weekly for 150 days.

At the end of the 180-day treatment period, subjects classified as complete or partial responders were followed until Day 360 (off treatment).

There were no deaths.

There were three subjects with SAEs: prostate cancer and ventricular tachycardia in tavaborole 1% group and sternal fracture in tavaborole 5% group –all assessed by the applicant and this reviewer as non-related to the treatment.

The case of prostate CA involves a 57 year old man with 2 years history of an enlarged prostate treated with terazosin. Subject was enrolled in tavaborole 1% arm and was diagnosed with adenocarcinoma of prostate 4 months later.

There were 2 subjects with severe AEs: sternal fracture and epilepsy in 5% group-both assessed by the applicant and this reviewer as not related to the treatment.

There were no reported severe application site reactions.

Summary of all AEs from this trial is presented below.

Table 23 Summary of AEs-Trial 203

	Tavaborole 1.0% QD 180 Days (N = 30)	Tavaborole 5% QD 30 Days Then 3× Weekly 150 Days (N = 30)
No. of Subjects Who Reported ≥1 AE	15 (50.0%)	16 (53.3%)
No. of Events	37	38
Serious ^a		
No	35 (94.6%)	37 (97.4%)
Yes	2 (5.4%)	1 (2.6%)
Severity ^a		
Mild	12 (32.4%)	13 (34.2%)
Moderate	25 (67.6%)	23 (60.5%)
Severe	0	2 (5.3%)
Relationship to Study Drug ^a		
Unrelated	31 (83.8%)	21 (55.3%)
Unlikely	6 (16.2%)	16 (42.1%)
Possible	0	0
Probably	0	1 (2.6%)
Related	0	0
AE Leading to Study Discontinuation ^b	1 (3.3%)	1 (3.3%)

Source: Applicant's Table 24 from Section 2.7.4

Study AN2690-ONYC-200/200A

This was a multi-center, randomized, double-blind, parallel-group, vehicle-controlled study utilizing tavaborole solutions 2.5%, 5.0%, and 7.5% and vehicle in adults with onychomycosis of the great toenail. Subjects applied study drug once daily for 90 days followed by 3× weekly for an additional 90 days for a total of 180 days. At the end of the 180-day treatment period, subjects who were classified as complete or partial responders were followed for an additional 180 days off treatment.

One death occurred during the trial. Subject 01-130 that was treated with 7.5% tavaborole died of trauma that was not considered by investigators as related to the treatment.

Case presentation: The subject was 61 years old female with previous history of high blood pressure, arthralgia of the knees, asthma, diabetes, and obesity. She was treated with tavaborole 7.5% from July 26, 2006 until November 6, 2006. On (b)(6) she fell down and, according to the death certificate, died of head trauma.

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Comment: I agree with the investigator's assessment that event was not likely related to the drug.

There were five subjects with 6 serious AEs (in vehicle group: wound infection following female sterilization, pneumonia and pleural effusion, left hip joint replacement; in 2.5% tavaborole solution group: meningitis, and in the tavaborole solution 5% group inguinal hernia repair) all judged unrelated to study drug by the applicant as well as this reviewer.

There were 10 subjects with severe AE: four subjects in the vehicle treatment group (acquired immunodeficiency syndrome, pneumonia, nail dystrophy, and joint arthroplasty), 2 subjects in the 2.5% tavaborole solution group (pharyngitis and skin infection), and four in the tavaborole solution 7.5% treatment group (bronchitis, pharyngitis, head injury, and prostatitis). These were all judged unrelated to study drug by the applicant as well as this reviewer. There is no mechanistic likelihood that tavaborole would impact the infection rate in 6 subjects, particularly given the level of systemic exposure from the topically applied antifungal solution.

There were no severe application site reactions.

Summary of all AEs is presented below.

Table 24 Summary of AEs-Trial 200/200A

	Vehicle QD 90 Days Then 3× Weekly 90 Days (N = 63)	Tavaborole 2.5% QD 90 Days Then 3× Weekly 90 Days (N = 33)	Tavaborole 5.0% QD 90 Days Then 3× Weekly 90 Days (N = 31)	Tavaborole 7.5% QD 90 Days Then 3× Weekly 90 Days (N = 60)
No. of Subjects Who Reported ≥1 AE	28 (44.4%)	14 (42.4%)	13 (41.9%)	30 (50.0%)
No. of Events	55	34	21	58
Serious ^a				
No	51 (92.7%)	33 (97.1%)	20 (95.2%)	57 (98.3%)
Yes	4 (7.3%)	1 (2.9%)	1 (4.8%)	1 (1.7%)
Severity ^a				
Mild	28 (50.9%)	25 (73.5%)	15 (71.4%)	34 (59.6%)
Moderate	23 (41.8%)	7 (20.6%)	6 (28.6%)	19 (33.3%)
Severe	4 (7.3%)	2 (5.9%)	0	4 (7.0%)
Relationship ^a				
Unrelated	48 (87.3%)	34 (100.0%)	20 (95.2%)	50 (86.2%)
Unlikely	6 (10.9%)	0	0	2 (3.4%)
Possible	1 (1.8%)	0	0	1 (1.7%)
Probable	0	0	0	3 (5.2%)
Related	0	0	1 (4.8%)	2 (3.4%)
AE Leading to Study Discontinuation ^b	0	0	0	1 (1.7%)

Source: Applicant's Table 25 from Section 2.7.4

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

Comment: Overall, phase 2 studies revealed thirteen SAEs, none of which raises safety concerns from this reviewer. There was no clustering of the cases, no reasonable mechanism, and there was no apparent dose related trend (1%=2SAEs, 2.5%=1SAE, 5%=3SAEs, 7.5%=3SAEs, vehicle =4SAEs).

There were 4 severe application skin reactions (one in 7.5% arm with 180 day dosing, and other three in 5% arm with 180 day dosing).

Total of 5 subjects discontinued studies due to AEs (all active treatment groups) and 2 of those were considered treatment related (local skin reaction in 7.5% arm and contact dermatitis in 5% arm).

7.2.3 Special Animal and/or In Vitro Testing

Two *in vitro* studies have shown that tavaborole solution 5%, at therapeutic concentrations, is unlikely to either inhibit or induce cytochrome P450 (CYP450) enzymes.

- DM27755: In Vitro Assessment of Human Liver Cytochrome P450 Inhibition Potential of SCH 900340 (AN2690)

This study was designed to evaluate the ability of AN2690 to inhibit the major CYP enzymes in human liver microsomes. The conclusion of the study was that tavaborole caused insufficient inhibition across the range of concentrations examined.

- DM27769: In Vitro Evaluation of SCH 900340 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes

This study was designed to evaluate the effect of tavaborole on the induction of CYP enzymes in primary cultures of human hepatocytes. Tavaborole caused little or no change in CYP enzyme activities.

7.2.4 Routine Clinical Testing

The schedule of clinical safety assessments for each of the studies consisted of vital signs, general physical examination, routine laboratory testing, and monitoring for AE (local and systemic). The methods and tests used as well as the frequency of testing were adequate.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

7.2.5 Metabolic, Clearance, and Interaction Workup

Routine testing was adequate to identify likely safety issues. Please see Section 4.4 Clinical Pharmacology. Safety overview of that trial is presented below.

There were no deaths in this study.

There was one subject (#000111) who experienced treatment-unrelated chest pain.

Case presentation: An 82-year-old white female suffered chest discomfort on Day 10 of dosing. The subject was observed in the ER overnight and was discharged the following morning with the primary diagnosis of atypical chest wall pain, likely musculoskeletal. The subject completed the study without further complication.

There were two subjects with application site reactions (tingling and warmth), none were severe.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The only other topical drug for onychomycosis treatment (Penlac®) does not belong to the same pharmacological class as tavaborole. However, it is worth mentioning that notable adverse events for Penlac® include application site erythema (5%) and potential to cause irritation as assessed by 21-Day Cumulative Irritancy Study.

Comment: The applicant's studies to detect these specific AEs were adequate.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in phase 3 trials. There was one death during tavaborole development that occurred in study 200/200A in subject treated with 7.5% solution.

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

The case is considered non-related to the drug (trauma) and described in section 7.2.2 Explorations for Dose Response.

7.3.2 Nonfatal Serious Adverse Events

In the two phase 3 trials, the incidence of SAEs was similar between subjects treated with tavaborole topical solution, 5%, and vehicle (2.5% versus 2.4%, respectively). All subjects with SAE are listed (per treatment arm) in the tables below.

Table 25 SAE in Tavaborole Solution 5% Arm-Phase 3

Subject number	Event
121033	Angina unstable
112021	Coronary artery disease
329024	Retinal artery occlusion; Femur fracture
332069	Appendicitis
112022	Vestibular neuronitis
110033	Pneumonia
112033	Cellulitis
304119	Arthralgia
121070	Intervertebral disc disorder
112052	Osteoarthritis
330069	Cystitis
117025	Prostate cancer
129011	Prostate cancer metastatic
112018	Syncope
304159	Cerebrovascular accident
328032	Anxiety
103009	Suicidal ideation
122033	Pulmonary embolism
311040	Deep vein thrombosis; Pulmonary embolism

Source: Applicant's Table 40 from section 2.7.4

Comment: None of the serious adverse events were deemed to be treatment-related by the applicant or this reviewer, and most occurred in only one subject. Events that occurred in 2 subjects will be presented below.

- *Subject 117025: 67 year old black man with PMH significant for benign prostatic hypertrophy was diagnosed on study day 184 with adenocarcinoma of prostate*

(Gleason score of 7/10) following a result of an elevated PSA. He underwent transurethral microwave thermotherapy, radiation, and anti-hormonal therapy while completing study participation. I agree with the applicant, that the event was likely related to the preexisting disease (subject's history of BPH).

- *Subject 129011: 58 year old white man with PMH significant for seasonal allergies and hypercholesterolemia was diagnosed with metastatic prostate cancer on study day 274. He was found to have elevated PSA (9.6) on study day 156 and elevated alkaline phosphatase (907) on study day 254. Body bone scan done on study day 268 showed widespread osseous metastatic disease and prostate biopsy done on study day 274 showed adenocarcinoma. Subject completed study treatment while receiving anti-hormonal therapy. Both, The PI and Medical Monitor for the study assessed the event as not related to study drug. I agree with that assessment. It is more likely that subject had undiagnosed prostate cancer prior to the start of the trial judging by the advanced stage of the disease at the time when diagnosis was made.*
- *Subject 122033: 61 year old white man with PMH significant for deep vein thrombosis, was diagnosed with pulmonary embolism on study Day 141. Previous history of DVT as well as recent history of twisted ankle, provide for more compelling explanation of causality than tavaborole use.*
- *Subject 311040: 46 years old white man with PMH significant for tinea pedis developed left leg DVT and PE on study day 176. His work up revealed recent long distance travel requiring a prolonged period of sitting which is more likely to contribute to the conditions than tavaborole.*

Table 26 SAE in Vehicle Arm-Phase 3

Subject number	Event
129026	Anemia
526004	Acute myocardial infarction; Cardiogenic shock; Ischemic cardiomyopathy
108067	Coronary artery disease
113049	Pancreatitis acute; Diabetic ketoacidosis
334005	Bronchitis
114014	Osteoarthritis
302013	Aortic aneurysm; Carotid artery disease; Peripheral artery aneurysm; Transient ischemic attack
122006	Aortic stenosis
126073	Suicide attempt
121086	Atrial fibrillation
409019	Chronic lymphocytic leukemia

Source: Source: Applicant's Table 40 from section 2.7.4

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

All SAEs that occurred in earlier tavaborole development are described in section 7.2.2 Explorations for Dose Response and considered unrelated to tavaborole treatment. The summary is presented in Table 27.

Table 27 SAEs from Phase 2 Trials

Trial	SAE	Arm
201 (open label)	cholecystectomy	active 7.5%
	hernia surgery	active 7.5%
	uterine hemorrhage	active 5%
203 (open label)	prostate CA	active 1%
	ventricular tachycardia	active 1%
	sternal fracture	active 5%
200/200A (controlled)	meningitis	active 2.5%
	inguinal hernia repair	active 5%
	wound infection	vehicle
	pneumonia	vehicle
	pleural effusion	vehicle
	hip replacement	vehicle

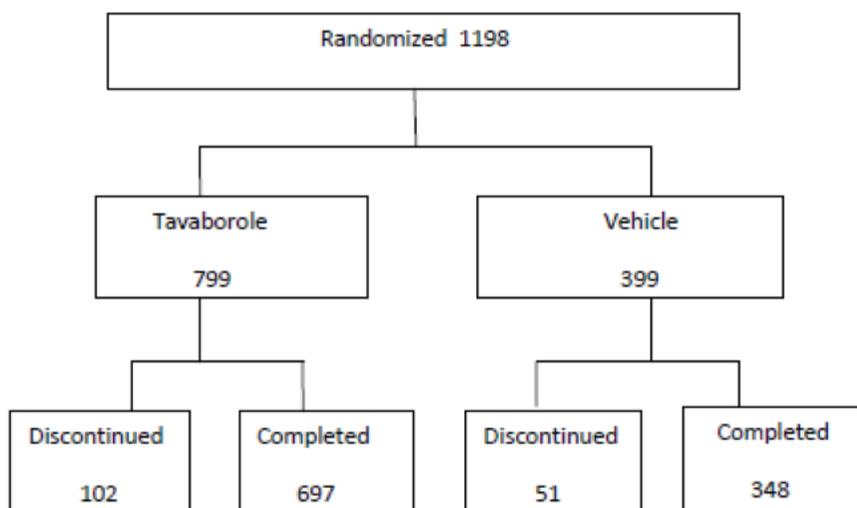
Source: Applicant's Tables 36,37, and 38 from section 2.7.4 combined by reviewer

Comment: Based on the reviewed narratives it is not likely that any of the SAEs was related to the treatment, particularly in light of the pharmacokinetic information described above which details the limited systemic exposure of tavaborole. Despite the numeric imbalance in occurrences of prostate cancer (3 occurrences) and pulmonary embolisms (2 occurrences) between tavaborole and vehicle group (0 occurrences), it is not likely that a safety signal exists due to either preexisting or concomitant disease as the alternative more likely causality. Considering low systemic tavaborole exposure, relatively short duration of exposure as well as negative carcinogenicity studies it is unlikely that tavaborole played a role in prostate cancer development.

7.3.3 Dropouts and/or Discontinuations

Total of 5075 subjects were screened, and 1198 were randomized in 301 and 302 trials.

Figure 7 Subjects Disposition



Source: Applicant's Figure 3 from section 5.3.5.1 for trials 302 and 302 combined by reviewer

Total of 1045 subjects completed trials and 153 subjects did not complete the trials for the reasons presented in Table 28.

Table 28 Subject Discontinuations

Reason	Tavaborole arm (N=799)	Vehicle arm (N=399)	Total (1198)
Adverse event	3 (<1%)	3 (1%)	6 (1%)
Subject's request (not related to drug)	47(6%)	23 (6%)	70 (6%)
Subject's request (related to drug)	7(1%)	8 (2%)	15 (1%)
Noncompliance	6 (1%)	4 (1%)	10 (1%)
Lost to follow up	28 (4%)	9 (2%)	37 (3%)
Other	11 (1%)	4 (1%)	15 (1%)
Total	102 (13%)	51 (13%)	153(13%)

Source: Applicant's Table 13 from section 2.7.4.

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Comment: Considering duration of the trial (52 weeks), the dropout rates are not surprising. There is no meaningful difference between active and vehicle arm in frequency and /or reasons for subject discontinuations from the studies.

There were 6 subjects with 8 AEs that caused subject's discontinuation from the trials and those are presented in Table 29.

Table 29 Summary of AEs Leading to Subject Discontinuation from the Trials

System Organ Class/ Preferred Term	Study (Subject ID)	Treatment Group (% tavaborole solution)	Severity	Relationship to Treatment
Endocrine Disorders				
Hypothyroidism	AN2690-ONYC-302 (301036)	Tavaborole Topical Solution, 5%	Moderate	Unlikely
General Disorders and Administration Site Conditions				
1. Application site erythema	AN2690-ONYC-301 (121073)	Tavaborole Topical Solution, 5%	1. Moderate	1. Possible
2. Application site exfoliation			2. Moderate	2. Possible
Nervous System Disorders				
Paresthesia	AN2690-ONYC-302 (313044)	Vehicle	Moderate	Unlikely
Respiratory, Thoracic and Mediastinal Disorders				
Pulmonary embolism	AN2690-ONYC-302 (311040)	Tavaborole Topical Solution, 5%	Severe	Not related
Skin and Subcutaneous Tissue Disorders				
Dermatitis	AN2690-ONYC-301 (105062)	Vehicle	Mild	Possible
Pruritus	AN2690-ONYC-301 (526019)	Vehicle	Severe	Probable
Pain of skin	AN2690-ONYC-302 (313044)	Vehicle	Moderate	Unlikely
Vascular Disorders				
Deep vein thrombosis	AN2690-ONYC-302 (311040)	Tavaborole Topical Solution, 5%	Severe	Not related

Source: Applicant's Table 45 from 2.7.4.2.1.6.2.2.2

Comment: Narratives were reviewed. Most of the discontinuations were result of AEs non-related to the treatment. One subject in the active arm and 2 subjects in the vehicle arm were discontinued due to adverse reactions. The rates and reasons for discontinuation from the trials do not raise safety concerns.

Table 30 Treatment Discontinuations

Reason	Tavaborole arm (N=799)	Vehicle arm (N=399)	Total (1198)
Adverse event	13 (2%)	4 (1%)	17 (1%)
Subject's request (not related to drug)	44 (6%)	22 (6%)	66 (6%)
Subject's request (related to drug)	6 (1%)	8(2%)	14 (1%)
Noncompliance	6 (1%)	5 (1%)	11 (1%)
Lost to follow up	28 (4%)	9 (2%)	37 (3%)

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Other	9 (1%)	4 (1%)	13 (1%)
Total	106 (13%)	52 (13%)	158 (13%)

Source: reviewer's analysis of ITT data set

Comment: Overall rate of treatment discontinuations is similar between active and vehicle arms and similar to the rates observed in Table 28 (discontinued subjects). However, some subjects remained in the study although the treatment may have been discontinued, accounting for the differences between Tables 28 and 30. For example, treatment discontinuations due to adverse events were more common in active arm (2%) v. vehicle arm (1%). Interestingly, more subjects in vehicle arm requested discontinuation of the treatment in relation to the study drug than in active arm, making interpretation of these differences difficult.

7.3.4 Significant Adverse Events

There were 60 severe adverse events reported by 38 subjects (4.8%) treated with tavaborole and 41 severe adverse events reported by 19 subjects (4.8%) treated with vehicle. Vast majority of severe adverse events were unrelated to the treatment. The adverse events that were assessed as related (thus adverse reactions) are mainly application site reactions and are presented below:

Table 31 Severe Adverse Reactions

Treatment	Trial	Subject	AE (preferred term)	Dosing
Tavaborole	301	110099	ingrown nail	interrupted
			application site pain	interrupted
	301	113056	application site discharge	interrupted
			application site exfoliation	continued
	301	123029	application site exfoliation(TGT)	interrupted
			application site edema	discontinued
	301	126040	edema peripheral	discontinued
			application site erythema	discontinued
			erythema (untreated toes)	discontinued
			application site induration	discontinued
			skin induration	continued
			application site reaction	discontinued
			skin maceration	discontinued
			application site pruritus	interrupted
pruritus (untreated toes)			discontinued	
302			306007	dermatitis contact
	application site dermatitis (TGT)	continued		
Vehicle	301	113052	application site scab (left GT)	discontinued
			application site exfoliation (left GT)	interrupted

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

			application site scab (right GT)	discontinued
			application site exfoliation (right GT)	interrupted
	301	526019	pruritis (above ankles)	discontinued

Source: Adapted from applicant's Table 43 from section 2.7.4

Comment: The proportion of subjects who experienced severe reactions did not differ between the groups (0.6% and 0.5% for active and vehicle, respectively) while the number of reactions was higher in active (2.1%) than in vehicle arm (1.3%). The discrepancy is the result of unbalanced frequency of AR, where more than half of all severe reactions in tavaborole arm were reported in a single subject. Severe adverse reactions were more likely than not to cause interruptions/discontinuations in dosing. However, only one subject (526019 from vehicle arm) was discontinued from the trial due to severe adverse reaction.

7.3.5 Submission Specific Primary Safety Concerns

More subjects treated with tavaborole experienced application site reactions (52 or 6.51%) than subjects treated with vehicle (7 or 1.75%). The breakdown of specific application site reactions is presented in Table 32.

Table 32 Application Site Reactions

PT	AN2690 5% TOPICAL SOLUTION (N = 791)			VEHICLE (N = 395)		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Application site exfoliation	33	21	2.65	2	1	0.25
Application site erythema	23	13	1.64	0	0	0
Application site dermatitis	17	10	1.26	0	0	0
Application site pain	14	8	1.01	1	1	0.25
Application site discharge	9	5	0.63	0	0	0
Application site haematoma	7	5	0.63	3	3	0.76
Application site vesicles	5	5	0.63	1	1	0.25
Application site pruritus	8	4	0.51	0	0	0
Application site induration	6	3	0.38	0	0	0
Application site reaction	3	3	0.38	1	1	0.25
Application site hypersensitivity	3	2	0.25	0	0	0
Application site anaesthesia	1	1	0.13	0	0	0
Application site bleeding	1	1	0.13	0	0	0
Application site discolouration	1	1	0.13	0	0	0
Application site dryness	1	1	0.13	0	0	0
Application site fissure	1	1	0.13	0	0	0
Application site infection	1	1	0.13	1	1	0.25
Application site irritation	1	1	0.13	0	0	0
Application site oedema	1	1	0.13	0	0	0
Application site scab	1	1	0.13	2	1	0.25

Source: Data sets ade.xpt and adsl.xpt and reviewer's analysis using MAED

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Local tolerability signs and symptoms were actively assessed at each visit rather than reported as AEs. Most frequent were scaling and erythema. Data are presented in the Table 33.

Table 33 Number of Subjects with Local Signs and Symptoms

Local reaction	Tavaborole (N=791)	Vehicle (N=395)
Scaling	186 (24%)	34(9%)
Erythema	99 (13%)	9 (2%)
Burning/stinging	55 (7%)	8 (2%)
Pruritus	34 (4%)	4 (1%)
Oozing and crusting	29 (4%)	3 (<1%)
Induration/edema	26 (3%)	1(<1%)

*Subject 126040 had longest duration of erythema from Week 24 to Week 36.
 Source: Data set adsl.xpt and adasr.xpt and reviewer's analysis using JMP

Comment: The treatment was supposed to be applied to the entire nail surface and under the tip of the each nail, thus skin exposure was likely to occur. The instruction for tavaborole use included that excess solution present on the skin around each treated nail be removed using a tissue. It is difficult to assess wheatear this was done after each application, but considering irritation capabilities of the solution, it is not surprising that these signs and symptoms have been observed at the presented rates. Per protocol, only those signs/symptoms that resulted in treatment with a medication or a drug holiday were considered AEs and as such included in the analysis of all AEs.

Most of the local signs and symptoms were mild to moderate, and severe ones are presented in the Table 34.

Table 34 Distribution of Severe Local Signs and Symptoms

Local reaction	Tavaborole	Vehicle
Scaling	5	2
Erythema	4	0
Induration/edema	2	0
Pruritus	2	0
Burning/stinging	1	0
Oozing and crusting	0	1

Source: ISS-Table 14.3.1.1.1.

Twenty-one subjects in the tavaborole group and one subject in the vehicle group had a drug holiday because of local reactions [due to Grade 2 (moderate reaction or higher)].

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Across both phase 3 studies, 61% subjects in tavaborole group (482/791) and 62% subjects in the vehicle group (244/395) reported AEs. Most common AEs are presented in Table 35.

Table 35 Most Common AEs Occurring in >1% of Subjects

PT	AN2690 5% TOPICAL SOLUTION (N = 791)			VEHICLE (N = 395)		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Tinea pedis	160	96	12.14	93	61	15.44
Nasopharyngitis	59	51	6.45	32	26	6.58
Upper respiratory tract infection	47	43	5.44	20	20	5.06
Back pain	26	26	3.29	5	5	1.27
Hypertension	25	25	3.16	17	17	4.3
Headache	29	22	2.78	21	13	3.29
Application site exfoliation	33	21	2.65	2	1	0.25
Ingrowing nail	21	20	2.53	1	1	0.25
Procedural pain	21	20	2.53	5	5	1.27
Muscle strain	21	19	2.4	8	7	1.77
Sinusitis	22	19	2.4	15	10	2.53
Arthralgia	17	17	2.15	6	6	1.52
Influenza	18	14	1.77	16	11	2.78
Application site erythema	23	13	1.64	0	0	0
Limb injury	14	13	1.64	4	4	1.01
Bronchitis	11	11	1.39	10	10	2.53
Pharyngitis	16	11	1.39	2	2	0.51
Application site dermatitis	17	10	1.26	0	0	0
Dermatitis contact	10	10	1.26	4	3	0.76
Nasal congestion	9	9	1.14	2	2	0.51
Application site pain	14	8	1.01	1	1	0.25
Depression	8	8	1.01	4	4	1.01
Hypercholesterolaemia	8	8	1.01	3	3	0.76
Pain in extremity	8	8	1.01	3	3	0.76

Source: Data sets adae.xpt and adsl.xpt and reviewer's analysis using MAED

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

The following table represents selected AEs that occurred at the rate of at least 2% of subjects and at the higher rate in active arm than in vehicle.

Table 36 Adverse Events Occurring in >2% of Tavaborole –Treated Subjects and at the Greater Frequency than Vehicle

PT	AN2690 5% TOPICAL SOLUTION (N = 791)			VEHICLE (N = 395)		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Upper respiratory tract infection	47	43	5.44	20	20	5.06
Back pain	26	26	3.29	5	5	1.27
Application site exfoliation	33	21	2.65	2	1	0.25
Ingrowing nail	21	20	2.53	1	1	0.25
Procedural pain	21	20	2.53	5	5	1.27
Muscle strain	21	19	2.4	8	7	1.77
Arthralgia	17	17	2.15	6	6	1.52

Source: Data sets adae.xpt and adsl.xpt and reviewer's analysis using MAED

Comment: Considering the mechanism of action and low level of systemic exposure, it is reasonable to conclude that only application site reactions and ingrowing nail are likely to be related to tavaborole. It should be noted that "procedural pain" does not imply the pain at the application site (that was captured separately) but rather pain following different type of procedures (e.g. perioperative pain).

Per protocol, subjects were encouraged not to trim their TGT between visits, however, an exception was made to allow subjects to trim their TGT at home only to alleviate discomfort, e.g., due to nail edge cracking, splitting or roughness. Some individuals with onychomycotic nails may be rather "aggressive" in their approach to nail care in an effort to remove affected portions of the nail, and that could have contributed to the development of the ingrown toenail in 21 subjects. This issue was not rigorously controlled in the trial, and ingrown toenails will be presented in labeling to inform prescribers and patients.

The following table summarizes causality relationship for ingrown toenail as assessed by investigators:

Treatment Arm	Causality to Treatment				
	not related	unlikely	possible	probable	definite
Tavaborole 5% Solution (N=20)	18	1	1	0	0
Vehicle (N=1)		1			

It is possible that more frequent “application and local skin reactions” in active arm in conjunction with more aggressive trimming are responsible for higher number of ingrown toenails in tavaborole arm. It is reassuring that most ingrown toenails in active arm were assessed as mild in severity (14/20) and only one was severe.

Despite the fact that only in one subject ingrown toenail was assessed as “possibly related to medication” and due to disparity in occurrences between active and vehicle arms, this data should be included in labeling.

It is my recommendation that the Section 6.1 Clinical Trials experience contains the following table (adverse reaction listed in descending frequency order):

Table 1: (b) (4) Adverse Reactions Occurring in $\geq 1\%$ of (b) (4) KERYDIN (b) (4) Topical Solution, 5%-Treated Subjects -and at (b) (4) a Greater Frequency than Observed with Vehicle (b) (4)

Preferred Term	(b) (4)	
	Tavaborole (N=791)	Vehicle (N=395)
(b) (4)		
(b) (4)		(b) (4)
<u>Application site exfoliation</u>	<u>21 (2.7%)</u>	<u>1 (0.3%)</u>
<u>Ingrown toenail</u>	<u>20 (2.5)</u>	<u>1(0.3)</u>
<u>Application site erythema</u>	<u>13 (1.6%)</u>	<u>0 (0%)</u>
<u>Application site dermatitis</u>	<u>10 (1.3%)</u>	<u>0 (0%)</u>
(b) (4)		(b) (4)

7.4.2 Laboratory Findings

There was no clinically meaningful trend observed in abnormal laboratory findings associated with tavaborole use. Data are presented in Table 37.

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Table 37 Laboratory Findings Occurring in >2 Tavaborole –Treated Subjects and at the Greater Frequency that Vehicle

PT	AN2690 5% TOPICAL SOLUTION (N = 791)			VEHICLE (N = 395)		
	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Hypercholesterolaemia	8	8	1.01	3	3	0.76
Blood creatinine increased	5	4	0.51	1	1	0.25
Blood glucose increased	4	3	0.38	1	1	0.25
Blood urea increased	3	3	0.38	0	0	0
Hyperglycaemia	4	3	0.38	1	1	0.25
Hyperlipidaemia	3	3	0.38	1	1	0.25

Source: Data sets adae.xpt and adsl.xpt and reviewer's analysis using MAED

7.4.3 Vital Signs

Vital sign assessments included temperature, pulse rate, respiratory rate, and blood pressure. There was no trend in clinically significant changes in these assessments.

7.4.4 Electrocardiograms (ECGs)

There were no clinically relevant electrocardiogram findings observed during phase 3 trials.

The effects of a suprathreshold dose of tavaborole 5% solution on ventricular repolarization (QT/QTc interval duration) was assessed in study AN2690-ONYC-102.

This study was randomized, single-site, open-label, 4-arm crossover study in 55 healthy adult subjects who were randomized to one of the following treatment groups:

- AN2690 Topical Solution, 5% q.d.
- AN2690 Topical Solution, 5% b.i.d.
- Moxifloxacin 400 mg P.O.
- Vehicle solution q.d.

All topical treatments were applied for 14 days on all 10 toenails and moxifloxacin was given as a single dose following AN2690 q.d. dosing.

The bid tavaborole dosing produced mean C_{max} values 10- to 21 -fold higher than that following the therapeutic dose of tavaborole 5% solution which is sufficient to cover high exposure clinical scenarios.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

According to the Interdisciplinary Review Team for QT Studies (QT-IRT) overall summary of findings was that “no significant QTc prolongation effects of AN2690 (doses of topical solution, 5% q.d. and topical solution, 5% b.i.d.) were detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between AN2690 and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.”

Comment: Considering observed low systemic exposure of tavaborole 5% solution and results of suprathreshold dose of tavaborole 5% solution on ventricular repolarization, there is no concern that tavaborole 5% solution may prolong QT interval.

Safety assessment of healthy volunteers from this study includes the following:

There were no deaths or discontinuations from the study.

There were no SAE's.

One subject had one severe AE (elevated CK) considered non-related to the treatment.

7.4.5 Special Safety Studies/Clinical Trials

Provocative dermal safety was evaluated in study AN2690-0NYC-103: A Randomized, Controlled Study to Evaluate the Sensitizing Potential and Cumulative Irritation Potential of AN2690 Topical Solution, 5% in Healthy Volunteers Using a Repeat Insult Patch Test and Cumulative Irritation Design

Cumulative Irritation Testing

This was a single-site, randomized, single-blind, controlled study conducted in 45 healthy subjects 18-73 years of age. Forty-two subjects completed the study. Three subjects were discontinued from the study: 1 due to an AE (tape reaction) and 2 who did not wish to continue for reasons unrelated to study treatment.

The potential of the product to cause irritation was tested using tavaborole 5% solution, vehicle, positive irritant control (lauryl sulfate solution 0.5% w/v) and negative irritant control (0.9% saline for injection).

During the 21 days subjects received semi-occluded treatments daily applied simultaneously to the infrascapular area of the back. Approximately 30 minutes (\pm 10 minutes) after test article removal on Days 2-22, a trained evaluator blinded to treatment allocation observed the application site for any signs of local irritation.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

The following scoring was utilized for irritation assessments:

Dermal Responses [grade, (score), definition]

- 0 (0) = no evidence of irritation
- 1 (1) = minimal erythema, barely perceptible
- 2 (2) = definite erythema, readily visible; minimal edema or minimal papular response
- 3 (3) = erythema and papules
- 4 (3) = definite edema
- 5 (3) = erythema, edema and papules
- 6 (3) = vesicular eruption
- 7 (3) = strong reaction spreading beyond application site

Other Effects (with corresponding numeric score)

- A (0) = slightly glazed appearance

- B (1) = marked glazed appearance
- C (2) = glazing with peeling and cracking
- F (3) = glazing with fissures
- G (3) = film of dried serous exudates covering all or part of the patch site
- H (3) = small petechial erosions and/or scabs

The summary of the irritation data is presented below:

Table 38 Summary of Mean Cumulative Data (Irritation Phase)

Test Article (N=45)	Cumulative Dermal Response Score (SD)
Tavaborole 5%	20.78 (11.04)
Vehicle	1.36 (3.54)
Positive control	16.33 (10.39)
Negative control	0.6 (1.67)

Source: Adapted from applicant's Table 54 from section 2.7.4

Comment: Tavaborole 5% solution demonstrated mean irritation response higher than the positive irritant control.

The intended use of Tavaborole 5% solution is primarily on and under the nail surface, but cutaneous irritation may occur due to the contact of the solution with the periungual skin. The applicant commented in the study report (p.68) that "AN2690 Topical Solution, 5% was found to have greater irritation potential than the other three test articles,

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

including its vehicle, 0.5% SLS, and 0.9% saline.

(b) (4)

Considering that irritancy testing was done with semi-occlusive patches (and not occlusive patches) and that it was confirmed in sensitization study (see comments below), the potential of tavaborole 5% solution to cause dermal irritation should be included in labeling.

Sensitization Testing

This was a single-site, randomized, single-blind, controlled study conducted in 234 subjects from age 18-75. Of all randomized subjects 215 completed the study. Nineteen (19) subjects were discontinued from the study: 12 who did not wish to complete the study for reasons unrelated to study treatment, 5 who were lost to follow-up, 1 who discontinued due to an AE (subject was hospitalized with dehydration and a bacterial infection), and 1 who was not compliant with the protocol.

The potential of the product to cause sensitization was tested using tavaborole 5% solution, vehicle, positive control (lauryl sulfate solution 0.1% w/v) and negative control (0.9% saline for injection). Study consisted of induction phase (21 days), rest period (10-14 days), and challenge phase.

Induction phase:

During the 21 days of induction phase subjects received 4 semi-occlusive applications three times/week applied simultaneously to their infrascapular area of the back. The sites were evaluated by clinical staff 9 times using the same scoring system as for irritation study presented above.

The summary of the irritation data is presented below:

Test Article (N=224)	Cumulative Dermal Response Score (SD)
Tavaborole 5%	4.75 (4.42)
Vehicle	0.65 (1.72)
Positive control	0.35 (1.25)
Negative control	0.21 (1.18)

Source: Adapted from applicant's Table 52 from section 2.7.4

Comment: It should be noted that tavaborole demonstrated again the highest irritancy scores despite the use of lower concentration of positive control and overall reduced number of applications.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

Challenge phase:

Following 14 days of rest period, 216 subjects began the challenge. The subjects received same patch applications to a naïve site of the back opposite to that treated during induction phase. The patches were removed after 48 hours and assessments of the sites of applications were made at approximately 30 minutes and 24, 48, and 72 hours for any signs of local irritation. The same rating scales were used as for induction phase.

There were no subjects who developed sensitization defined as a reaction grade 4 (definite edema) or greater.

Comment: Sensitization potential of Tavaborole 5% was assessed using the modified Draize test emphasizing that the test drug is capable of producing a greater response on subsequent challenges than on the initial exposure. Based on the results, it does not appear that Tavaborole 5% solution is skin sensitizer.

Phototoxicity and photosensitivity testing

None of the components of the drug product absorb light corresponding to wavelengths of 290 to 700 nm, thus dermal photoprovocation studies with tavabore 5% solution were not conducted. This was acceptable to the Agency.

Comment: Proposed language for Section 6.1. Clinical Trials Experience:

A cumulative irritancy study revealed the potential for KERYDIN (b) (4) to cause skin irritation. There was no evidence that KERYDIN (b) (4) causes contact sensitization.

7.4.6 Immunogenicity

This drug product is not expected to induce systemic immunogenicity.

7.5 Other Safety Explorations

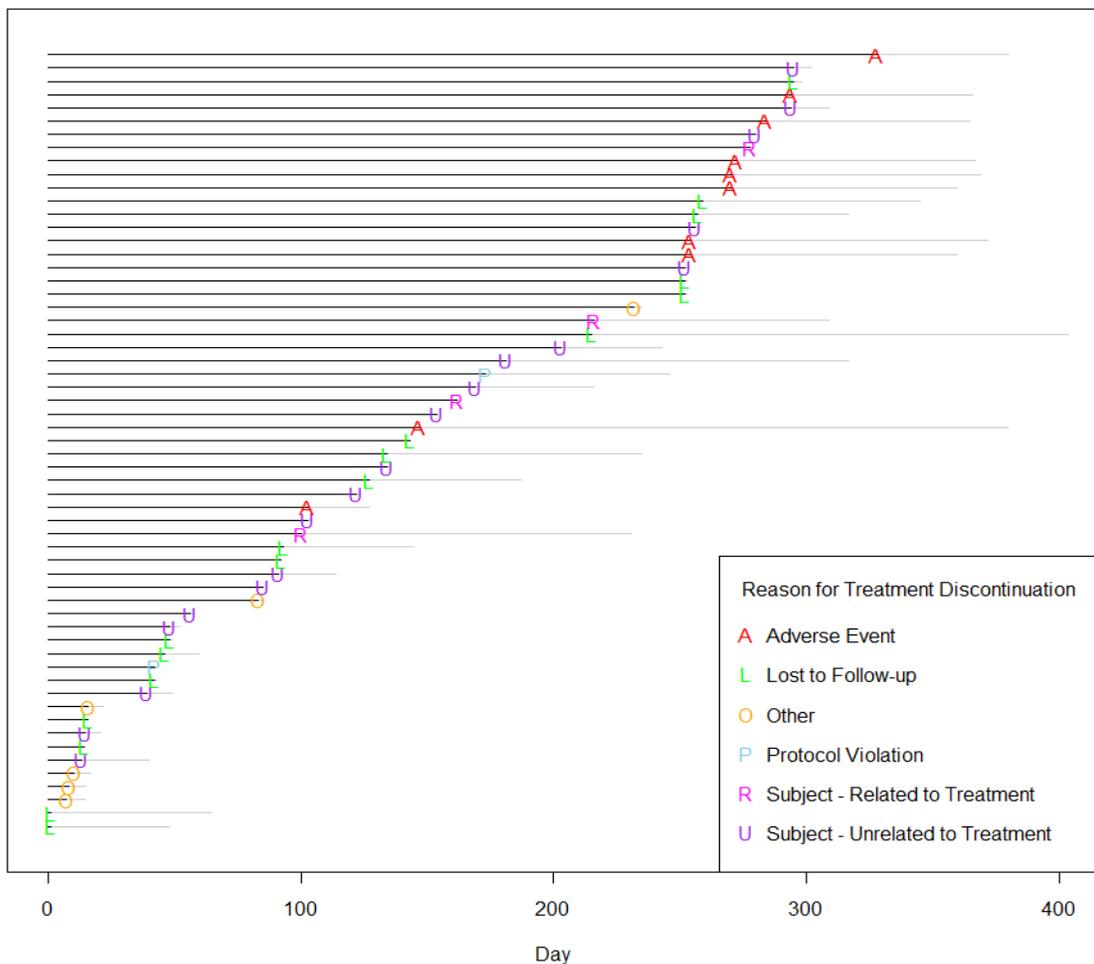
7.5.1 Dose Dependency for Adverse Events

Dose dependency was not explored, and none is anticipated during clinical use.

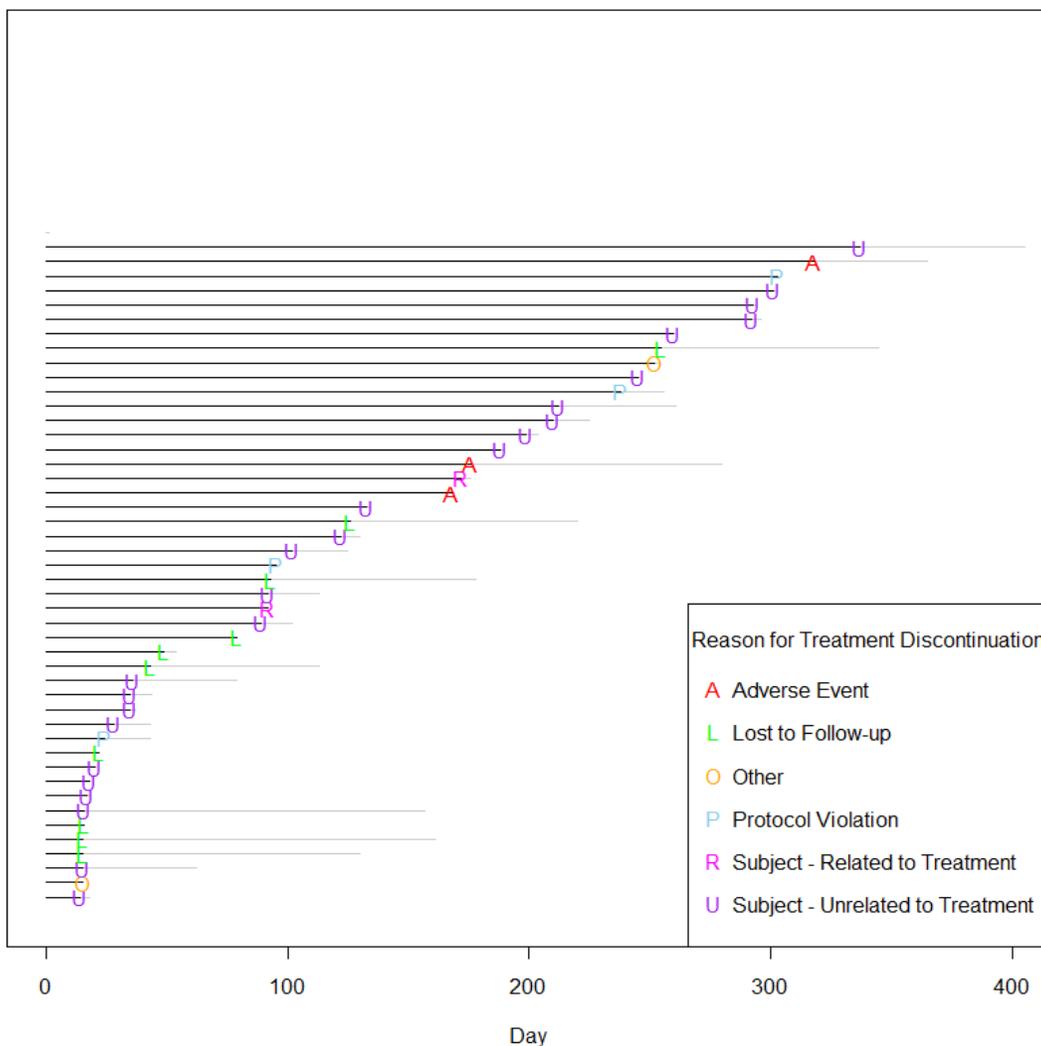
7.5.2 Time Dependency for Adverse Events

Only those AEs that caused treatment discontinuation were explored and are presented in the figures below (courtesy of statistical reviewer Kathleen Fritch, Ph.D.) Each line represents duration of treatment for single subject and letter "A" denotes adverse event as the reason for discontinuation.

Treatment Discontinuation Day for Discontinuing Tavaborole Subjects (Study 301)



Treatment Discontinuation Day for Discontinuing Tavaborole Subjects (Study 302)



Comment: Adverse events that lead to the treatment discontinuation occurred mainly in the second half of the treatment (8/13).

7.5.3 Drug-Demographic Interactions

Age

As presented in Table 21 Demographics-Safety Population, the majority of the population was younger than 65 years of age. However, a sufficient number of subjects aged 65 years and older was exposed to tavaborole 5% solution for a safety comparison that is sufficient for labeling.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

Application site reactions were reported in 7% of subjects exposed to tavaborole (52/791) and in 2% vehicle treated subjects (7/395). The breakdown of overall application site reactions by age group showed that in the 65 years of age and above group, 8% (12/150) had some type of application site reaction v. 3% (2/79) in vehicle group. Same analysis for subjects younger than 65 years of age showed that 6% in the active arm and 2% in the vehicle arm had application site reactions.

Considering the two most frequently reported AEs in tavaborole arm (application site exfoliation and ingrown toenail) more subjects in older group (7/150, 5%) reported application site reaction than those in the younger age group (14/641, 2%). However, the frequency was reversed for ingrown toenail where more subjects in the younger age group (18/641, 3%) had ingrown toenails compared to the older group (2/150, 1%).

Comment: Overall, safety results between older and younger population were comparable. Recommended labeling for Section 8.5 (deletion is noted as ~~striketrough~~ and additions are noted as double underlines):

[REDACTED] (b) (4)

In clinical trials of 791 subjects who were exposed to KERYDIN Topical Solution, 19% were 65 years of age and over (4% were 75 years of age and over). No overall differences in safety were observed between these subjects and younger subjects but greater sensitivity of some older individuals cannot be ruled out.

Gender

Women had higher rates of application site reactions than men (10% v. 4% for tavaborole groups; 0% vs. 1% for vehicle groups). The difference is mostly influenced by the application site “dermatitis” reaction reported by 7 (5%) women v. 3 (1%) men. Other application site reactions were reported in similar frequency in both genders.

Comment: Considering disproportionate sample sizes and imbalanced occurrences of events the clinical significance of gender differences for adverse reactions is unclear. (b) (4)

[REDACTED] (b) (4)

Race

There was no difference among racial groups in reporting application site reactions.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

Ethnicity

Subjects identified as Hispanic/Latino ethnicity had a higher rate of application site reactions than non-Hispanic/non-Latino subjects (10% vs. 3% for tavaborole groups; 0% vs. 1% for vehicle groups) mostly as result of higher number of Hispanic/Latino subjects with application site dermatitis (8 or 5%) then non- Hispanic/Latino subjects (2 or <1%).

Comment: While the higher rate may reflect random statistical variation, perhaps the difference is more influenced by the geographic or environmental factors applicable to Mexico, since all of the Hispanic/Latino subjects with application site dermatitis were from Mexican investigational sites. It should be noted that the both, the applicant and microbiology reviewer Dr. Roche concluded that there were no significant differences in the species of dermatophytes causing disease among US and non-US sites.

7.5.4 Drug-Disease Interactions

Drug -disease interaction was not explored due to the findings of pharmacokinetic studies which suggest very low systemic exposure to tavaborole. It is unlikely that decreased renal or hepatic function will affect the low systemic exposure of tavaborole at the proposed clinical dose.

7.5.5 Drug-Drug Interactions

The drug-drug interaction potential of tavaborole was assessed in the *in vitro* inhibition and induction studies (7.2.3 Special Animal and/or In Vitro Testing). The conclusion of *in vitro* testing is that tavaborole is not likely to affect the activity of cytochrome P450 enzyme complex. No evaluations of drug-drug interactions *in vivo* were conducted.

Comment: Recommended labeling for Section 7 Drug Interactions (additions are underlined):

 ^{(b) (4)} In vitro studies have shown that tavaborole, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No signals for carcinogenicity were noted in pre-clinical carcinogenicity studies. No formal clinical trials in human carcinogenicity were neither recommended nor conducted.

7.6.2 Human Reproduction and Pregnancy Data

No trials with tavaborole were conducted in pregnant women and women of child-bearing potential. Subjects who enrolled in any of the clinical trials were required to use an effective form of birth control. Pregnancy was reported for three women participating in clinical studies (none in pivotal trials):

- Subject 06-048 (AN2690-ONYC-203) became pregnant during 5th month of treatment with tavaborole 5.0% solution. Her last application of study drug was 5 weeks after the reported pregnancy at which point she was discontinued from the study. Patient was lost to follow up.
- Subject 05-017 (AN2690-ONYC-200/200A) a 40-year-old female reported her method of contraception at the time of entry into the study as tubal ligation performed 10 years earlier. Therefore, she did not have a pregnancy test during treatment. She completed 7 weeks of treatment with tavaborole 7.5% solution prior to pregnancy confirmation and discontinued study drug. Pregnancy resulted in delivery of a healthy child.
- Subject 03-016 (AN2690-ONYC-200/200A) became pregnant 8 months after initiation of treatment with tavaborole 5.0% solution. Pregnancy resulted in delivery of a healthy child.

Comment: This drug product should be labeled to reflect the lack of data for use in pregnant women. I concur with labeling language recommended by the Pharmacology/toxicology reviewer and classification of the product as Pregnancy Category C. I concur with the recommendation for labeling in Section 8 that tavaborole solution 5% should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

7.6.3 Pediatrics and Assessment of Effects on Growth

In original submission, the applicant requested a waiver of the requirement to conduct clinical studies with tavaborole in pediatric patients ages (b) (4) and a deferral for studies in patients ages (b) (4) in addition to conducting supportive nonclinical juvenile toxicology studies. The rationale for a waiver was that “studies are impossible or highly impractical (because, for example, the number of pediatric patients is so small or geographically dispersed). The literature that was provided in support of this pediatric plan was reviewed; however, the information on prevalence of onychomycosis in pediatric population was supportive of waiver for studies in children 0-12 years.

The rationale and supportive literature reference for the submitted Pediatric Study Plan (PSP) were discussed with the applicant during the Mid Cycle Communication teleconference. The Agency inquired about the interpretation of literature submitted to characterize the incidence and prevalence of onychomycosis in pediatric age groups. The applicant stated that (b) (4)

Agreement was reached that clinical studies could be waived in the pediatric population below 12 years of age, because the product is unlikely to be used in a substantial number of pediatric patients in younger children. A small PK/safety trial was recommended for subjects between 12-17 years of age, and the Agency concurred that efficacy could be extrapolated from the adult population. The applicant was advised to submit an amendment with a revised PSP reflective of this advice.

The NDA was amended on January 22, 2014 with a revised Pediatric Study Plan. The applicant requested (b) (4)

In addition, applicant proposed to extrapolate the efficacy (b) (4) data from the adult population to the adolescent population (age 12 to 17 years) given that the disease characteristics and the type of the microorganisms that cause onychomycosis are the same in the adult and adolescent populations. (b) (4)

The Division maintained its position that only a partial waiver could be granted for children 0-12 years of age. (b) (4)

Division’s recommendation for a partial waiver in children less than 12 years of age and deferral for studies in 12-17 years of age. The rationale for Division’s position was *that*

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

“onychomycosis (b) (4) is not prevalent in population younger than 12 years of age. The Division concludes that the product may not be used in a substantial number of patients in this age group and that the studies are not feasible.” The Division’s position on deferral for studies in children 12-17 years 11 month was based on the need to provide for safety labeling and pharmacokinetic information in that age group (and agreed with the sponsor that efficacy could be extrapolated).

The Committee also disagreed (b) (4) but recommended a partial waiver for children less than 6 years based on the fact that “the PeRC noted that several publications describe treatment of onychomycosis in patients less than 12 years of age.”

*Comment: It is my recommendation that a (b) (4) The only approved topical product for onychomycosis (Penlac) has an age indication down to 12 years. Although onychomycosis of the toenails is predominantly disease of adults, there are several publications that describe various types of onychomycosis and treatment options in children^{5,6,7}. However, due to disagreement with PeRC’s age recommendation and in order to justify the age for partial waiver, I have considered only data that are reflective of the recommended indication for tavaborole –“onychomycosis of the toenail due to *T. rubrum* or *T. mentagrophytes*.”*

In older literature⁷, there were no reported cases of onychomycosis in children younger than 12 years.

In one North American study⁸ out of 2500 children under the age 18 with (mean age 11.2±0.1) with abnormal-appearing nails, mycologically confirmed toenail onychomycosis due to dermatophytes was present in 7 children. The same author in a different publication⁶ presented results from a literature search covering 35 years of onychomycosis treatment in children (mostly case reports). The breakdown by age (reviewer’s analysis) showed 8 children less than 12 years of age, 38 children 12 years, and older and 24 children that fall into group of mean age of 10.

Some retrospective surveys outside USA^{9,10} showed similar age distribution. In Belgium over a 10-year period out of 296 children with onychomycosis, dermatophytes were causative organism in 58 children 6-12 years of age and in 69 that were older than 12. During 20-years period in Spain out of 181 children diagnosed with onychomycosis, 22 children had onychomycosis of the toenails due to dermatophytes (0-7 years=5, 8-11years=6 and 12 years and older=11 children).

In conclusion, data on pediatric toenail onychomycosis caused by dermatophytes (with documented positive cultures) is scarce. However, it appears that incidence increases with age and that subpopulation of 12 and older consistently shows a higher incidence. It is possible that age related trend is driven by more frequently negative cultures in younger children. Overall, mycological cultures may be falsely negative in 30-50% of

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

samples⁴. Sensitivity increases with larger sample (e.g. 3mm thick nail clipping) which may be difficult to achieve in younger age patients.

Therefore, I recommend a partial waiver from conducting studies in pediatric population younger than 12 years and a deferral of pediatric studies in subjects 12-17 years 11 months of age. Review of the referenced literature points that clinical presentation and micro-organisms in adolescents are similar to adults, thus tavaborole efficacy can be extrapolated from adult studies. However, safety may differ (systemic exposure and adverse reactions), thus I recommend that PMR be issued for safety/PK study in adolescents to inform the label about safety of tavaborole in this population. Nonclinical juvenile animal toxicity studies for tavaborole solution would not be required to support clinical studies in this age group.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is minimal to no risk of overdose or abuse for tavaborole solution based on available data from the trials, as well as the proposed mechanism of action of tavaborole.

7.7 Additional Submissions / Safety Issues

The 120 day safety update was submitted on November 25, 2013. Per applicant: "Anacor has no new nonclinical or clinical safety information to report for NDA 204427, as there are no ongoing nonclinical or clinical studies at this time."

8 Postmarket Experience

Not applicable; tavaborole is not currently marketed in any country.

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

9 Appendices

9.1 Literature Review/References

References are provided at the end of the document.

9.2 Labeling Recommendations

Office of Medication Error Prevention and Risk Management accepted the proposed proprietary name Kerydin in January 2014.

Labeling recommendations are under negotiations with the applicant. Key clinical recommendations that differ from the applicant's proposal have been incorporated though-out the Review. Agreed upon labeling will be attached to the Approval letter.

9.3 Advisory Committee Meeting

Advisory Committee (AC) meeting was deemed not necessary. Although tavaborole is an NME, no novel or complex regulatory were raised during the review to warrant AC meeting. Information related to safety and efficacy was adequately presented in the application to inform a regulatory decision.

9.4. Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure Review Template

Application Number: 204,427

Submission Date: 07/29/213

Applicant: Anacor Pharmaceuticals Inc.

Product: Tavaborole solution 5%

Reviewer: Milena Lolic, MD, MS

Date of Review: 10/3/2013

Covered Clinical Study (Name and/or Number): AN2690-ONYC-301 and AN2690-ONYC-302

Clinical Review
 Milena Lolic, MD, MS
 NDA 204,427
 Kerydin (tavaborole) Topical Solution, 5%

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 80		
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		
<p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (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 <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

¹ See [web address].

Clinical Review
Milena Lolic, MD, MS
NDA 204,427
Kerydin (tavaborole) Topical Solution, 5%

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Financial disclosure forms were reviewed, and all investigators reported no financial interests. The applicant certified in Form 3454 that they had not entered into any financial arrangements with any of the clinical investigators. It was also affirmed that none of the clinical investigators disclosed any proprietary interest in the product, or significant equity interest in the sponsor company. Certification was made that no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f).

¹ Ghannoum MA, Hajjeh RA et al. A large-scale North American study of fungal isolates from nails: The frequency of onychomycosis, fungal distribution, and antifungal susceptibility patterns. J Am Acad Dermatol 2000;43:641-8.

² Wade Foster K, Ghannoum MA et al. Epidemiologic surveillance of cutaneous fungal infection in the United States from 1999 to 2002. J Am Acad Dermatol 2004;50:748-52.

³ Tosti A, Piraccini Bm et al. Relapses of onychomycosis after successful treatment with systemic antifungals: a three-year follow-up. Dermatology 1998;197(2):162

⁴ Berker D. Fungal nail disease. N Engl J Med 2009; 360:2108-16

⁵ Gupta AK, Chang P et al. Onychomycosis in children: prevalence and management. Pediatric Dermatology 1998;15(6):464-471)

⁶ Gupta AK, Paquet M Systemic antifungals to treat onychomycosis in children: a systemic review. Pediatric Dermatology 2012;1-9

⁷ Finlay GH, Vismar HF et al. The spectrum of paediatric dermatology-analysis of 10,000 cases. British Journal of Dermatology 1974;91:379-387

⁸ Gupta AK, Sibbald RG et al. The prevalence of onychomycosis in children and treatment strategies. J Am Acad Derm 1997;36:395-402

⁹ Lateur N, Mortaki A et al. Two-hundred ninety cases of onychomycosis in children and teenagers: a 10-year laboratory survey. Pediatric dermatology 2003;20 (5)385-88.

¹⁰ Rodriguez-Pazos L, Pereiro-Ferreiros M et al. Onychomycosis observed in children over a 20-year period. Mycoses 2010;54:450-53

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MILENA M LOLIC
03/26/2014

DAVID L KETTL
03/27/2014

CLINICAL FILING CHECKLIST FOR NDA

NDA Number: 204427

**Applicant: Anacor
Pharmaceuticals Inc.**

Stamp Date: July 29, 2013

Drug Name: Tavaborole Topical Solution, 5% NDA Type: standard

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD format through the Electronic Submission Gateway
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			ISE and ISS are split across M2 and M5
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			Navigation is acceptable but difficult because of ISS and ISE splitting between M2 and M5
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Narrative portion is included in M2
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Narrative portion is included in M2
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: AN2690-ONYC- 200/200A Study Title: A Randomized, Double-Blind, Vehicle-Controlled, Multi-Center Study to Evaluate the Safety and Efficacy of Topically Applied AN2690 2.5%, 5.0%, and 7.5% Solutions vs. Vehicle for the Treatment of Adult	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
	Subjects with Onychomycosis of the Great Toenail Sample Size: 180 Arms:4 Location in submission: 5.3.5.1				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 AN2690-ONYC-301/ Randomized, double-blind, vehicle-controlled, multi-center study to evaluate the efficacy and safety of Tavaborole Topical Solution, 5%, vs.vehicle in the treatment of onychomycosis of the toenail in adults (48 weeks of dosing) Indication: Treatment of onychomycosis of the toenail Pivotal Study #2AN2690-ONYC-302/ Randomized, double-blind, vehicle-controlled, multi-center study to evaluate the efficacy and safety of Tavaborole Topical Solution, 5%, vs. vehicle in the treatment of onychomycosis of the toenail in adults (48 weeks of dosing) Indication: Treatment of onychomycosis of the toenail	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	This is NME

CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	This is NME
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	Division requested CRF for deaths, serious adverse events, and adverse dropouts only.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Submit a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine.

Milena Lolic, MD, MS

 Reviewing Medical Officer

August 28, 2013

 Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MILENA M LOLIC
09/05/2013

DAVID L KETTL
09/05/2013