CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204427Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

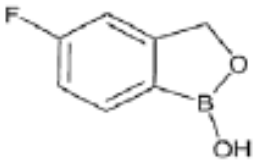
Division of Anti-Infective Products
Clinical Microbiology Review
Dermatology and Dental Consult

NDA type: 505 (b)(1)
Date Company Submitted: 7-26-13
Date Received by CDER: 7-29-13
Date Assigned: 8-7-13

NAME AND ADDRESS OF APPLICANT:
Anacor Pharmaceuticals, Inc.
1 020 East Meadow Circle
Palo Alto, CA 94303

Contact Person:
Carmen R. Rodriguez, M.Sc.
VP, Regulatory Affairs and Quality

DRUG PRODUCT NAMES:
Proprietary Name: Kerydin
Established Name/Code Name(s): Tavaborole Topical Solution, 5%/AN2690
Molecular Weight: 151.9 Daltons
Chemical Name: 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole
Molecular Formula: $C_7H_6BFO_2$
Structure:



DRUG CATEGORY
Antifungal (topical)

PROPOSED INDICATION
Treatment of onychomycosis (b) (4)

PROPOSED DOSAGE FORM, STRENGTH AND ROUTE OF ADMINISTRATION:
Dosage Form: Solution
Route of Administration: Topical
Dosage: Once daily
Strength: 5%
Duration of Treatment: 48 weeks

DISPENSED:
Prescription Product

RELATED DOCUMENTS:
Not Applicable

REMARKS
This is a New Drug Application for Tavaborole Topical Solution, 5%, which is being submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and under the provisions of Title 21CFR§314.50. This application proposes the use of Tavaborole Topical Solution, 5% for the treatment of patients with onychomycosis (b) (4)

A consult request was received on 7-29-13 by the Division of Anti-infective Products (DAIP) from the Division of Dermatology and Dental Products (DDDP), with a desired completion date of March 7, 2014. The consult was as follows:
"During development of Tavaborole Topical Solution, 5% under IND 71 206, you provided consults for EOP2 meeting (consult date October 21, 2009) and for Guidance meeting (consult date October 31, 2012). On July 29, 2013 we received NDA 204427 with data from Phase 3 trials submitted in support of Tavaborole Topical Solution, 5% marketing approval for the treatment of onychomycosis. We have the following question: Did the applicant provide sufficient information to support labeling claim of mycological cure associated with Tavaborole Topical Solution, 5% treatment in subjects with onychomycosis (b) (4)

SUMMARY AND RECOMMENDATIONS
From a clinical microbiology perspective the information provided by the Applicant supports the efficacy of tavaborole for the treatment of onychomycosis (b) (4) *Trichophyton rubrum* and *T. mentagrophytes*. No susceptibility testing interpretive criteria for tavaborole are proposed.

See Section 6.2 of this review for the FDA's proposed labeling for the clinical microbiology subsection of the tavaborole package insert. There are recommendations to communicate to the Applicant.

TABLE OF CONTENTS

EXECUTIVE SUMMARY .....**Error! Bookmark not defined.**
1. INTRODUCTION 7
2. *IN VITRO* ACTIVITY 8
2.1. Mechanism(s) of action..... 8
2.2. Antimicrobial spectrum of activity 12
2.3. Antifungal Activity .....**Error! Bookmark not defined.**
2.4. Intracellular Antimicrobial Concentration Assessment ..... **Error! Bookmark not defined.**
2.5. Development of Resistance and Resistance Mechanisms 20
2.6. Effect of medium, inoculum size, pH and serum on *in vitro* activity..... 23
2.7. Susceptibility Test Methods..... 23
2.8. Antimicrobial interactions and fixed combination studies 28
3. ANIMAL MODELS OF INFECTION..... 29
3.1. Murine model of systemic candidiasis..... 29
4. PHARMACOKINETICS/PHARMACODYNAMICS **Error! Bookmark not defined.**
4.1. In vitro pharmacokinetics/pharmacodynamics .....**Error! Bookmark not defined.**
4.2. In vivo pharmacokinetics/pharmacodynamics..... 32
4.3. Human pharmacokinetics/pharmacodynamics .....**Error! Bookmark not defined.**
5. CLINICAL TRIALS..... 34
5.1. Phase 2 Trials..... 34
5.2. Phase 3 Trials..... 37
5.3. In Vitro Susceptibility Testing and Interpretive Criteria 42
6. LABELING..... 54
6.1. Applicant's Proposed Labeling..... 54
6.2. FDA's Version of The Labeling 55
7. RECOMMENDATIONS..... 56
8. REFERENCES 57

EXECUTIVE SUMMARY

AN2690, is an oxaborole that demonstrates broad-spectrum antifungal activity against dermatophytes, yeasts, molds, and other filamentous fungi. AN2690 penetrates through the nail plate and achieves concentrations greater than the minimum fungicidal concentrations (MFCs) determined in vitro. The degree of penetration through the nail plate was superior to ciclopirox (the only topical treatment currently approved in the United States for distal subungual onychomycosis).

Tavaborole Topical Solution, 5% is an antifungal agent. The active ingredient is tavaborole, a (b) (4) boronic acid complex (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole). Tavaborole exerts its pharmacologic activity through inhibition of fungal protein synthesis by inhibiting cytoplasmic leucyl-tRNA synthetase (LeuRS), an aminoacyl-tRNA synthetase, via an oxaborole-tRNA trapping mechanism. Tavaborole was specifically designed to improve nail unit bioavailability when applied topically and to retain its pharmacologic activity in the presence of keratin in the nail plate.

The safety and efficacy of Tavaborole Topical Solution, 5% was studied in two double-blind vehicle-controlled clinical Phase 3 studies in subjects with onychomycosis (b) (4) Results from these studies confirmed the antifungal efficacy and established clinical safety of Tavaborole Topical Solution, 5% when applied topically to the affected nail once daily for 48 weeks.

Tavaborole is anantifungal agent developed for topical treatment of onychomycosis (b) (4) . Microbiologic studies were completed to determine mechanism of action, mechanism of resistance, spectrum of antimicrobial activity of tavaborole, and comparison to commercially available antifungals approved for the treatment of onychomycosis. The microbiology studies included examination of the spectra of activity of tavaborole and characterization of the mycology and susceptibility of strains of *Trichophyton rubrum* and *Trichophyton mentagrophytes,* obtained from clinical isolates of subjects treated with Tavaborole Topical Solution, 5% for 48 weeks.

The following are the Agency's proposed recommendations for labeling (only the sections pertinent to Clinical Microbiology are provided below):

12.4 Microbiology

Mechanism of Action

The mechanism of action of tavaborole is inhibition of fungal protein synthesis. Tavaborole inhibits protein synthesis by inhibition of an aminoacyl-transfer ribonucleic acid (tRNA) synthetase. (b) (4)

Activity in vitro and in clinical infections

Tavaborole has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections (b) (4)

INDICATIONS AND USAGE (b) (4)

Trichophyton mentagrophytes
Trichophyton rubrum

(b) (4)

(b) (4)

Mechanism of Resistance

(b) (4)

(b) (4)

1. INTRODUCTION

Onychomycosis is a fungal infection of the nail unit. The signs of infection include a thickening of the nail plate, discoloration, splitting of the nail plate, and lifting of the nail plate from the nail bed. The disease is often caused by dermatophytes, which are ubiquitous in the environment. A large proportion of the population is susceptible to dermatophyte infections, and there does not appear to be a protective adaptive immune response, so reinfection is common in the susceptible population.

The difficulty in treating onychomycosis may result from the inability of some drugs to effectively reach all compartments of the nail unit. Current treatment options include both oral (PO) and topical drugs, with PO therapies giving better outcomes. Limitations of currently approved PO therapies include drug interactions and systemic adverse effects, including hepatotoxicity and cardiotoxicity. Currently approved topical agents are limited by their relatively low efficacy. Hence, there is a clear need for more effective topical agents to treat onychomycosis.

AN2690 (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) is an investigational antifungal topical solution being developed by Anacor Pharmaceuticals, Inc. for the treatment of onychomycosis. AN2690 is an oxaborole that demonstrates broad-spectrum antifungal activity against dermatophytes, yeasts, molds, and other filamentous fungi, with minimum inhibitory concentration (MIC) values in the low microgram-per-milliliter (mcg/mL) range. AN2690 penetrates through the nail plate and achieves concentrations greater than the minimum fungicidal concentrations (MFCs) determined in vitro. The degree of penetration through the nail plate was superior to ciclopirox (the only topical treatment currently approved in the United States for distal subungual onychomycosis), making this compound a candidate for topical treatment.

REGULATORY HISTORY

None. This is a new molecular entity.

2. *IN VITRO* ACTIVITY

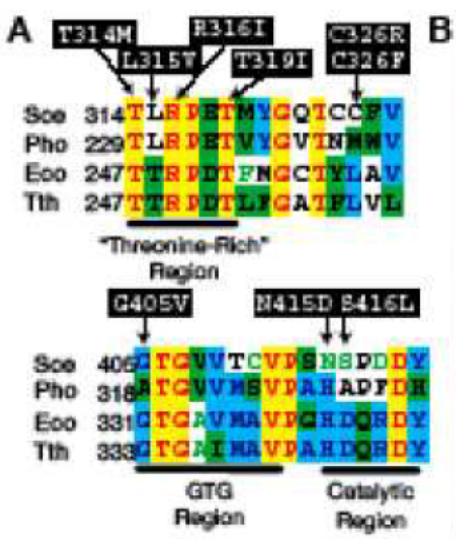
A summary of data related to the in vitro activity of tavaborole is below:

2.1. Mechanism(s) of action

The mechanism of action of tavaborole is inhibition of fungal protein synthesis. Tavaborole inhibits protein synthesis by inhibition of an aminoacyl-transfer ribonucleic acid (tRNA) synthetase (AARS). AARS performs a role in the translation of the genetic code by catalyzing the attachment of the correct amino acid to the corresponding tRNA. AARS are essential housekeeping enzymes for fungi. The inhibition of AARS occurs via an oxaborole-tRNA trapping mechanism. Tavaborole forms an adduct with the leucine-specific tRNA ($tRNA^{Leu}$) in the editing site of leucyl-tRNA synthetase. The trapping of $tRNA^{Leu}$ in the editing site prevents the synthetic site from binding the 3′ terminal end of $tRNA^{Leu}$, thus inhibiting synthesis of leucine-$tRNA^{Leu}$ and consequentially blocking protein synthesis in the target microorganism.

To identify the target of AN2690, mutants resistant to AN2690 were selected in *Saccharomyces cerevisiae*. The frequency of resistance to AN2690 for *S. cerevisiae* was 1.2×10^{-7} at 4× the MIC. Characterization of 11 resistant mutants showed that they had an 8- to 64-fold increase in resistance to AN2690. Isolates resistant to AN2690 were not resistant to other classes of antifungal agents with known modes of action. Isolation of three different plasmids bearing CDC60 from plasmid libraries generated from the three independently isolated mutants implicated CDC60 in AN2690 resistance. CDC60 is the gene encoding the cytoplasmic leucyl-tRNA synthetase. Sequence analysis of CDC60 from 11 mutants revealed that the mutations were all located in the editing domain of this enzyme. Furthermore, introducing additional copies of the CDC60 gene in *S. cerevisiae* gave rise to an 8-fold increase in resistance to AN2690. These findings are indicative of a link between the editing activity of the enzyme and the inhibition by AN2690. The target and mechanism of action were confirmed by enzymatic studies showing inhibition of fungal leucyl-tRNA synthetase. AN2690 acts as a slow, tight-binding inhibitor with an inhibition constant (Ki) ~2 μM. Structural studies have confirmed the covalent modification of the terminal adenosine residue on the leu-tRNA within the editing domain of the leucyl-tRNA synthetase.

Figure 1: *The S. cerevisiae* AN2690 resistance mutations lie in the editing active site of the cytoplasmic leucyl-tRNA synthetase (Cdc60p)



(A). Alignment of the conserved regions of the LeuRS editing domain from *S. cerevisiae* (Sce) from CAA97865, *Pyrococcus borikoshii* (Pho) from O58698, *Escherichia coli* (Eco) from AA73743 and *Thermus thermophiles* (Tth) from BAD69984. The amino acid substitutions that confer resistance in *S. cerevisiae* to AN2690 are in black (Table 1 below). (B) (b) (4)

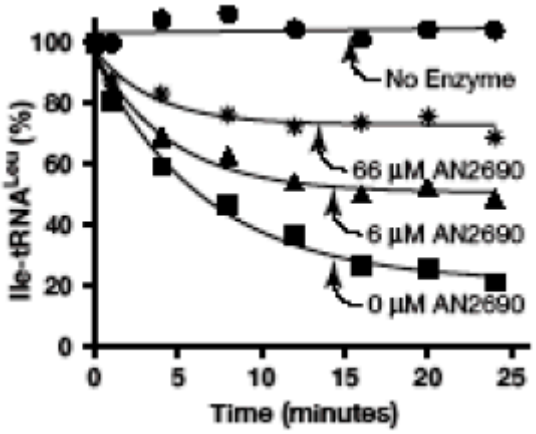
Source: Study 0002-NCL PP-001-01[1]

Table 1: List of *S. cerevisiae* AN2690 resistant mutants

S. cerevisiae	MIC (µg/mL)	Mutation in *CDC60*
ATCC201388	0.125	None
ANA320	4	N415D
ANA321	16	R316I
ANA322	16	C326F
ANA323	16	G405V
ANA324	16	C326R
ANA326	16	L315V
ANA327	32	T314M
ANA358	32	S416L
ANA360	32	T319I

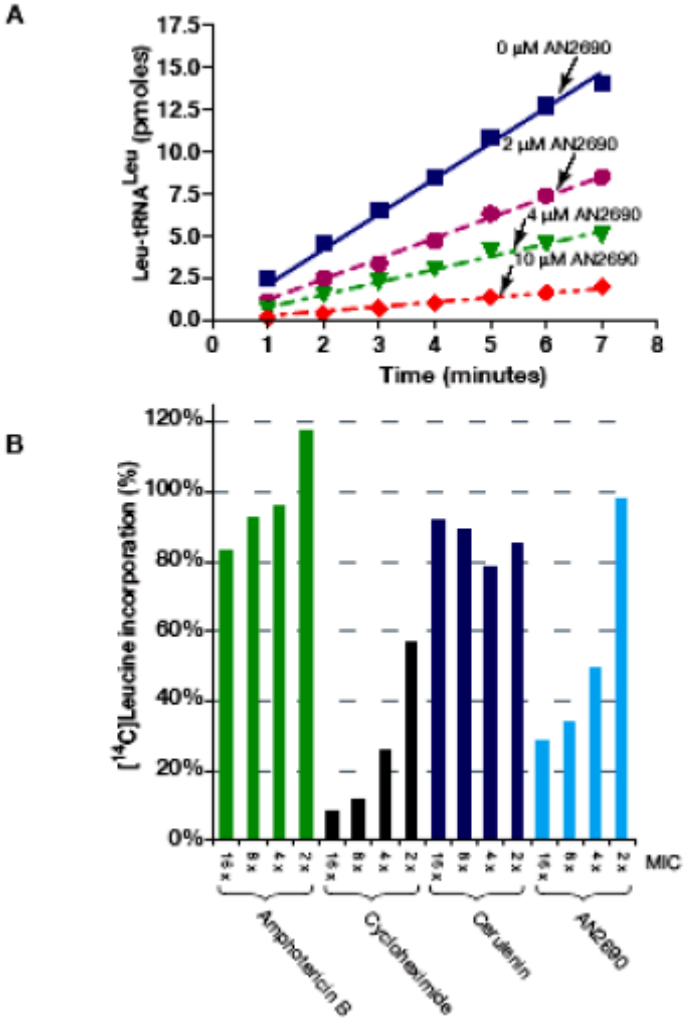
Minimal inhibitory concentrations (MIC) were determined according to the M27-A2 CLSI guidelines for testing yeasts with the exception that YPD media was used (CLSI 2002a). The mutants ANA320-327 were selected spontaneously and ANA358 and 360 were induced by ethyl methanesulfonate (EMS).
Source: Study 0002-NCL PP-001-01[1]

Figure 2: AN2690 Inhibits Post-transfer Editing.



Deacylation of total brewer's yeast tRNA mischarged with isoleucine, no enzyme control (circles), enzyme control (squares), Cdc60p treated with 6 µM AN2690 (triangles) and enzyme treated with 66 µM AN2690 (asterisks). All reactions were performed in triplicate and the mean values were plotted.

Source: Study 0002-NCL PP-001-01[1]
Figure 3: AN2690 inhibits aminoacylation in vitro and in vivo protein synthesis.



(A) Aminoacylation of total brewer's yeast tRNA by Cdc60p. Cdc60p was incubated with total brewer's yeast tRNA, Leucine and AN2690 for 20 minutes, then the aminoacylation reaction was initiated by the addition of 4 mM ATP. Cdc60p was treated 10μM AN2690 (red diamond). 4μM AN2690 (green triangle), 2μM AN2690 (purple circles), and no compound (blue squares). All the reactions were performed in triplicate and the mean values were plotted. (B) AN2690 inhibits in vivo protein synthesis. The incorporation of [^{14}C] leucine was measured in the presence of antifungal compounds that exceed their MIC. The antifungals amphotericin B and cerulenin were used as negative controls. Cycloheximide, a known protein synthesis inhibitor, was the positive control. The percent of [^{14}C] leucine incorporation was obtained by comparing the incorporation of [^{14}C] leucine in untreated cells to cells treated with the respective antifungal compounds. These experiments were repeated twice and the average was graphed. The MICs for *S. cerevisiae* in synthetic defined media minus leucine was 1 mcg/mL for amphotericin B, 0.5 mcg/mL for cycloheximide, 0.5 mcg/mL for cerulenin and 0.05 mcg/mL for AN2690.
Taken from 0002-NCL PP-001-01[1]

2.2. Antimicrobial spectrum of activity
Initial Studies Performed on Test Strains (Report 002-NCL PP-002-01)
Minimum inhibitory concentrations values were determined for tavaborole and four comparators (ciclopirox, terbinafine, fluconazole and itraconazole) using the microbroth dilution method described by CLSI standard M38-A for filamentous fungi and M27-A2 for yeasts. MIC determinations with the *Malassezia* species used urea broth instead of the regular RPMI media, due to the fact that this fungus does not grow well in the latter medium (Nakamura et al., 2000).The antifungal spectrum of tavaborole activity was evaluated in vitro against 19 test strains of fungi: *Aspergillus fumigatus, Candida albicans* (both fluconazole-sensitive and fluconazole-resistant strains), *Candida glabrata, Candida krusei, Cryptococcus neoformans, Candida parapsilosis, Candida tropicalis, Epidermophyton floccosum, Fusarium solani, Malassezia furfur, Malassezia pachydermatis, Malassezia sympodialis, Microsporum audouinii, Microsporum canis, Microsporum gypseum, Trichophyton mentagrophytes, Trichophyton rubrum,* and *Trichophyton tonsurans*. In addition, the MIC for tavaborole against *T. rubrum* in the presence of 5% (w/v) keratin powder and the minimum fungicidal concentration (MFC) for tavaborole against *T. rubrum* and *T. mentagrophytes* were also determined. Tavaborole was shown to exhibit broad-spectrum antifungal activity, as presented in Table 1, with MIC values ranging from 0.25–2 μg/mL against the 19 test strains of fungi. Both *T. rubrum* F296 and *T. mentagrophytes* F311 showed MIC values against tavaborole of 1 μg/mL. Addition of 5% keratin powder to the media did not appreciably

affect the MIC value against *T. rubrum* F296 (tavaborole MIC of 2 µg/mL), suggesting the in vitro activity of tavaborole is unaffected in the presence of the nail matrix. As shown in Table 2, tavaborole had MFC values of 8 µg/mL and 16 µg/mL against *T. rubrum* F311 and *T. mentagrophytes* F296, respectively.

Table 1: Minimum Inhibitory Concentration (MIC) for Tavaborole, Ciclopirox, Terbinafine, Fluconazole and Itraconazole (Comparator Drugs) Against 19 Strains of Fungi

		MIC (µg/mL)				
Species	**Broth used**	**Tavaborole**	**Ciclopirox**	**Terbinafine**	**Fluconazole**	**Itraconazole**
Aspergillus fumigatus ATCC 13073	RPMI	0.25	NT	NT	>64	0.25
Candida albicans ATCC 90028	RPMI	1	0.5	NT	0.25	≤ 0.12
C. albicans F56	RPMI	0.5	NT	NT	>64	0.25
Candida glabrata ATCC 90030	RPMI + MOPs	≤ 0.5	≤ 0.5	64	NT	≤ 0.5
Candida krusei ATCC 44507	RPMI + MOPs	1	≤ 0.5	64	NT	≤ 0.5
*Cryptococcus neoformans*F285	RPMI	0.25	NT	NT	2	≤ 0.12
Candida parapsilosis ATCC 22019	RPMI + MOPs	≤ 0.5	≤ 0.5	≤ 0.5	NT	≤ 0.5
Candida tropicalis ATCC 13803	RPMI + MOPs	≤ 0.5	≤ 0.5	256	NT	1
Epidermophyton floccosum ATCC 52066	RPMI + MOPs	≤ 0.5	≤ 0.5	≤ 0.5	NT	≤ 0.5
Fusarium solani ATCC 36031	RPMI + MOPs	≤ 0.5	4	64	NT	>256
Malassezia furfur ATCC 44344	Urea	1	≤ 0.5	2	NT	≤ 0.5
Malassezia pachydermatis ATCC 96746	Urea	1	≤ 0.5	≤ 0.5	NT	≤ 0.5
Malassezia sympodialis ATCC 44031	Urea	1	≤ 0.5	≤ 0.5	NT	≤ 0.5
Microsporum audouinii ATCC 42558	RPMI + MOPs	2	1	≤ 0.5	NT	≤ 0.5
Microsporum canis ATCC 10214	RPMI + MOPs	2	≤ 0.5	≤ 0.5	NT	≤ 0.5
Microsporum gypseum ATCC 24103	RPMI + MOPs	2	≤ 0.5	≤ 0.5	NT	≤ 0.5
Trichophyton mentagrophytes F311	RPMI + MOPs	1	0.5	≤ 0.5	32	≤ 0.12

Table 1: Minimum Inhibitory Concentration (MIC) for Tavaborole, Ciclopirox, Terbinafine, Fluconazole and Itraconazole (Comparator Drugs) Against 19 test Strains of Fungi (Continued)

		MIC (µg/mL)				
Species	**Broth used**	**Tavaborole**	**Ciclopirox**	**Terbinafine**	**Fluconazole**	**Itraconazole**
Trichophyton rubrum F296	RPMI/MOPS	1	1	≤ 0.5	1	≤ 0.12
T. rubrum F296	RPMI/MOPS + 5% keratin powder	2	1	NT	1	NT
Trichophyton tonsurans ATCC 28942	RPMI/MOPS	2	≤ 0.5	≤ 0.5	NT	≤ 0.5

MOPS, 3-(N-morpholino)propanesulfonic acid; NT, not tested.
Source: Report 002-NCL PP-002-01[2], Table 1

Table 2: Minimum Fungicidal Concentration (MFC) for Tavaborole, Ciclopirox, Terbinafine, Fluconazole and Itraconazole (Comparator Drugs) *Against Trichophyton rubrum* and *Trichophyton mentagraphytes*

		MFC (µg/mL)			
Species	**Broth used**	**Tavaborole**	**Ciclopirox**	**Terbinafine**	**Itraconazole**
Trichophyton rubrum F296	RPMI/MOPS	8	2	≤ 0.5	4
Trichophyton mentagrophytes F311	RPMI/MOPS	16	1	≤ 0.5	4

MOPS, 3-(N-morpholino) propanesulfonic acid.
Source: Report 002-NCL PP-002-01[2], Table 2.

Antibacterial Activity (Report 002-NCL PP-001-01)
The antibacterial spectrum of tavaborole was investigated in vitro against 12 strains of bacteria obtained from ATCC: *Staphylococcus aureus* (both methicillin-sensitive and methicillin resistant strains), *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Propionibacterium acnes*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus mutans*, *Escherichia coli*, *Haemophilus actinomycetemcomitans*, and *Porphyromonas gingivalis*.

All MIC testing followed the CLSI guidelines for antimicrobial testing of aerobic (M7-A5) and anaerobic bacteria (M11-A6), with the exception that lysed horse blood was not added to the broth, using the microbroth dilution method.
As shown in Table 3, tavaborole was shown to have limited antibacterial activity with MIC values against typical skin pathogens such as *S. aureus* (both methicillin-sensitive and methicillin-resistant), *S. epidermidis*, *S. pyogenes*, *P. acnes* and *P. aeruginosa* ranging from 8 to >64 µg/mL. Tavaborole was also shown to have limited antibacterial activity against oral or intestinal pathogens such as *E. faecalis*, *E. faecium*, *S. mutans*, *E. coli*, *H. actinomycetemcomitans* and *P. gingivalis*, with MIC values ranging from 4 – >64 µg/mL. In comparison, ciprofloxacin exhibited MIC values ranging from ≤ 0.12-1 µg/mL for most strains tested with exception of that for *E. faecium* (>64 µg/mL).

Table 3: Minimum Inhibitory Concentration for Tavaborole and Ciprofloxacin (a Comparator Drug) Against 12 Strains of Bacteria

	MIC (µg/mL)	
Bacteria	**Tavaborole**	**Ciprofloxacin**
Staphylococcus aureus ATCC 29213 (MSSA)	32	0.25
Staphylococcus aureus ATCC 33591 (MRSA)	64	≤ 0.12
Staphylococcus epidermidis ATCC 12228	8	≤ 0.12
Streptococcus pyogenes ATCC 19615	16	0.25
Propionibacterium acnes ATCC 11827	32	0.5
Pseudomonas aeruginosa ATCC 27853	> 64	≤ 0.12
Enterococcus faecalis ATCC 29212	> 64	0.5
Enterococcus faecium CT-26	> 64	> 64
Streptococcus mutans ATCC 25175	64	1
Escherichia coli ATCC 25922	4	≤ 0.12
Haemophilus actinomycetemcomitans ATCC 29523	16	≤ 0.12
Porphyromonas gingivalis ATCC 33277	4	0.5

MSSA, methicillin-sensitive *S. aureus*; MRSA: methicillin-resistant *S. aureus*.
Source: Report 002-NCL PP-001-01[1], Table 1

MIC Determination: Clinical Samples
Samples Obtained from Culture Banks (Report 002-NCL PP-003-02)
Early in the tavaborole development program and prior to the initiation of the Phase 3 clinical trials, in vitro studies were performed by the (b) (4) (b) (4) following a modification of the CLSI M38-A standard developed at (b) (4) in order to assess the activity of tavaborole against clinical isolates of *Trichophyton rubrum* and *Trichophyton mentagrophytes* obtained from their culture collection. The MIC values

for tavaborole against 100 strains each of *T. rubrum* and *T. mentagrophytes* ranged from 1.0–8.0 µg/mL and 4.0-8.0 µg/mL, respectively. The MIC_{50} and MIC_{90} for tavaborole were 4.0 µg/mL and 8.0 µg/mL, respectively, against both *T. rubrum* and *T. mentagrophytes*. Ciclopirox was tested as a comparator and had an MIC range of 0.06-1.0 µg/mL, MIC_{50} of 0.25, MIC_{90} of 0.5 µg/mL against *T. rubrum*, and an MIC range of 0.125-0.5 µg/mL, MIC_{50} of 0.25, and MIC_{90} of 0.5 µg/mL against *T. mentagrophytes*. Tavaborole had an MFC_{90} value of 64 µg/mL against 80 *T. rubrum* isolates and 128 µg/mL against 76 *T. mentagrophytes* isolates. MIC and MFC values obtained from the initial studies with clinical isolates are summarized in Table 4.

Table 4: Minimum Inhibitory Concentration (MIC) (in mcg/mL) and Minimum Fungicidal Concentration (MFC) (in mcg/mL) of Tavaborole and Ciclopirox Assessed in Clinical Isolates

Tavaborole						
Species	**MIC Range**	**MIC_{50}**	**MIC_{90}**	**MFC Range**	**MFC_{50}[a]**	**MFC_{90}[a]**
Trichophyton rubrum	1.0-8.0	4.0	8.0	8.0-128	64	64
Trichophyton mentagrophytes	4.0-8.0	4.0	8.0	16->128	64	128
Ciclopirox						
Species	**MIC Range**	**MIC_{50}**	**MIC_{90}**	**MFC Range**	**MFC_{50}**	**MFC_{90}**
Trichophyton rubrum	0.06-1.0	0.25	0.5	0.5->16	>16	>16
Trichophyton mentagrophytes	0.125-0.5	0.25	0.5	1.0->16	>16	>16

MFC, minimum fungicidal concentration; MFC_{50}, minimum fungicidal concentration required to kill (defined at a > 99.9% reduction in colony count from the original inoculum) 50% of the strains tested; MFC_{90}, minimum fungicidal concentration required to kill (defined at a > 99.9% reduction in colony count from the original inoculums) 90% of the strains tested; MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of isolates tested; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates tested.
Source: Report 002-NCL PP-003-02[3], Table1

2.3. Antifungal Activity
The Phase 2 and Phase 3 studies of antifungal activity are below. See also description of study 002-NCL PP-002-01 above.

2.3.1. Antifungal Activity Evaluated in Phase 2 Studies
Phase 2 Studies Report 002-NCL PP-018-01

The antifungal activity of tavaborole against the dermatophytes *T. rubrum* and *T. mentagrophytes* was assessed by (b) (4) through determination of MIC and MFC of tavaborole against dermatophytes isolated from subungual samples obtained from subjects participating in Phase 2 tavaborole clinical studies AN2690-ONYC-200/200A, AN2690-ONYC-201, AN2690-ONYC-202, AN2690-ONYC-203 and AN2690-ONYC-205. Subungual samples for culture were obtained both at screening and following treatment in these studies; however, no correlation between MIC/MFC values at screening versus those following treatment was determined, and results are simply reported for all cultures. Furthermore, because the microbiologic testing was initiated prior to establishment of the dermatophyte QC strains, two CLSI yeast QC strains, *Candida parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258, were run on each day for the first two sets of testing. Thereafter, *T. rubrum* MYA 4438 and *T. mentagrophytes* MYA 4439 were tested with each run, following the identification of these dermatophytes as CLSI QC strains. MIC_{50} and MIC_{90}, as well as MFC_{50} (the concentration at which 50% of the isolates tested were killed) and MFC_{90} (the concentration at which 90% of the isolates tested were killed), were computed for all isolates.

Reviewer's Comment

CLSI recommended Quality Control strains of *Candida* species were initially used for the determination of antifungal activity because microbiologic testing began before dermatophyte QC strains had been established. The Quality Control strains were subsequently changed to *T. rubrum* and *T. mentagrophytes* as recommended by CLSI for any further testing of antifungal activity.

As shown in Table 5 and Table 6, there were no differences in antifungal activity between the isolates collected from subjects participating in the Phase 2 clinical studies in the US (n=132) and isolates collected from subjects participating in Phase 2 clinical studies in Mexico (n=97).

Table 5: Tavaborole MIC data Against Viable Isolates of *Trichophyton rubrum* and *Trichophyton mentagraphytes* by Country for Phase 2 Studies

Country	*Trichophyton rubrum*				*Trichophyton mentagrophytes*			
	Number of Isolates	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	Number of Isolates	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
United States	129	2-16	4	16	3	4-8	ND	ND
Mexico	93	2-32	16	16	4	8-32	ND	ND

MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of isolates tested; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates tested; ND, Not Determined (fewer than 10 isolates).
Source: Report 002-NCL PP-018-01[4], Table 2

Table 6: Tavaborole MFC Data Against Viable Isolates of *Trichophyton rubrum* and *Trichophyton mentagraphytes* by Geographic Area

Country	*Trichophyton rubrum*				*Trichophyton mentagrophytes*			
	Number of Isolates	MFC Range (µg/mL)	MFC_{50} (µg/mL)	MFC_{90} (µg/mL)	Number of Isolates	MFC Range (µg/mL)	MFC_{50} (µg/mL)	MFC_{90} (µg/mL)
United States	129	2->32	>32	>32	3	32->32	ND	ND
Mexico	93	4->32	>32	>32	4	>32	ND	ND

MFC, minimum fungicidal concentration; MFC_{50}, minimum fungicidal concentration required to kill 50% of isolates tested; MFC_{90}, minimum fungicidal concentration required to kill 90% of isolates tested; ND, Not Determined (fewer than 10 isolates).
Source: Report 002-NCL PP-018-01[4], Table 3

Isolates from both regions had an MIC_{90} of 16 µg/mL and an MFC_{90} of >32 µg/mL. There were no significant differences in MIC values of the isolates from different geographical regions. These findings were used to support inclusion of subjects from both the US and Mexico in the subsequent Phase 3 studies.

Reviewer's Comment
It is not recommended that a claim be made for this product stating that it has fungicidal activity because methods for the determination of fungicidal activity (Determination of MFC, for example) have not yet been standardized. Additionally, the clinical significance of fungicidal activity expressed as the in vitro MFC of a topical drug is difficult to determine. The MBC/MIC ratio was not less than or equal to 4 for *T. rubrum or T.*

mentagraphytes, suggesting that tavaborole does not have fungicidal activity for either of these fungi.

2.3.2. Antifungal Activity Evaluated in Phase 3 Studies
Phase 3 Studies: Recent Isolates (Report 002-NCL PP-017-01)
The antifungal activity of tavaborole and two comparators, ciclopirox and terbinafine, was determined in vitro against 100 recent (collected within the last three years) clinical strains each of *Trichophyton rubrum* and *Trichophyton mentagrophytes*. These clinical strains were obtained at screening prior to treatment from subjects participating in the Phase 3 clinical Studies AN2690-ONYC-301 and AN2690-ONYC-302 and from (b) (4) culture collection in accordance with CLSI document M38-A2. Results of this study are shown in Table 7, tavaborole, ciclopirox and terbinafine each exhibited equivalent antifungal activity against each of the two dermatophyte strains tested, based on the MIC range, MIC_{50} and MIC_{90} for each drug tested against *T. rubrum* and *T. mentagrophytes*.

Table 7: MIC Data of Tavaborole and in Vitro Comparators Against *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

	Tavaborole (µg/mL)			Ciclopirox (µg/mL)			Terbinafine (µg/mL)		
Species	MIC Range	MIC_{50}	MIC_{90}	MIC Range	MIC_{50}	MIC_{90}	MIC Range	MIC_{50}	MIC_{90}
T. rubrum	1-8	4	4	0.125-0.5	0.25	0.5	0.002-0.03	0.008	0.016
T. mentagrophytes	1-8	4	4	0.125-0.5	0.25	0.5	0.002-2.0	0.004	0.008

MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of isolates tested; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates tested.
Source: Report 002-NCL PP-017-01[5], Table 1

MIC results for tavaborole against the two CLSI dermatophyte QC strains are shown in Table 8. Comparator ranges for the two CLSI QC strains were equivalent to published CLSI ranges on all days of testing.

Table 8: MIC Data (in mcg/mL) of Tavaborole and in Vitro Comparators Against Quality Control Strains

	Tavaborole (µg/mL)			Ciclopirox (µg/mL)			Terbinafine (µg/mL)		
QC Strain	MIC Range	MIC_{50}	MIC_{90}	MIC Range	MIC_{50}	MIC_{90}	MIC Range	MIC_{50}	MIC_{90}
T. rubrum MYA 4438	1-8	2	4	0.25-1[a]	0.25	0.5	>0.5[b]	>0.5[b]	>0.5[b]
T. mentagrophytes MYA 4439	2-8	4	8	0.25-2[a]	0.25	0.5	0.004-0.008	0.008	0.008

MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of isolates tested; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates tested.
[a] Internal range of 0.25-2.0 mcg/mL established by the (b) (4).
[b] *T. rubrum* MYA 4438 was selected as a CLSI candidate strain specifically because it is resistant to terbinafine.
Source: Report 002-NCL PP-017-01[5], Table 3.

2.3.3. Mycological Testing
Mycological testing (fungal culture and KOH wet mount) was performed in five Phase 2 studies and in two Phase 3 studies of subjects with onychomycosis due to dermatophytes.

2.4. Intracellular antimicrobial concentration assessment
Not Applicable.

2.5. Development of Resistance and Resistance Mechanisms
Information on the development of resistance and resistance mechanisms is below.
See also "Mechanism of Action" section above for further information.

2.5.1. Selection of Spontaneous mutants (Single-Step Mutation)
AN2690 is a new class of antifungal agent; therefore, there is limited information on the development of resistance during treatment. Single-step selection for resistance was performed in the laboratory for *Saccharomyces cerevisiae* and *Candida albicans*. Resistant isolates were obtained at a frequency of 10^{-7} to 10^{-8}. The MICs for resistant isolates increased by up to 512-fold. Mutations that were shown to cause resistance mapped to the proposed target gene, CDC60. No cross-resistance to other classes of antifungal agents was observed. It is difficult to provide a perspective on the frequency of selection for resistance because the actual viable fungal burden associated with onychomycosis has not been established. Additionally, given the high levels of AN2690 exposure at the site of infection, based on in vitro nail penetration studies and nail samples taken during the Phase 2 studies (Section 4.3.3.2 and Section 5.3.1), it is uncertain what MIC value may be considered to be "resistant."

2.5.2. Alteration of Target Sites
Mechanism of AN2690 Resistance in *C. albicans* ATCC 90028 (Study 002-NCL PP-016-02)
Objectives: The isolation and initial characterization of *C. albicans* ATCC90028 mutants resistant to AN2690.
Methods:
Determination of MICs
The minimum inhibitory concentration (MIC) was determined for AN2690 and for other antifungal agents including amphotericin B, cerulenin, itraconazole, aculeacin A, ciclopririox, terbinafine, nikkomycin Z and tunicamycin. Assays followed the CLSI guidelines outlined in the M27-A2 protocol.
Isolation of Spontaneous Resistant Mutants
The wild-type *C. albicans* ATCC90028 was grown overnight in YPD (Yeast extract, Peptone, alpha-D-Glucose) broth at 30°C and
1 mL of cells was plated out onto YPD agar plates containing16 µg/mL AN2690 (equivalent to 16-fold the MIC value for AN2690). Resistant mutants appeared after 2 days incubation at 30 °C. Frequency of resistance was determined by dividing the number of resistant mutants by the total number of cells plated as determined by plating dilutions of the overnight culture on YPD plates.
DNA Sequencing
Performed by Sequetech Corporation (Mountain View, CA USA)
Mapping Mutations
To further map the mutations to specific domains in *CDC60*, the following two pairs

of primers were used:5' GAGCCATGGGTCCACAAGAATATGTTGG 3' and 5' GAACTCGAGTTCTGGTTCATTGTAAACAAAAGC 3'.

Results and Conclusions:
AN2690 demonstrated activity against *C. albicans* ATCC90028, with a MIC value of 1 µg/mL (Table 9). AN2690-resistant mutants were obtained at a frequency of 5.5×10^{-8} when selected at 16 µg/mL (Table 9). Four *C. albicans* ATCC90028 mutants, which had MIC values of between 64 and >64 µg/mL, were selected for further characterization (Table 10). Since a previously conducted *Saccharomyces cerevisiae* genetics study (002-NCL PP-011-01) demonstrated that all AN2690 mutants mapped to the editing portion of the gene for cytoplasmic leucyl-tRNA synthetase (*CDC60*), the editing domain portion of the *C. albicans CDC60* gene was amplified and the PCR product sequenced. All four mutants bore a mutation in the *CDC60* gene (Table 10), as was elsewhere observed in *S. cerevisiae*. These findings suggest that the in vitro fungal mechanism of resistance to AN2690 is due to a mutational change in the editing active site of cytoplasmic leucyl-tRNA synthetase. Resistant mutant *CDC60*T321I does not confer any cross-resistance to other antifungal agents (Table 11). Because AN2690 has a mechanism of action that differs from other antifungal agents, it is unlikely to cause cross-resistance to any of the known classes of antifungal agents.

Table 9: *C. Albicans* ATCC 90028 Spontaneous Frequency of Resistance at 16x MIC of AN2690

Antifungal Agent	MIC (µg/mL)	*C. Albicans* ATCC90028 Spontaneous Frequency of Resistance
AN2690	1	5.5×10^{-8}

MIC: Minimum Inhibitory Concentration
Source: Study 002-NCL PP-016-02[6]

Table 10: MICs of WT and AN2690 Resistant Mutants, Amino Acid Substitution

C. Albicans WT and Mutants	MIC (µg/mL AN2690	Mutation in CDC60
WT	1	none
Mutant-1	>64	T3211
Mutant-2	>64	T3211
Mutant-3	>64	T3211
Mutant-4	64	K510E

MIC: minimum inhibitory concentration; WT: wild type.
Source: Study 002-NCL PP-016-02[6]

Table 11: *C. albicans* ATCC 90028 MICs to Various Antifungal Agents

Antifungal Agent	MIC (µg/mL)	
	Wild Type	CDC60 T321I
AN2690	0.5	64
Amphotericin B	0.5	0.5
Cerulenin	2	2
Itraconazole	0.5	0.5
Aculeacin A	0.5	0.25
Ciclopririox	0.5	0.5
Terbinafine	16	16
Nikkomycin Z	2	4
Tunicamycin	4	4

MIC: minimum inhibitory concentration; WT: wild type.
Source: (Study 002-NCL PP-016-02[6])

2.6. Effect of medium, inoculum size, pH and serum on *in vitro* activity
No information provided.

2.7. Susceptibility Test Methods
No interpretive criteria were provided for potential pathogens. Methods for in vitro susceptibility testing were according to recommendation of the Clinical and Laboratory Standards Institute (CLSI) with minor modifications. Information on susceptibility test methods is below:

2.7.1. Dilution Techniques
Methods for MIC Determination
Early exploratory MIC studies evaluating the antibacterial and antifungal spectra of activity of tavaborole were conducted by (b) (4) (b) (4) followed the methods for dilution antimicrobial susceptibility testing for aerobic bacteria outlined in CLSI document M7-A5 and the methods for antimicrobial susceptibility testing for anaerobic bacteria outlined in CLSI document M11-A6, with the exception that lysed horse blood was not added to the broth, in the study reported in 002-NCL PP-001-01. (b) (4) followed the method for antifungal susceptibility testing of

yeast outlined in CLSI document M27-A2 and the method for broth dilution antifungal susceptibility testing of filamentous fungi outlined in CLSI document M38-A, except for the *Malassezia* species which were incubated in a urea broth (Nakamura et al., 2000), in the study reported in 002-NCL PP-002-01.
Most recently, (b) (4) conducted the MIC testing of tavaborole against clinical isolates of *T. rubrum* and *T. mentagrophytes* (obtained both from the (b) (4) culture collection and collected from subjects participating in the two Phase 3 clinical studies), and identified appropriate dermatophyte QC strains and ranges following a modification of the CLSI M38-A2 standard developed at (b) (4) ((b) (4) SOPs A10 and A10.7).

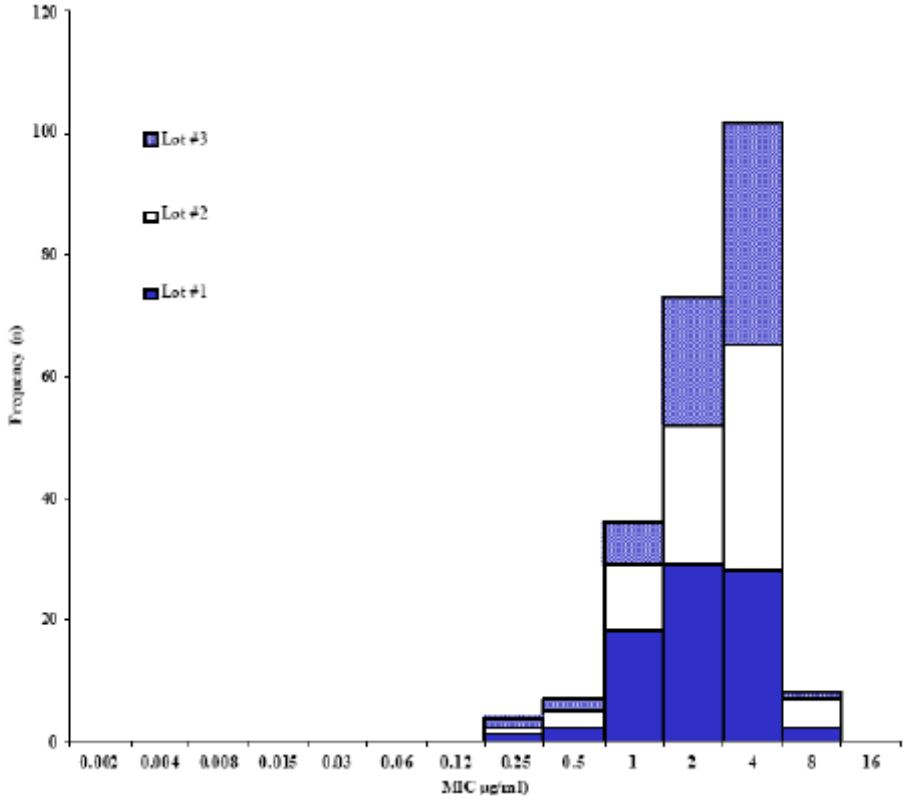
2.7.2. Development of interpretive criteria (Breakpoints) for MIC testing
None proposed.

2.7.3. Development of interpretive criteria for Disk diffusion testing
None proposed.

2.7.4. Quality Control Parameters
Information on quality control parameters is below. See also the quality control from Phase 3 trials as shown in Table 8 above.
Identification of Quality Control Ranges (Report 002-NCL PP-015-01)
A multi-laboratory study was conducted under the guidelines of the Clinical and Laboratory Standards Institute® (CLSI) document M23-A2 to determine the reproducibility of minimum inhibitory concentration (MIC) test values and quality control (QC) ranges for tavaborole activity against the two dermatophyte QC strains, *Trichophyton rubrum* MYA 4438 and *Trichophyton mentagrophytes* MYA 4439 (Ghannoum, 2006), as well as other clinical strains, with the aim of identifying suitable QC isolates for use in testing the spectrum and potency of tavaborole. This study was conducted to support inclusion of tavaborole in the CLSI microdilution standard method for filamentous fungi (M38-A2).The study was conducted in accordance with advice provided to Schering-Plough by the Division of Dermatology and Dental Products (DDDP) at the guidance meeting on 11 June 2007 (Guidance meeting minutes dated 29 June 2007), and the September 2009 FDA Guidance for Industry, *Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation*. Posaconazole and terbinafine were used as controls for the study. The six American Type Culture Collection (ATCC) strains provided by the (b) (4) culture collection were *T. rubrum* MYA 4438, *T. rubrum* ATCC 28188, *T. rubrum* ATCC 18759, *T. mentagrophytes* MYA 4439, *T. mentagrophytes* ATCC 24953, and *T. mentagrophytes* ATCC 28187. *Trichophyton mentagrophytes* MYA 4439 was also tested against posaconazole and terbinafine as a control for each testing run. Each of eight laboratories tested the six candidate strains ten times in three different

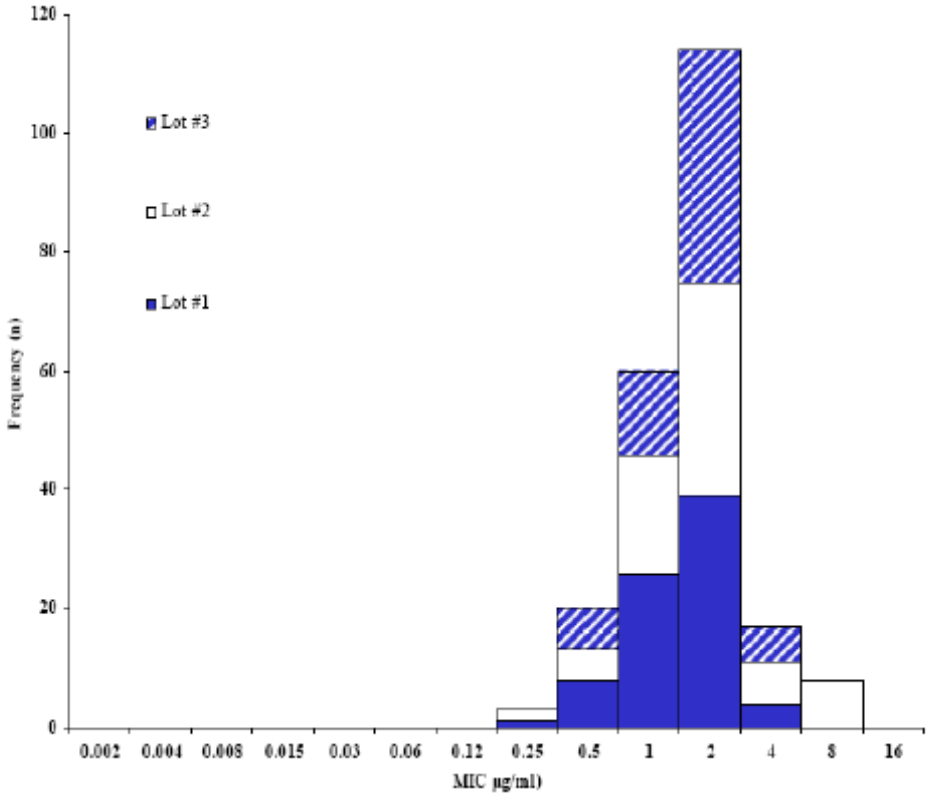
lots of RPMI-1640 media for a total of 30 MIC values for each strain per laboratory or a final count of 240 MIC values per isolate per antifungal agent. The MICs for QC isolates were within range for both posaconazole and terbinafine (99.1% and 97.4%, respectively), and there were no differences between the three lots of RMPI media. Tavaborole demonstrated consistent MIC values among the eight participant laboratories, with an MIC range of 1.0–4.0 µg/mL in 89.9% of replicate tests for all strains tested. The dermatophyte QC strains currently included in CLSI document M38-A2, *T. rubrum* MYA 4438 and *T. mentagrophytes* MYA 4439, satisfied QC parameters specified by CLSI document M23-A2 for use as QC strains for tavaborole. Figure 4 and Figure 5 show the tavaborole MIC ranges for *T. mentagrophytes* MYA 4439 and *T. rubrum* MYA 4438, respectively. Tavaborole MIC ranges for *T. mentagrophytes* MYA 4439 were 1.0-8.0 µg/mL with a mode MIC of 4 µg/mL and a 0.5-4.0 µg/mL range with a mode MIC of 2 µg/mL for *T. rubrum* MYA 4438. These MIC ranges were met in 95.2% of replicate tests, thus qualifying these as recommended QC ranges for tavaborole.

Figure 4: MIC Range of Tavaborole Against *Trychophyton mentagraphytes* MYA 4439 in Three Different Lots of RPMI Media



MIC, minimum inhibitory concentration.
Source: Report 002-NCL PP-015-01[7], Figure 1

Figure 5: MIC Range of Tavaborole Against *Trichophyton rubrum* MYA 4438 in Three Different Lots of RPMI Media



MIC, minimum inhibitory concentration.
Source: Report 002-NCL PP-015-01[7], Figure 2

The proposed QC ranges for the testing of tavaborole against *T. mentagrophytes* MYA 4439 and *T. rubrum* MYA 4438 are presented in Table 12. These QC ranges for tavaborole are planned for presentation to the CLSI committee for inclusion in the CLSI microdilution standard method for filamentous fungi (M38-A2).

Table 12: Proposed Antifungal MIC Ranges for Tavaborole (in mcg/mL)

Organism	Purpose	Antifungal Agent	MIC Range	Mode	Percentage of MIC Values Within Range
T. mentagrophytes MYA 4439	QC	tavaborole	1.0–8.0	4.0	95.2
T. rubrum MYA 4438	QC	tavaborole	0.5–4.0	2.0	95.2

MIC, minimum inhibitory concentration; QC, quality control.
Source: Report 002-NCL PP-015-01[7], Table 1.

2.8. Antimicrobial interactions and fixed combination studies
Checkerboard MIC Testing of Tavaborole and Terbinafine
(Report 002-NCL PP-009-01)
The possibility of synergistic inhibitory effect of terbinafine with tavaborole was investigated by observing *Trichophyton rubrum* F296 fungal growth in the presence of both compounds over a range of concentrations. All MIC testing followed CLSI guidelines for antimicrobial testing of yeasts and filamentous fungi (M38-A). The results from this study indicated that tavaborole was not antagonistic to terbinafine when both drugs are just below their typical MIC threshold.

Reviewer's Comments:
Clinical and laboratory isolates were evaluated for their susceptibility to tavaborole and other comparators. Clinical isolates were collected mostly from the United States and Mexico. Guidelines for susceptibility testing of filamentous fungi have been established (CLSI M38P and M38-A), and these methods were employed by the applicant with minor modifications. For dermatophytes, the methods used in susceptibility testing were either the macrobroth or microbroth dilution methods.
There were no studies provided that evaluated the effects of culture conditions on the in vitro activity of tavaborole, however the central laboratory confirmed that CLSI methods were used.
Information on the development of resistance and mechanisms of resistance to tavaborole involved determination of target mutations within the editing active site of cytoplasmic leucyl-tRNA synthetase.

3. ANIMAL MODELS OF INFECTION

The activity of tavaborole and comparators were evaluated in murine models of systemic candidiasis:

3.1. Murine models of systemic candidiasis

Evaluation of the *In Vivo* Efficacy of AN2690 Against Systemic *Candida albicans* Infection in Mice

SUMMARY

Introduction

The purpose of this study was to determine the therapeutic activity and safety of AN2690 against systemic *Candida albicans* infection in mice. The effect of AN2690 was tested using survival as the endpoint.

Materials and Methods

Thirty (30) virus-antibody-free (VAF) male Balb/c mice (5-6 weeks-old mice; 18-22 g) were injected intravenously (iv) into the lateral tail vein with 0.2 mL of 5 x 10^5 CFU per mouse of a *Candida albicans* suspension. One hour following the injection of *Candida albicans*, the mice were administered 30 mg/kg of AN2690 by either oral gavage (n=5) or subcutaneous injection (n=5), or AN2690 vehicle (n=10) or fluconazole (n=5) at 1 mg/kg by oral gavage. The second dose was administered 10 h after the first dose. On all subsequent study days up through Day 7, the mice were dosed twice, with a 12 h interval between doses. AN2690 was formulated in 1% carboxymethylcellulose (CMC). A satellite group of 5 mice was not infected and was dosed with 30 mg/kg of AN2690 by oral gavage to evaluate the safety of AN2690 in healthy animals. The mice were monitored daily for survival and general health.

Results and Conclusions

AN2690 did not prevent the death of the mice induced by the lethal injection of *Candida albicans*. The positive control fluconazole completely protected the mice. Noninfected mice dosed with AN2690 survived with no ill effects.

In conclusion, AN2690, given at 30 mg/kg by either the oral or subcutaneous route, was ineffective at preventing mortality in mice caused by an injection of *Candida albicans*.

Table 13: Survival of Mice Post Infection: The Number of Surviving Mice on Each Day of the Study

			Number of Surviving Mice (% survival)							
Group	Compound	Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
1	Vehicle	0 mg/kg, PO	10 (100%)	10 (100%)	10 (100%)	7 (70%)	5 (50%)	2 (20%)	2 (20%)	2 (20%)
2	Fluconazole	1 mg/kg, PO	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)
3	AN2690	30 mg/kg, PO	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	2 (40%)	0 (0%)	0 (0%)
4	AN2690	30 mg/kg, SC	5 (100%)	5 (100%)	4 (80%)	4 (80%)	4 (80%)	4 (80%)	1 (20%)	1 (20%)
5*	AN2690	30 mg/kg SC	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)

+ Animals in Group 5 for safety evaluation of AN2690 only were not infected.
Source: Study 002-NCL PP-012-01[8]

Efficacy of AN2690 Against Systemic Murine Candidiasis

SUMMARY

Introduction

The purpose of this study was to determine the therapeutic activity and safety of AN2690 against systemic *Candida albicans* infection in mice. The effect of AN2690 was tested using kidney *C. albican*s CFU and mouse survival as endpoints.

Materials and Methods

A murine model of systemic candidiasis was established in five-week old male CD-1 mice. All mice were infected intravenously with 1.95×10^5 yeast of *C. albicans* strain #5. Therapy was initiated four days after infection, with groups of 10 animals receiving one of the following treatments: No treatment (untreated controls), 1% carboxymethylcellulose (CMC) (diluent control), fluconazole (FCZ) 30 mg/kg QD, FCZ 30 mg/kg or 100 mg/kg BID, and AN2690 at 30 mg/kg or 100 mg/kg BID. All treatments were given orally in 0.1 mL and were formulated using 1% CMC. Therapy was given for 12 consecutive days. On Day 19 post-infection, all surviving animals were euthanized and the CFU remaining in the kidneys were determined by quantitative plating of organ homogenates.

Results and Conclusions

AN2690 did not prevent the death of the mice induced by the lethal injection of *C. albicans* at either dose level, nor did it significantly decrease the *C. albicans* CFUs in the kidneys. In contrast, the positive control fluconazole significantly protected the mice using both dosing paradigms as measured using either endpoint. In conclusion, AN2690 was ineffective at preventing mortality in mice caused by a systemic injection of *C. albicans* when given at 30 or 100 mg/kg BID by the oral route.

Reviewer's Comments:
AN2690 was ineffective at preventing mortality in mice caused by systemic *C. albicans*. The in vivo efficacy studies with *C. albicans* were not relevant to the submission because the submission is for the proposed indication of onychomycosis, an infection of the nail plate, and the animal models were models of systemic infection.

4. PHARMACOKINETICS/PHARMACODYNAMICS

4.1. In vitro pharmacokinetics/pharmacodynamics

Tavaborole was specifically designed to have high nail unit bioavailability when applied topically and to retain its pharmacologic activity in the presence of keratin in the nail plate.

In Vitro Human Nail Penetration
In vitro penetration of AN2690 into and through human cadaver nail plates was studied by mounting nails on a small cotton ball wetted with saline in a Teflon one-chamber diffusion cell, exposing a surface area of 0.785 cm^2 at room temperature. Penetration of AN2690 into and through human cadaver nail plates relative to ciclopirox in Penlac was assessed after 14 days of dosing. No statistical significance in the extent of nail penetration was found between the drugs in the dorsal/intermediate nail layer on Day 15. The concentration of AN2690 in the ventral/intermediate nail layer, the part of the nail in which the disease resides, was significantly higher for AN2690 than ciclopirox at all time points, providing a total accumulation over the 15-day period that was ~60-fold greater for AN2690 than for ciclopirox.

Distribution
Using equilibrium dialysis, AN2690 was 66% ± 4% (mean ± SD) bound to mouse plasma proteins. Protein binding was 43%, 55%, 75%, and 56% in rat, dog, minipig, and human

plasma, respectively (however, loss on incubation was 18%, 93%, 8%, and 27%, respectively, in these species).

4.2. In vivo pharmacokinetics/pharmacodynamics

In support of the clinical development of AN2690, pharmacokinetic (PK) studies were conducted in CD-1 and C57BL/6 mice, Sprague-Dawley rats, Göttingen minipigs, and beagle dogs. Tavaborole was found to be rapidly absorbed and excreted in rats and dogs following oral administration. However, systemic exposure was found to be low, and in some cases below the level of quantitation, following subcutaneous and topical tavaborole administration to rats and minipigs. To determine the extent of distribution of tavaborole in tissues, a tissue distribution study of [^{14}C]-tavaborole was conducted in the mouse. After a single dermal dose to pigmented mice,[^{14}C]-tavaborole was rapidly and incompletely absorbed, then widely distributed to tissues. Concentrations of [^{14}C]-tavaborole had fallen below quantifiable limits in all tissues 168 hours (7 days) post-dose.

Absorption studies have demonstrated that tavaborole is absorbed at much higher levels when administered as an IV or oral solution versus the topical route of administration to the skin. Studies conducted to demonstrate the distribution of tavaborole showed that protein binding of [^{14}C]-tavaborole was low to moderate across species, with minor species differences, and in an inversely concentration-dependent manner. Qualitative whole body autoradiography data generated from both a rat and a mouse study showed that tissue concentrations of drug-derived radioactivity were below detection limits at 168 hours post-dose with the exception of some skin sections. This suggests that there is a low likelihood of long-term concentrations of tavaborole in tissues.

The in vivo metabolism of AN2690 was investigated in mice, rats, rabbits, and humans. In vivo metabolic studies of [^{14}C]-tavaborole administered to mice and rats revealed similar metabolic profiles in both species. The most important route of elimination of absorbed radiocarbon was via the urine, with lesser amounts excreted in feces in both species.

4.3. Human pharmacokinetics/ pharmacodynamics

4.3.1Phase 2 Safety and Pharmacokinetic Studies

4.3.1.1 Study AN2690-ONYC-202

Study AN2690-ONYC-202 was an open-label, multiple-dose study of the absorption and systemic pharmacokinetics of tavaborole applied once daily as a 7.5% solution to all toenails of 15 adult subjects with moderate to severe onychomycosis. All subjects were required to have a positive fungal culture and positive KOH wet mount from at least one

great toenail at study entry. Clinic staff applied tavaborole solution 7.5% once daily to all 10 toenails and not more than 1 mm of skin around each nail plate for 28-days. KOH wet mounts and fungal cultures from the treatment-targeted great nail were performed by (b) (4) using samples obtained at Screening, Days 14, 28, 42, 180 and 360. Sample collection was standardized using procedures provided by (b) (4).
Baseline analysis showed 80% (24 cultures) of the fungal culture results were positive; 20% (6 cultures) were negative. In addition, 97% (29 results) of the KOH results were positive; 3% (1 result) was negative.
Of the great toenails with a positive fungal culture at baseline, 92% (22/24 cultures) were negative at Day 14 and 100% (24/24 cultures) were negative at Day 28; 65% (13/20 cultures) were still negative at Day 180, and 67% (4/6 cultures) were still negative at Day 360. Of the great toenails with a positive KOH result at baseline, 0% (0/29 results) were negative at Day 14 and 4% (4/29 results) were negative at Day 28; 35% (8/23 cultures) were negative at Day 180, and 38% (3/8 results) were negative at Day 360.

4.3.1.2 Study AN2690-ONYC-205
Study AN2690-ONYC-205 was an open-label, multiple-dose study of the absorption and systemic pharmacokinetics of tavaborole applied once daily as a 7.5% solution to all toenails of 20 adult subjects with moderate to severe onychomycosis. All subjects were required to have a positive fungal culture and positive KOH wet mount from at least one great toenail at study entry. Clinic staff applied tavaborole solution 7.5% once daily to all 10 toenails and 5 mm of skin around each nail plate for 28-days. KOH wet mounts and fungal cultures from the treatment-targeted great nail were performed by (b) (4) using samples obtained at Screening, Days 14, 28 and 42. Sample collection was standardized using procedures provided by (b) (4). Baseline analysis showed 63% (25 cultures) of the fungal culture results were positive; 38% (15 cultures) were negative. In addition, 88% (35 results) of the KOH results were positive; 13% (5 results) was negative. Of the great toenails with a positive fungal culture at baseline, 96% (24/25 cultures) were negative at Day 14 and Day 42. Of the great toenails with a positive KOH result at baseline, 26% (9/35 results) were negative at Day 14 and 40% (14/35 results) were negative at Day 42.

Reviewer's Comment
Eight clinical trials (five Phase 1 [one safety study, four PK] studies and three Phase 2 studies) have been conducted with AN2690 solutions at concentrations ranging from 1.0% to 7.5% and involving a total of 43 healthy subjects and 395 subjects with onychomycosis. After topical application to toenails of human subjects, AN2690 is absorbed through the nail and surrounding skin and can be found in plasma. Plasma levels of the parent compound, AN2690, remained low across all subjects, with a mean peak maximum observed plasma concentration (Cmax) of approximately 3.54 ng/mL after a single topical application and a steady-state exposure of 1-2 ng/mL after repeated

dosing. AN2690 is extensively metabolized, primarily to a sulfate-conjugate. AN2690 appears to have a relatively short half-life and is rapidly cleared. Approximately 29% of the effective dose was excreted in urine.

5. CLINICAL TRIALS

5.1. Phase 2 trials

Phase 2 Safety and Efficacy Studies

Open Label Studies AN2690-ONYC-201, Cohorts 1 and 2 and AN2690-ONYC-201, Cohort 3

The first proof-of-concept Phase 2 study, AN2690-ONYC-201, was an open-label, multiple-cohort, dose-rising study with topical daily doses of tavaborole solution 5% (Cohort 1) or tavaborole solution 7.5% (Cohort 2) for 6 months in patients with onychomycosis. Fungal culture and KOH testing from the affected target great toenail were obtained at Screening and at Day 180 for Cohorts 1 and 2 after 6 months of daily topical dosing with tavaborole solution 5% and tavaborole solution 7.5%, with additional cultures performed 6 months (360 days) after the completion of dosing. A longer duration of treatment (360 days) with tavaborole solution 5% was evaluated in Cohort 3 following completion of cohorts 1 and 2. Fungal culture and KOH testing were performed at Screening and on Days 180 and 360 for subjects in Cohort 3. All mycologic testing was performed by (b) (4). Results of fungal culture testing are presented in Table 14.

Table 14: Summary of Mycological Response (ITT/MITT Population-AN2690-ONYC-201)

	Cohort 1 Tavaborole 5% QD for 180 Days	Cohort 2 Tavaborole 7.5% QD for 180 Days	Cohort 3 Tavaborole 5% QD for 360 Days
Mycological Response Day 180			
No. of Evaluable Subjects[a]	17	18	29
Success[b]	12 (70.6%)	18 (100.0%)	29 (100.0%)
Failure	5 (29.4%)	0 (0.0%)	0 (0.0%)
95% CI for % Success	(48.9%, 92.2%)	(100.0%, 100.0%)	(100.0%, 100.0%)
Mycological Response Day 360			
No. of Evaluable Subjects[a]	13	16	29
Success[b]	9 (69.2%)	11 (68.8%)	28 (96.6%)
Failure	4 (30.8%)	5 (31.3%)	1 (3.4%)
95% CI for % Success	(44.1%, 94.3%)	(46.0%, 91.5%)	(89.9%, 100.0%)

CI, confidence interval; ITT, Intent-to-Treat, MITT, modified Intent-to-Treat; QD, one time a day.

[a] Modified ITT population includes subjects who had positive fungal culture and KOH results at baseline. ITT population included all subjects dispensed study drug. Subjects

were dispensed study drug prior to receiving the fungal culture results in Cohorts 1 and 2, while subjects in Cohort 3 were not dispensed study drug until positive baseline fungal culture results had been received.

[b] Treatment response (investigator's clinical evaluation) was Success if "Complete Responder" or "Partial Responder" for Day 180 and "Complete Responder" for Day 360. Investigator's Clinical Evaluation was recorded on CRF at the Day 180 and Day 360 visits for Cohorts 1 and 2. Treatment response was Success if, using the best clinical judgment, the investigator made a clinical assessment of clear and negative fungal culture of the TGT at Day 360 for Cohort 3.

Last observation carried forward was used to impute missing observations.

Source: AN2690-ONYC-201[9] Cohorts 1 and 2 CSR, Tables 11.4.1-1, 11.4.1.2-1, and 11.4.1,2-3; AN2690-ONYC-201 Cohort 3 CSR, Table 11.4.1.2-3.

Open Label Study AN2690-ONYC-203

Study AN2690-ONYC-203 was an open-label, single-country (US), multi-center, dose-escalation study that explored whether lower exposures (tavaborole solution 1% QD for 6 months or tavaborole solution 5% QD for 1 month, then 3× weekly for 5 months) would provide efficacy similar to the higher doses and more frequent dosing regimens already studied in other Phase 2 studies. Inclusion criteria included confirmation of a clinical diagnosis of onychomycosis of at least one great toenail included a positive KOH wet mount and a positive fungal culture. Evaluations were scheduled for Screening and on Baseline (Day 1), Days 14±2, 30±7, 60±7, 90±7, 120±7, 150±7, 180±7, 240 ± 14, 300 ± 14, and 360 ± 14.Samples for KOH wet mounts and fungal cultures were taken from the treatment-targeted great toenail at each visit except Baseline (Day 1). Sixty subjects were analyzed in the study, with 30 in each treatment cohort. Mycological response in the study was defined as eradication (negative dermatophyte culture) or persistence (fungal culture positive for dermatophytes) of the targeted great toenail and was determined at Day 180 and 360. Mycology results are presented in Table 15.

Table 15: Summary of Mycological Response (ITT Population-AN2690-ONYC-203)

	Tavaborole Solution 1%, QD for 180 days	Tavaborole Solution 5%, QD for 1 month, then 3× weekly for 5 months
No. of Subjects	30	30
Mycological Response[a] Day 180		
No. of Evaluable Subjects	30	30
Eradication	27 (90%)	28 (93%)
Persistence	3 (10%)	2 (7%)
Mycological Response[a] Day 360		
No. of Evaluable Subjects[b]	21	23
Eradication	15 (71%)	14 (61%)
Persistence	6 (29%)	9 (39%)

CI, confidence interval; ITT, Intent-to-Treat; QD, one time a day.
[a] Eradication is defined as fungal culture negative for dermatophyte. Persistence is defined as a fungal culture positive for dermatophyte.
[b] Includes subjects who were complete or partial responders at the DAY 180 visit. Last observation carried forward was used to impute missing observations for all subjects.
Source: AN2690-ONYC-203[10] CSR, Tables 11.4.1.2-1

Double-blind Study AN2690-ONYC-200/200A
Study AN2690-ONYC-200 (Mexico)/200A (US) was a randomized, multi-center, double-blind, vehicle-controlled study. This dose-ranging study evaluated the efficacy of tavaborole solutions 2.5%, 5%, and 7.5% and was intended to identify a tavaborole solution concentration for the Phase 3 studies. Fungal cultures and KOH testing of samples obtained from the affected target great toenail were performed at Screening and at end-of-treatment (Day 180), after daily topical dosing for 90 days followed by 3× weekly for 90 days. Mycological response in the study was defined as eradication (negative dermatophyte culture) or persistence (fungal culture positive for dermatophytes) of the targeted great toenail and was determined at Day 180 and 360. All mycologic testing was performed by (b) (4). Results of fungal culture testing are presented in Table 16.

Table 16: Summary of Mycological Response (ITT population-AN2690-ONYC-200/200A)

	Vehicle QD for 90 Days, Then 3× Weekly for 90 Days	Tavaborole 2.5% QD for 90 Days, Then 3× Weekly for 90 Days	Tavaborole 5% QD for 90 Days, Then 3× Weekly for 90 Days	Tavaborole 7.5% QD for 90 Days, Then 3× Weekly for 90 Days
No. of Subjects	63	33	31	60
Mycological Response[a] Day 180				
No. of Evaluable Subjects	63	33	31	60
Eradication	53 (84.1%)	32 (97.0%)	29 (93.5%)	57 (95.0%)
Persistence	10 (15.9%)	1 (3.0%)	2 (6.5%)	3 (5.0%)
P-value vs. Vehicle		0.091	0.325	0.076
		P-value slope = 0.046; P-value linearity = 0.249		
Mycological Response[a] Day 360				
No. of Evaluable Subjects[b]	37	27	24	40
Eradication	27 (73.0%)	19 (70.4%)	17 (70.8%)	31 (77.5%)
Persistence	10 (27.0%)	8 (29.6%)	7 (29.2%)	9 (22.5%)
P-value vs. Vehicle		1.000	1.000	0.792
		P-value slope = 0.642; P-value linearity = 0.843		

ITT, Intent-to-Treat; QD, one time a day.
[a] Eradication is defined as fungal culture negative for dermatophyte. Persistence is defined as fungal culture positive for dermatophyte.
[b] Includes subjects who were complete or partial responders at the Day 180 visit. Last observation carried forward was used to impute missing observations.
P-values vs. vehicle from a Fisher's Exact test and for slope and linearity from Chi-square tests of slope and linearity, as described by Fleiss (1981).
Source: AN2690-ONYC-200/200A[11] CSR, Tables 11.4.1.2-1, 11.4.1.2-2, and 11.4.1.2-4.

5.2. Phase 3 trials.
The two Phase 3 clinical studies (AN2690-ONYC-301 and AN2690-ONYC-302) were identically designed randomized, double-blind, vehicle-controlled, multi-center, parallel-group studies to evaluate the efficacy and safety of tavaborole compared with vehicle alone in treating distal subungual onychomycosis of the toenail in adults. An eligible affected great toenail ("target great toenail" [TGT]) had 20% to 60% involvement of the toenail with at least 3 mm of clear nail (CN) measured from the proximal nail fold to the most proximal visible mycotic border, and distal toenail plate thickness of ≤ 3 mm with both a positive KOH wet mount and positive fungal culture for a dermatophyte from a sample obtained during the screening period. Subungual samples obtained from the TGT of all subject in the Phase 3 trials were sent to a central mycology laboratory ((b) (4) for

KOH wet mount and culture evaluations. Specimen collection and sample shipment instructions were provided in the central mycology laboratory manual, which was provided to study sites that participated in the Phase 3 clinical studies. The mycological confirmation of study eligibility was done as follows:

1. If the initial sample was KOH (+) and culture (+) for a dermatophyte, the subject was eligible for randomization.
2. If the initial sample was KOH (+) and culture (−) for a dermatophyte, or no dermatophyte was isolated, the subject was not eligible for randomization. A repeat sample may have been obtained once from the same TGT and assessed as follows:
   - If the repeat sample was KOH (+) and culture (+) for a dermatophyte, the subject was eligible for randomization as long as the subject was randomized within the maximum period of 10 weeks (i.e., within 70 days) from the Screening visit.
   - If the repeat sample was KOH (+) and culture (−) for a dermatophyte, or no dermatophyte was isolated, the subject was not eligible for randomization.
   - If the repeat sample was KOH (−), the sample was not cultured. The subject was not eligible for randomization or subsequent KOH/culture attempts.
3. If the initial sample was KOH (−) it was not cultured. A repeat sample may have been obtained once from the same TGT and assessed as follows:
   - If the repeat sample was KOH (+) and culture (+) for a dermatophyte, the subject was eligible for randomization as long as the subject was randomized within the maximum period of 10 weeks (i.e., within 70 days) from the Screening visit.
   - If the repeat sample was KOH (+) and culture (−) for a dermatophyte, or no dermatophyte was isolated, the subject was not eligible for randomization.
   - If the repeat sample was KOH (−), the sample was not cultured. The subject was not eligible for randomization or subsequent KOH/culture attempts. Subungual samples for KOH wet mount and fungal culture were obtained at Screening, at Weeks 12, 24, 36, 48 and 52, and, if applicable, 12 weeks following completion of dosing at Week 60 and/or the Early Termination visit, as well as any visit at which the target great toenail was first observed to be completely CN or almost CN.

Results of mycological testing at Week 52 for each of the individual Phase 3 studies are presented in Table 17 and Table 18. Additional pooled data from Phase 3 studies AN2690-ONYC-301 and AN2690-ONYC-302 are provided in Table 19. These data reflect findings in support of the primary efficacy endpoint analyzed at study Week 52 following 48 weeks of dosing.

Table 17: Summary of Mycology-Target Toenail (Intent-to-Treat Subjects)(Study AN2690-ONYC-301)

Culture Negative	Week 24	Week 30	Week 36	Week 48	Week 52
Active (N=399)					
Success	379 (95.0%)	377 (94.5%)	375 (94.0%)	374 (93.7%)	347 (87.0%)
Failure	20 (5.0%)	22 (5.5%)	24 (6.0%)	25 (6.3%)	52 (13.0%)
Vehicle (N=194)					
Success	155 (79.9%)	153 (78.9%)	145 (74.7%)	138 (71.1%)	93 (47.9%)
Failure	39 (20.1%)	41 (21.1%)	49 (25.3%)	56 (28.9%)	101 (52.1%)
KOH Negative					
Active (N=399)					
Success	87 (21.8%)	86 (21.6%)	107 (26.8%)	144 (36.1%)	128 (32.1%)
Failure	312 (78.2%)	313 (78.4%)	292 (73.2%)	255 (63.9%)	271 (67.9%)
Vehicle (N=194)					
Success	9 (4.6%)	10 (5.2%)	13 (6.7%)	15 (7.7%)	17 (8.8%)
Failure	185 (95.4%)	184 (94.8%)	181 (93.3%)	179 (92.3%)	177 (91.2%)
Negative Mycology[a]					
Active (N=399)					
Success	87 (21.8%)	86 (21.6%)	107 (26.8%)	143 (35.8%)	124 (31.1%)
Failure	312 (78.2%)	313 (78.4%)	292 (73.2%)	256 (64.2%)	275 (68.9%)
Vehicle (N=194)					
Success	9 (4.6%)	10 (5.2%)	12 (6.2%)	14 (7.2%)	14 (7.2%)
Failure	185 (95.4%)	184 (94.8%)	182 (93.8%)	180 (92.8%)	180 (92.8%)

[a] Negative mycology is defined as negative KOH and negative fungal culture.
Note: Last observation carried forward was used to impute missing data prior to analysis.
Source: AN2690-ONYC-301[12] CSR Table 14.2.1.1

Table 18: Summary of Mycology-Target Toenail (Intent-to-Treat Subjects)(Study AN2690-ONYC-302)

	Week 24	Week 30	Week 36	Week 48	Week 52
Culture Negative					
Active (N=396)					
Success	371 (93.7%)	371 (93.7%)	366 (92.4%)	367 (92.7%)	338 (85.4%)
Failure	25 (6.3%)	25 (6.3%)	30 (7.6%)	29 (7.3%)	58 (14.6%)
Vehicle (N=205)					
Success	153 (74.6%)	153 (74.6%)	154 (75.1%)	156 (76.1%)	105 (51.2%)
Failure	52 (25.4%)	52 (25.4%)	51 (24.9%)	49 (23.9%)	100 (48.8%)
KOH Negative					
Active (N=396)					
Success	76 (19.2%)	80 (20.2%)	102 (25.8%)	142 (35.9%)	147 (37.1%)
Failure	320 (80.8%)	316 (79.8%)	294 (74.2%)	254 (64.1%)	249 (62.9%)
Vehicle (N=205)					
Success	13 (6.3%)	14 (6.8%)	18 (8.8%)	21 (10.2%)	35 (17.1%)
Failure	192 (93.7%)	191 (93.2%)	187 (91.2%)	184 (89.8%)	170 (82.9%)
Negative Mycology[a]					
Active (N=396)					
Success	75 (18.9%)	79 (19.9%)	101 (25.5%)	141 (35.6%)	142 (35.9%)
Failure	321 (81.1%)	317 (80.1%)	295 (74.5%)	255 (64.4%)	254 (64.1%)
Vehicle (N=205)					
Success	12 (5.9%)	13 (6.3%)	16 (7.8%)	19 (9.3%)	25 (12.2%)
Failure	193 (94.1%)	192 (93.7%)	189 (92.2%)	186 (90.7%)	180 (87.8%)

[a] Negative mycology is defined as negative KOH and negative fungal culture.
Note: Last observation carried forward was used to impute missing data prior to analysis.
Source: AN2690-ONYC-302 CSR Table 14.2.1.1.

[a] Negative mycology is defined as negative KOH and negative fungal culture.
Note: Last observation carried forward was used to impute missing data prior to analysis.
Source: AN2690-ONYC-302[13] CSR Table 14.2.1.1

Table 19: Summary of Mycology-Target Toenail (Intent-to-Treat Subjects)(Study AN2690-ONYC-301 and AN2690-ONYC-302 Pooled)

Culture Negative	Week 12	Week 24	Week 30	Week 36	Week 48	Week 52
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%)
KOH Negative						
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%)
Negative Mycology[a]						
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%)

[a] Negative mycology is defined as negative KOH and negative fungal culture.
Note: Last observation carried forward was used to impute missing data prior to analysis.
Source: ISE Table 14.2.1.1

Results of mycological testing in a subset of subjects followed through Week 60, 12 weeks after the completion of dosing, are provided in Table 20. These data, combined with clinical observation, were used to assess the durability of clinical benefit in a subset of subjects. Subjects participating in the Week 60 (Visit 13) post study follow up (PSFU) were included in a blinded fashion on the basis of visual assessment of clear or almost clear nail at Week 48. Information regarding their mycological status was not known at Week 48 when they were identified for the Week 60 follow-up and thus subjects with positive mycology at Week 48 were eligible for inclusion in the subset of subjects followed to Week 60.

Table 20: Week 60 Mycology Results for Post-Study Follow-Up Subjects in Studies AN2690-ONYC-301 and AN2690-ONYC-302

Mycological Status 12 weeks after completion of treatment	Study AN2690-ONYC-301[a]		Study AN2690-ONYC-302	
	Tavaborole Topical Solution, 5% N=18	Tavaborole Topical Solution, Vehicle N=2	Tavaborole Topical Solution, 5% N=31	Tavaborole Topical Solution, Vehicle N=11
Negative Fungal Culture	13	0	18	4
Negative KOH	13	1	21	5

Subjects 110091 in AN2690-ONYC-301 CSR listing 16.2.6.3.2 was not included in the Post-Study Follow-Up population due to not having a clear or almost clear toenail at Week 48 and therefore not included in the tabulations presented.
Source: AN2690-ONYC-301[12] CSR, Listing 16.2.6.3.2; AN2690-ONYC-302[13] CSR, Listing 16.2.6.3.2.

5.3. In Vitro Susceptibility Testing and Interpretive Criteria
Antimicrobial susceptibility testing was performed as described below. Interpretive criteria were not recommended.

Susceptibility Testing
As discussed with DDDP at a guidance meeting on 13 August and in accordance with the Phase 3 clinical study protocol AN2690-ONYC-301 submitted under the SPA agreement (and with the identically designed clinical study AN2690-ONYC-302), microbiology assessment and susceptibility testing of tavaborole was performed against each viable subungual isolate collected at screening and also against the isolate collected from the last viable mycology-positive visit sample for each enrolled subject treated with tavaborole and with vehicle in the Phase 3 trials. (b) (4) served as the central mycology laboratory responsible for all fungal cultures and prepared direct KOH smears and mycological cultures from all samples collected at sites throughout the studies, storing all obtained dermatophyte isolates at -80 ºC as part of the culture collection. (b) (4) was blinded to treatment assignment throughout all testing and remained blinded until after the last culture was read and data reconciled. MIC results from each study were provided as clinical study reports for Studies AN2690-ONYC-301 and AN2690-ONYC-302.
The MIC endpoint was determined visually for baseline and post-baseline samples as 80% inhibition as compared to the growth control. *Trichophyton rubrum* MYA 4438 and *Trichophyton mentagrophytes* MYA 4439, the QC isolates approved by the CLSI for dermatophyte susceptibility testing, were run in parallel on each day of testing. Two in

vitro comparators, ciclopirox and terbinafine, were also tested against each viable screening isolate
and each last viable mycology-positive isolate. A total of 1543 isolates (769 from Study AN2690-ONYC-301 and 774 from Study AN2690-ONYC-302) from two *Trichophyton* species, *T. rubrum* and *T. mentagrophytes*, were recovered from subjects enrolled in the two Phase 3 clinical studies at screening and last culture-positive visit. Of these, a total of 877 isolates of *T. rubrum* and 33 isolates of *T. mentagrophytes* were isolated from subjects enrolled in the tavaborole treatment group across the two studies with approximately equal distribution across the two studies. *T. rubrum* and *T. mentagrophytes* were the only dermatophytes identified in the trials.

Results of Screening Isolates Susceptibility Testing, Tavaborole
Screening isolates were tested to establish a baseline MIC value for tavaborole. Of 1153 (577 from Study AN2690-ONYC-301, 576 from Study AN2690-ONYC-302) screening isolates obtained and stored for study, 1122 were viable upon subculture from frozen storage and were tested. The MIC data for tavaborole tested against screening isolates collected from subjects randomized to both the tavaborole and vehicle treatment groups in studies AN2690-ONYC-301 and AN2690-ONYC-302, but not yet treated, are presented by dermatophyte species and randomized treatment group in Table 21. The MIC range, MIC_{50}, and MIC_{90} of tavaborole against all isolates collected at screening are listed.

Table 21: Tavaborole MIC data of Viable screening Isolates Collected from Randomized (Untreated) Subjects in Studies AN2690-ONYC-301 and AN2690-ONYC-302, by Treatment Group and Dermatophyte Species

	Tavaborole Topical Solution, 5%				Vehicle			
Species	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)
Trichophyton rubrum								
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
Trichophyton mentagrophytes								
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

MIC, Minimum Inhibitory Concentration; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of isolates tested; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates tested; ND, not determined (fewer than 10 isolates).
Source: AN2690-ONYC-301[12] CSR, Appendix 16.1.13, Mycology and Susceptibility Report, Table 2; AN2690-ONYC-302[13] CSR, Appendix 16.1.13, Mycology and Susceptibility Report, Table 2.

Viable screening isolates from Study AN2690-ONYC-301 were collected from subjects enrolled at sites in 20 states in the U.S. and in Mexico. Subjects were male (81.0%) or female (19.0%), ranging in age from 18 to 88 years of age. The MIC range, MIC_{50}, and MIC_{90} by geographic distribution, sex, and age are shown in Table 22. Similarly, screening isolates from Study AN2690-ONYC-302 were collected from subjects enrolled at sites in 22 states in the U.S. and in Canada. Subjects were male (83.0%) or female (17.0%), ranging in age from 20 to 81 years of age. The MIC range, MIC_{50}, and MIC_{90} by geographic distribution, sex, and age are shown in Table 23.

Table 22: MIC Data of Viable Screening Isolates from Study AN2690-ONYC-301 by Geographic Distribution, Sex, and Age

	No. of Isolates	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Geographic distribution	**562**			
Eastern US (Including MD, NY, RI)	82	1-8	2	4
Midwest (Including IN, KS, MN, NE, OH)	127	1-8	2	4
Southern US (Including AR, FL, NC, TN, TX, VA)	116	0.5-8	2	4
Western US (Including AZ, CA, CO, ID, OR, WA)	151	1-8	2	4
Mexico	86	0.5-8	2	4
Sex	**562**			
Male	455	0.5-8	2	4
Female	107	1-8	2	4
Age	**562**			
≤ 65	474	0.5-8	2	4
> 65	88	0.5-8	2	4

MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of isolates tested; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates tested.
Source: AN2690-ONYC-301[12] CSR, Appendix 16.1.13, Mycology and Susceptibility Report, Table 3.

Table 23: MIC Data of Viable screening Isolates from Study AN2690-ONYC-302 by Geographic Distribution, Sex, and Age

	No. of Isolates	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Geographic distribution	**560**			
Eastern US (Including NJ, NY, PA)	24	1-4	2	4
Midwest (Including IL, IN, MI, MO, OH)	56	1-8	4	4
Southern US (Including AL, FL, GA, NC, SC, TN, TX, VA)	154	1-8	4	4
Western US (Including AZ, CA, ID, NM, OR, UT)	213	0.5-8	4	4
Canada	113	1-8	4	4
Sex	**560**			
Male	464	0.5-8	4	4
Female	96	1-8	2	4
Age	**560**			
≤ 65	456	0.5-8	4	4
> 65	104	1-8	4	4

MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of isolates tested; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates tested.
Source: AN2690-ONYC-302[13] CSR, Appendix 16.1.13, Mycology and Susceptibility Report, Table3.

Results of Paired Samples from Subjects on Study Drug

A total of 387 dermatophytes (192 from Study AN2690-ONYC-301 and 195 from Study AN2690-ONYC-302) were isolated from last culture-positive samples, obtained and stored for study, of which 372 were viable upon subculture and were tested. Table 24 and Table 25 show the tavaborole MIC distribution by study period in which the last culture-positive samples were obtained for *T. rubrum and T. mentagrophytes* strains, respectively. The much larger numbers of Week 52 samples were due to the fact that this was the last visit included in susceptibility testing, and included all subjects who remained positive at the end of study (last culture-positive sample = end of study). Of the 240 total viable strains isolated from Week 52 samples across both Phase 3 studies, a total of 76 isolates were obtained from subjects in the tavaborole treatment group, and none of these showed significantly different tavaborole MIC values when compared with their respective screening MIC values. The lack of elevated MIC values shows that the occurrence of a positive culture was not due to a development of resistance to tavaborole following repeated exposure over the course of the trial.

Table 24: Summary of In Vitro Susceptibility Data for Isolates of *Trichophyton rubrum* Against Tavaborole for all Subjects in Both Treatment Groups for Study AN2690-ONYC-301[12] and Study AN2690-ONYC-302[13]

Week	Country	No. of Isolates	No. of Isolates Inhibited at Tavaborole Concentration (µg/mL)				
			0.5	1	2	4	8
Screening	US[a]	463/428	1/1	105/49	170/142	173/216	14/20
	Mexico	79	1	14	36	24	4
	Canada	106	-	8	41	48	9
	All[b]	**1076**	**3**	**176**	**389**	**461**	**47**
Baseline	US[a]	5/3	-	2/-	-/3	2/-	1/-
	Mexico	7	-	3	-	4	-
	Canada	-	-	-	-	-	-
	All[b]	**15**	**-**	**5**	**3**	**6**	**1**
Week 2	US[a]	-/2	-	-/1	-/1	-	-
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	**2**	**-**	**1**	**1**	**-**	**-**
Week 6	US[a]	-	-	-	-	-	-
	Mexico	-	-	-	-	-	-
	Canada	1	-	-	1	-	-
	All[b]	**1**	**-**	**-**	**1**	**-**	**-**
Week 12	US[a]	7/11	-	-	2/6	5/5	-
	Mexico	-	-	-	-	-	-
	Canada	2	-	1	-	1	-
	All[b]	**20**	**-**	**1**	**8**	**11**	**-**
Week 24	US[a]	8/9	-	1/-	4/5	3/4	-
	Mexico	-	-	-	-	-	-
	Canada	1	-	-	-	1	-
	All[b]	**18**	**-**	**1**	**9**	**8**	**-**
Week 30	US[a]	1/2	-	-	1/1	-/1	-
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	**3**	**-**	**-**	**2**	**1**	**-**
Week 36	US[a]	11/10	-	1/-	3/3	7/7	-
	Mexico	2	-	-	2	-	-
	Canada	-	-	-	-	-	-
	All[b]	**23**	**-**	**1**	**8**	**14**	**-**

Source: Studies AN2690-ONYC-301, AN2690-ONYC-302

Table 24: Summary of In Vitro Susceptibility Data for Isolates of *Trichophyton rubrum* Against Tavaborole for all Subjects in Both Treatment Groups for Study AN2690-ONYC-301 and Study AN2690-ONYC-302 (Continued)

Week	Country	No. of Isolates	No. of Isolates Inhibited at Tavaborole Concentration (µg/mL)				
			0.5	1	2	4	8
Week 42	US[a]	-/2	-	-	-/1	-/1	-
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	**2**	**-**	**-**	**1**	**1**	**-**
Week 48	US[a]	10/14	-	1/-	4/7	5/7	-
	Mexico	3	-	-	1	2	-
	Canada	-	-	-	-	-	-
	All[b]	**27**	**-**	**1**	**12**	**14**	**-**
Week 52	US[a]	99/101	1/-	25/3	35/35	37/63	1/-
	Mexico	20	-	7	8	5	-
	Canada	17	-	-	3	14	-
	All[b]	**237**	**1**	**35**	**81**	**119**	**1**
Early Termination	US[a]	6/4	-	2/1	3/2	1/1	-
	Mexico	-	-	-	-	-	-
	Canada	1	-	-	1	-	-
	All[b]	**11**	**-**	**3**	**6**	**2**	**-**

[a] Data for Study AN2690-ONYC-301[12]/Study AN2690-ONYC-302[13]. A single dash in cell represents a zero value in both studies.
[b] Summed value of both studies.
Source: AN2690-ONYC-301[12] CSR, Appendix 16.1.13, Mycology and Susceptibility Report, Table 4; AN2690-ONYC-302[13] CSR, Appendix 16.1.13, Mycology and Susceptibility Report, Table 4.

Table 25: Summary of In Vitro Susceptibility Data for Viable Isolates of *Trichophyton mentagraphytes* Against Tavaborole for all Subjects in Both Treatment Groups for Study AN2690-ONYC-301 and Study AN2690-ONYC-302

Week	Country	No. of Isolates	No. of Isolates Inhibited at Tavaborole Concentration (µg/mL)				
			0.5	1	2	4	8
Screening	US[a]	13/19	-	1/-	6/3	5/14	1/2
	Mexico	7	-	-	6	1	-
	Canada	7	-	-	-	7	-
	All[b]	**46**	-	**1**	**15**	**27**	**3**
Baseline	US[a]	1/-	-	-	-	1/-	-
	Mexico	1	-	1	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	**2**	-	**1**	-	**1**	-
Week 2	US[a]	-	-	-	-	-	-
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	-	-	-	-	-	-
Week 6	US[a]	-	-	-	-	-	-
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	-	-	-	-	-	-
Week 12	US[a]	-/1	-	-	-	-/1	-
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	**1**	-	-	-	**1**	-
Week 24	US[a]	-/1	-	-	-	-/1	-
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	**1**	-	-	-	**1**	-
Week 30	US[a]	-	-	-	-	-	-
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	-	-	-	-	-	-
Week 36	US[a]	-/1	-	-	-	-/1	-
	Mexico	-	-	-	-	-	-
	Canada	1	-	-	-	1	
	All[b]	**2**	-	-	-	**2**	

Source: Studies AN2690-ONYC-301[12], AN2690-ONYC-302[13]

Table 25: Summary of In Vitro Susceptibility Data for Viable Isolates of *Trichophyton mentagraphytes* Against Tavaborole for all Subjects in Both Treatment Groups for Study AN2690-ONYC-301 and Study AN2690-ONYC-302 (Continued)

Week	Country	No. of Isolates	No. of Isolates Inhibited at Tavaborole Concentration (µg/mL)				
			0.5	1	2	4	8
Week 42	US[a]	-/2	-	-	-/1	-/1	-
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	**2**	-	-	**1**	**1**	-
Week 48	US[a]	10/14	-	1/-	4/7	5/7	-
	Mexico	3	-	-	1	2	-
	Canada	-	-	-	-	-	-
	All[b]	**27**	-	**1**	**12**	**14**	-
Week 52	US[a]	99/101	1/-	25/3	35/35	37/63	1/-
	Mexico	20	-	7	8	5	-
	Canada	17	-	-	3	14	-
	All[b]	**237**	**1**	**35**	**81**	**119**	**1**
Early Termination	US[a]	6/4	-	2/1	3/2	1/1	-
	Mexico	-	-	-	-	-	-
	Canada	1	-	-	1	-	-
	All[b]	**11**	-	**3**	**6**	**2**	-

[a] Data provided for Study AN2690-ONYC-301/Study AN2690-ONYC-302. A single cell represents a zero value in both studies.
[b] Summed value of both studies.
Source: AN2690-ONYC-301[12] CSR, Appendix 16.1.13, Mycology and Susceptibility Report, Table 4; AN2690-ONYC-302[13] CSR, Appendix 16.1.13, Mycology and Susceptibility Report, Table 4.

Table 25: Summary of In Vitro Susceptibility Data for Viable Isolates of *Trichophyton mentagraphytes* Against Tavaborole for all Subjects in Both Treatment Groups for Study AN2690-ONYC-301 and Study AN2690-ONYC-302 (Continued)

Week	Country	No. of Isolates	No. of Isolates Inhibited at Tavaborole Concentration (µg/mL)				
			0.5	1	2	4	8
Week 42	US[a]	-	-	-	-	-	-
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	-	-	-	-	-	-
Week 48	US[a]	1/-	-	-	-	1/-	
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	**1**	-	-	-	**1**	-
Week 52	US[a]	3/1	-	-	1/-	2/1	-
	Mexico	-	-	-	-	-	-
	Canada	2	-	-	-	2	-
	All[b]	**6**	-	-	**1**	**5**	-
Early Termination	US[a]	-	-	-	-	-	-
	Mexico	-	-	-	-	-	-
	Canada	-	-	-	-	-	-
	All[b]	-	-	-	-	-	-

[a] Data provided for Study AN2690-ONYC-301/Study AN2690-ONYC-302. A single dash in a cell represents a zero value in both studies.
[b] Summed value of both studies.
Source: AN2690-ONYC-301[12] CSR, Appendix 16.1.13, Mycology and susceptibility Report, Table 5; AN2690-ONYC-302[13] CSR, Appendix 16.1.13, Mycology and Susceptibility Report, Table 5.

Results of Last Culture-Positive Samples Susceptibility Testing, Tavaborole
Table 26 shows the overall MIC range, MIC_{50}, and MIC_{90} values for tavaborole tested against the viable last culture-positive samples collected from subjects enrolled in the Phase 3 studies.

Table 26: MIC Data of Viable Isolates Collected at Last Culture-Positive Visits from Study AN2690-ONYC-301 and Study AN2690-ONYC-302 by Treatment Group and Dermatophyte Species

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)
Trichophyton rubrum								
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
Trichophyton mentagrophytes								
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

MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of isolates tested; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates tested; ND, Not Determined (fewer than 10 isolates).
No range is provided because all MICs were identical.
Source: AN2690-ONYC-301[12] CSR, Appendix 16.1.13, Mycology and Susceptibility Report, Table 6; AN2690-ONYC-302[13] CSR, Appendix 16.1.13, Mycology and Susceptibility Report, Table 6.

Results of Quality Control Data for Tavaborole and In Vitro Comparators
CLSI QC strains *T. rubrum* MYA 4438 and *T. mentagrophytes* MYA 4439 were tested following CLSI methodology each day that susceptibility testing was performed. Table 27 shows there were no instances of out-of-range MIC values for either reference strain, thus validating the methods used.

Table 27: MIC Data (in mcg/mL) of Tavaborole and in Vitro Comparators Against Quality Control Strains from study AN2690-ONYC-301 and Study AN2690-ONYC-302

Quality Control strain	Tavaborole (µg/mL)			Ciclopirox (µg/mL)			Terbinafine (µg/mL)		
	MIC Range	MIC_{50}	MIC_{90}	MIC Range	MIC_{50}	MIC_{90}	MIC Range	MIC_{50}	MIC_{90}
T. rubrum MYA 4438	1-8	4	4	0.25-1[a]	0.25	0.5	>0.5[b]	>0.5[b]	>0.5[b]
T. mentagrophytes MYA 4439	2-8	4	8	0.25-2[a]	0.25	0.5	0.004-0.008	0.004	0.008

MIC, minimum inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of isolates tested; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates tested.
[a] Internal range of 0.25-2.0 mcg/mL established by the (b) (4).
[b] *T. rubrum* MYA 4438 was selected as a CLSI candidate strain specifically because it is resistant to terbinafine.
Source: AN2690-ONYC-302[13] CSR Appendix 16.1.13, Mycology and Susceptibility Report, Table 13.

Reviewer's Comments:
AN2690 (Tavaborole) demonstrated clinical efficacy in three Phase 2 clinical trials.
In the three Phase 2 clinical trials where AN2690 was administered for 180 and 360 days, topical administration of AN2690 Solution at 1%, 2.5%, 5%, and 7.5% showed a therapeutic effect. In the studies with a treatment duration of 180 days, comparable efficacy was seen at Day 180 with solution concentrations of 2.5%, 5%, and 7.5%, whereas efficacy with a 1% solution was suboptimal. Of the higher concentrations (2.5%, 5%, and 7.5%), AN2690 5% had the highest efficacy trend ($p = 0.09$) (defined as clear nail, negative fungal culture, and negative KOH) at the Day 360 follow-up.

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.

6. LABELING

The applicant has provided the proposed labeling (only the microbiology subsection of the labeling is discussed below).

6.1. Applicant's Proposed Labeling

The labeling in the submission dated x is as follows:

12.4 Microbiology

Mechanism of Action

The mechanism of action of tavaborole is inhibition of fungal protein synthesis. Tavaborole inhibits protein synthesis by inhibition of an aminoacyl-transfer ribonucleic acid (tRNA) synthetase (AARS) (b) (4)

.

(b) (4)

(b) (4)

Trichophyton mentagrophytes and *T. rubrum* strains from isolates collected in the (b) (4) clinical (b) (4) have not demonstrated resistance following repeated exposure to tavaborole.

6.2. FDA's Version Of The Labeling

12.4 Microbiology

Mechanism of Action

The mechanism of action of tavaborole is inhibition of fungal protein synthesis. Tavaborole inhibits protein synthesis by inhibition of an aminoacyl-transfer ribonucleic acid (tRNA) synthetase (AARS) (b) (4)

Activity in vitro and in clinical infections

Tavaborole has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections (b) (4) INDICATIONS AND USAGE (b) (4).

Trichophyton mentagrophytes

Trichophyton rubrum

(b) (4)

(b) (4)

Mechanism of Resistance

(b) (4)

(b) (4)

Reviewer's Comments:
The following changes to the proposed label (Subsection 12.4 Microbiology) are recommended:

- The detail in the Mechanism of Action section should be reduced.
- Replace sections (b) (4) with section (b) (4) for consistency with recently approved antifungal labels in DDDP. Also, a (b) (4) of pathogens (organisms not evaluated in clinical studies) is not recommended .
- Information pertaining to the use of (b) (4) is not necessary and should be deleted.
- Replace (b) (4) section with section " Mechanism of Resistance".
- Based on the available information, no susceptibility testing interpretive criteria for tavaborole are recommended at this time

7. RECOMMENDATIONS
The application is approvable pending an accepted version of the labeling.

8. REFERENCES

1. 002-NCL PP-001-01 Antibacterial spectrum of activity, Lab: (b) (4) Section 4.1.2

2. 002-NCL PP-002-01 Antifungal spectrum of activity, Lab: (b) (4) Section 4.1.1.1

3. 002-NCL PP-003-02 Determination of MIC and MFC (Initial Study, 2005), Lab: (b) (4) Section 4.2.1

4. 002-NCL PP-018-01 The antifungal activity of tavaborole against the dermatophytes *T. rubrum* and *T. mentagrophytes* assessed by (b) (4) through determination of MIC and MFC of tavaborole against dermatophytes isolated from subungual samples obtained from subjects participating in Phase 2 tavaborole clinical studies.

5. 002-NCL PP-017-01 Determination of MIC (Recent Study, 2013), Lab: (b) (4) Section 4.2.3
6. 002-NCL PP-016-02
7. 002-NCL PP-015-01 Interlaboratory study for determination of quality control
8. isolates, Lab: (b) (4), Section 3.1
9.

10. 002-NCL PP-012-01 Evaluation of the In Vivo Efficacy of AN2690 Against Systemic *Candida albicans* Infection in Mice

9. AN2690-ONYC-201 Protocol No. AN2690-ONYC-201. An open-label, rising multiple-dose, multi-center study to evaluate the safety and efficacy of topically applied AN2690 5.0% and 7.5% solution for the treatment of adult subjects with onychomycosis of the great toenail. Anacor Pharmaceuticals, Inc. Study Report No. 002-CLN CL-002-01 and 002-CLN CL-005-01

10. AN2690-ONYC-203: Protocol No. AN2690-ONYC-203: An open-label, multi-center study to evaluate the safety and efficacy of topically applied AN2690 1.0% and 5.0% solutions for the treatment of adult subjects with onychomycosis of the great toenail. Anacor Pharmaceuticals, Inc. Study Report No. 002-CLN CL-003-02.

11. AN2690-ONYC-200/200A: Protocol No. AN2690-ONYC-200/200A: 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 subjects with onychomycosis of the great toenail. Anacor Pharmaceuticals, Inc. Study Report No. 002-CLN CL-001-03.

12. AN2690-ONYC-301: A Randomized, Double-Blind, Vehicle-Controlled, Multi-Center Study to Evaluate the Efficacy and Safety of AN2690 Topical Solution, 5%, vs. Solution Vehicle in the Treatment of Onychomycosis of the Toenail in Adults

13. AN2690-ONYC-302: A Randomized, Double-Blind, Vehicle-Controlled, Multi-Center Study to Evaluate the Efficacy and Safety of AN2690 Topical Solution, 5%, vs. Solution Vehicle in the Treatment of Onychomycosis of the Toenail in Adults

Kerian K. Grande Roche, Ph.D.
Clinical Microbiology Reviewer, DAIP

Kerry Snow, MS
Clinical Microbiology Team Leader, DAIP
1 March 2014

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

/s/

KERIAN K GRANDE ROCHE
03/06/2014

KERRY SNOW
03/06/2014

DIVISION OF ANTI-INFECTIVE PRODUCTS
CLINICAL MICROBIOLOGY REVIEW
Date review completed: 12-10-13

Date Company Submitted Document: 7-26-13
Received for Review: 8-7-13
Date Assigned: 8-7-13

CDER Date Received: 7-29-13
Reviewer: Kerian Grande Roche

NAME AND ADDRESS OF SPONSOR
Anacor Pharmaceuticals, Inc.
1 020 East Meadow Circle
Palo Alto, CA 94303

CONTACT PERSON
Carmen R. Rodriguez, M.Sc.
VP, Regulatory Affairs and Quality

DRUG PRODUCT NAME
Proprietary Name: Tavaborole Topical Solution, 5%
Established Name/Code Name(s): AN2690
Chemical Name: 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole
Chemical Formulae: $C_7H_6BFO_2$

DRUG CATEGORY:
Antifungal

PROPOSED INDICATION(S)
Treatment of onychomycosis (b) (4)

PROPOSED DOSAGE FORM, DOSAGE, ROUTE OF ADMINISTRATION, STRENGTH AND DURATION OF TREATMENT

Dosage Form: Solution
Route of Administration: Topical
Dosage: Once daily
Strength: 5%
Duration of Treatment: 48 weeks

DISPENSED:
Rx

RELATED DOCUMENTS:
N/A

REMARKS

This is a New Drug Application for Tavaborole Topical Solution, 5%, which is being submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and under the provisions of Title 21CFR§314.50. This application provides for the use of Tavaborole Topical Solution, 5% for the treatment of patients with onychomycosis (b) (4)

CONCLUSIONS

The clinical microbiology review is on-going. No significant review issues have been identified, and we expect the review to be complete by the designated target date.

COMMENTS FOR SPONSOR

None.

Introduction

AN2690, is a novel oxaborole that demonstrates broad-spectrum antifungal activity against dermatophytes, yeasts, molds, and other filamentous fungi. AN2690 penetrates through the nail plate and achieves concentrations greater than the minimum fungicidal concentrations (MFCs) determined in vitro. The degree of penetration through the nail plate was superior to ciclopirox (the only topical treatment currently approved in the United States for distal subungual onychomycosis).

Tavaborole Topical Solution, 5% is an antifungal agent. The active ingredient is tavaborole, a (b) (4) boronic acid complex. Tavaborole exerts its pharmacologic activity through inhibition of fungal protein synthesis by inhibiting cytoplasmic leucyl-tRNA synthetase (LeuRS), an aminoacyl-tRNA synthetase, via an oxaborole-tRNA trapping mechanism. Tavaborole was specifically designed to improve nail unit bioavailability when applied topically and to retain its pharmacologic activity in the presence of keratin in the nail plate.

The safety and efficacy of Tavaborole Topical Solution, 5% was studied in two double-blind vehicle-controlled clinical Phase 3 studies in subjects with onychomycosis due to dermatophytes. Results from these studies confirmed the antifungal efficacy and established clinical safety of Tavaborole Topical Solution, 5% when applied topically to the affected nail once daily for 48 weeks.

Midcycle Summary

Tavaborole is a (b) (4) boronic acid (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) antifungal agent developed for topical treatment of onychomycosis (b) (4)
The microbiology program for tavaborole was designed with the following in mind: the September 2009 Draft Guidance for Industry, *Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation*, and in the advice received from the Division of Dermatology and Dental Products throughout the development program.

Microbiologic studies were completed to determine mechanism of action, mechanism of resistance, spectrum of antimicrobial activity of tavaborole, and comparison to commercially available antifungals approved for the treatment of onychomycosis. The submission summary focuses on microbiology studies that examined the spectra of activity of tavaborole and characterized the mycology and susceptibility of strains of *Trichophyton rubrum* and *Trichophyton mentagrophytes* obtained from clinical isolates of subjects treated with Tavaborole Topical Solution, 5% for 48 weeks.
An overview of the microbiology and mycology studies conducted for tavaborole is provided in Table 1 (taken from this submission) below:

Table 1: Microbiology Studies Conducted to Support the Tavaborole Topical Solution, 5% Clinical Development Program

Study Type/ Summary Section/ Study Report Number	Species Tested	Test Material	Summary of Results
Identification of Quality Control Strains			
Interlaboratory study for determination of quality control isolates Lab (b) (4) Section 3.1 002-NCL PP-015-01	*Trichophyton rubrum* MYA 4438, *T. rubrum* ATCC 28188, *T. rubrum* ATCC 18759, *Trichophyton mentagrophytes* MYA 4439, *T. mentagrophytes* ATCC 24953, *T. mentagrophytes* ATCC 28187	Tavaborole Positive controls: terbinafine, posaconazole	Tavaborole demonstrated consistent MIC values across the eight participant laboratories, with an MIC range of 1.0–4.0 µg/mL in 89.9% of replicate tests for all strains tested. For *T. mentagrophytes* MYA 4439, the MIC range for tavaborole was 1.0–8.0 µg/mL in 95.2% of replicate tests, while for *T. rubrum* MYA 4438 the MIC range was 0.5–4.0 µg/mL in 95.2% of replicate tests. These results satisfied QC parameters specified by the CLSI M23-A2 document. The MIC values for QC isolates were within range for both control drugs (99.1% and 97.4% for posaconazole and terbinafine, respectively), and there were no differences between the three lots of RPMI media.
MIC Determination: In Vitro Studies			
Antifungal spectrum of activity Lab (b) (4) Section 4.1.1.1 002-NCL PP-002-01	*Aspergillus fumigatus, Candida albicans* (fluconazole sensitive & resistant strains), *Candida glabrata, Candida krusei, Cryptococcus neoformans, Candida parapsilosis, Candida tropicalis, Epidermophyton floccosum, Fusarium solani, Malassezia furfur, Malassezia pachydermatis, Malassezia sympodialis, Microsporum audouinii, Microsporum canis, Microsporum gypseum, Trichophyton mentagrophytes, Trichophyton rubrum* (±5% keratin powder), *Trichophyton tonsurans*	Tavaborole Positive controls: ciclopirox, terbinafine, fluconazole, itraconazole	Tavaborole had MIC values of 0.25–2 µg/mL against all fungi tested. Addition of 5% (w/v) keratin powder to the media did not affect the MIC against *T. rubrum*. Tavaborole had fungicidal activity against *T. rubrum* and *T. mentagrophytes* with MFC values of 8 and 16 µg/mL, respectively.

Table 1: Microbiology Studies Conducted to Support the Tavaborole Topical Solution, 5% Clinical Development Program

Study Type/ Summary Section/ Study Report Number	Species Tested	Test Material	Results
MIC Testing: checkerboard study Lab: (b) (4) Section 4.1.1.2 002-NCL PP-009-01	*Trichophyton rubrum* F296	Tavaborole Positive control: terbinafine	• Tavaborole and terbinafine do not inhibit the efficacy of each other and may work in synergy when both drugs are just below their independent MIC threshold. • 90% inhibition: tavaborole ≥1 µg/mL or terbinafine ≥4 µg/mL. • 90% inhibition: tavaborole ≥0.5 µg/mL and terbinafine ≥1 µg/mL.
Antifungal Activity of Topical Drug Vehicle Lab: (b) (4) Section 4.1.1.3 002-NCL PP-010-01	*Trichophyton rubrum* F296	Ethanol/propylene glycol vehicle	Ethanol/propylene glycol (80/20, v/v) completely inhibited *T. rubrum* F296 fungal growth at concentrations ≥12.5% in test medium. Growth inhibition of approximately 20% was attained at a concentration of 6.25% and concentrations below 6.25% did not possess the ability to inhibit the strain tested.
Antibacterial spectrum of activity Lab: (b) (4). Section 4.1.2 002-NCL PP-001-01	*Staphylococcus aureus* (methicillin sensitive & resistant strains), *Staphylococcus epidermidis, Streptococcus pyogenes, Propionibacterium acnes, Pseudomonas aeruginosa, Enterococcus faecalis, Enterococcus faecium, Streptococcus mutans, Escherichia coli, Haemophilus actinomycetemcomitans, Porphyromonas gingivalis*	Tavaborole Positive control: ciprofloxacin	• Tavaborole had only limited antibacterial activity. • MIC values against typical skin, oral, and intestinal bacteria ranged from 4 to >64 µg/mL.

Table 1: Microbiology Studies Conducted to Support the Tavaborole Topical Solution, 5% Clinical Development Program (Cont'd)

Study Type/ Summary Section/ Study Report Number	Species Tested	Test Material	Results
MIC Determination: Clinical Samples			
Determination of MIC and MFC (Initial Study, 2005) Lab: (b) (4) Section 4.2.1 002-NCL PP-003-02	100 clinical isolates each of *Trichophyton rubrum* and *Trichophyton mentagrophytes*	Tavaborole Positive control: ciclopirox	• The MIC values ranged from 1.0-8.0 µg/mL and 4.0-8.0 µg/mL for *T. rubrum* and *T. mentagrophytes*, respectively. • MIC_{50} and MIC_{90} were 4.0 and 8.0 µg/mL, respectively, against both dermatophyte species. • Tavaborole had an MFC_{90} value of 64 µg/mL and 128 µg/mL against 80 *T. rubrum* isolates and 76 *T. mentagrophytes* isolates, respectively.
Determination of MIC (Recent Study, 2013) Lab: (b) (4) Section 4.2.3 002-NCL PP-017-01	100 recent clinical isolates each of *Trichophyton rubrum* and *Trichophyton mentagrophytes* collected from subjects participating in the two Phase 3 clinical trials and from the culture collection at the Center for Medical Mycology	Tavaborole Positive controls: ciclopirox, terbinafine	• Tavaborole exhibited antifungal activity against the dermatophyte strains tested, with a very tight MIC range of 1-8 µg/mL against both species. The tavaborole MIC_{50} and MIC_{90} were 4 µg/mL against both species. These MIC values are effectively within the acceptable ranges for the QC strains *T. rubrum* MYA 4438 and *T. mentagrophytes* MYA 4439 of 0.5-4 µg/mL and 1-8 µg/mL, respectively. • The MIC values for tavaborole, ciclopirox and terbinafine with the QC dermatophytes, *T. rubrum* MYA 4438 and *T. mentagrophytes* MYA 4439 were within acceptable values.

Table 1: Microbiology Studies Conducted to Support the Tavaborole Topical Solution, 5% Clinical Development Program

Study Type/ Summary Section/ Study Report Number	Species Tested	Test Material	Results
Clinical Samples: Mycology Testing (fungal culture, KOH)			
Phase 2 Clinical Study Mycology Lab (b) (4) Section 4.3.1.1 AN2690-ONYC-202	Fungal culture and KOH testing of subungual samples for presence of *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Mycologic testing performed at Screening and on study Days 14, 28, 42, 180 and 360 following 28 days of once daily dosing.	Test materials used in the clinical study: Tavaborole solution 7.5%	• 80% (24 cultures) of the fungal culture results were positive at Screening. 97% (29 results) of the KOH results were positive at Screening. • Of the great toenails with a positive fungal culture at baseline, 92% (22/24 cultures) were negative at Day 14 and 100% (24/24 cultures) were negative at Day 28; 65% (13/20 cultures) were still negative at Day 180, and 67% (4/6 cultures) were still negative at Day 360. • Of the great toenails with a positive KOH result at baseline, 0% (0/29 results) were negative at Day 14 and 4% (4/29 results) were negative at Day 28; 35% (8/23 cultures) were negative at Day 180, and 38% (3/8 results) were negative at Day 360.
Phase 2 Clinical Study Mycology Lab (b) (4) Section 4.3.1.2 AN2690-ONYC-205	Fungal culture and KOH testing of subungual samples for presence of *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Mycologic testing performed at Screening and on study Days 14, 28 and 42 following 28 days of once daily dosing.	Test materials used in the clinical study: Tavaborole solution 7.5%	• 63% (25 cultures) of the fungal culture results were positive at Screening; 88% (35 results) of the KOH results were positive at Screening. • Of the great toenails with a positive fungal culture at baseline, 96% (24/25 cultures) were negative at Day 14 and Day 42. • Of the great toenails with a positive KOH result at baseline, 26% (9/35 results) were negative at Day 14 and 40% (14/35 results) were negative at Day 42.

Table 1: Microbiology Studies Conducted to Support the Tavaborole Topical Solution, 5% Clinical Development Program (Cont'd)

Study Type/ Summary Section/ Study Report Number	Species Tested	Test Material	Results
Phase 2 Clinical Study Mycology Lab (b) (4) Section 4.3.2.1 AN2690-ONYC-201, Cohorts 1 and 2 AN2690-ONYC-201, Cohort 3	Fungal culture and KOH testing of subungual samples for presence of *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Mycologic testing was performed at Screening and on Days 180 and 360.	Test materials used in the clinical study: Tavaborole solution 5% for 6 months (Cohort 1) Tavaborole solution 7.5% for 6 months (Cohort 2) Tavaborole solution 5% for 360 days (Cohort 3)	• 100% of subjects had a fungal culture and KOH positive result at Screening. • 71% (12/17) of subjects in Cohort 1 had a successful mycologic response at Day 180. Of the 13 subjects in this Cohort evaluable at Day 360, 69% maintained their mycologic success after completion of treatment. • 100% (18/18) of subjects in Cohort 2 had a successful mycologic response at Day 180. Of the 16 subjects in this Cohort evaluable at Day 360, 69% maintained their mycologic success 6 months after completion of treatment. • 100% (29/29) of subjects in Cohort 3 had a successful mycologic response at Day 180, half way through their treatment. 97% of the subjects in this Cohort had a successful mycologist response at Day 360 following completion of dosing.

Table 1: Microbiology Studies Conducted to Support the Tavaborole Topical Solution, 5% Clinical Development Program (Cont'd)

Study Type/ Summary Section/ Study Report Number	Species Tested	Test Material	Results
Phase 2 Clinical Study **Mycology** Lab: (b) (4) Section 4.3.2.2 AN2690-ONYC-203	Fungal culture and KOH testing of subungual samples for presence of *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Evaluations were scheduled for Screening and on Baseline (Day 1), Days 14±2, 30±7, 60±7, 90±7, 120±7, 150±7, 180±7, 240 ± 14, 300 ± 14, and 360 ± 14.Samples for KOH wet mounts and fungal cultures were taken from the treatment-targeted great toenail at each visit except Baseline (Day 1), and mycologic response was calculated at Days 180 and 360.	Test materials used in the clinical study: Tavaborole solution 1%, QD for 180 days Tavaborole solution 5%, QD for 1 month, then 3× weekly for 5 months	• 100% of subjects in the tavaborole solution 1% Cohort had a negative fungal culture and KOH positive result at Screening. • 100% of subjects in the tavaborole solution 5% Cohort had a KOH positive result at Screening; 97% (29) of the subjects in the tavaborole solution 5% Cohort had a positive fungal culture at Screening with 3% (1) having a negative fungal culture at Screening. • Mycological response for subjects in the tavaborole solution 1% cohort revealed most subjects to have eradication (negative fungal culture) at Day 180 (27/30 subjects), with the majority of subjects still maintaining eradication at Day 360 (15/21 subjects), 180 days after treatment ended. • Mycological response for subjects in the tavaborole solution 5% cohort revealed most subjects to have eradication (negative fungal culture) at Day 180 (28/30 subjects), with the majority of subjects still maintaining eradication at Day 360 (14/23 subjects), 180 days after treatment ended.

Table 1: Microbiology Studies Conducted to Support the Tavaborole Topical Solution, 5% Clinical Development Program (Cont'd)

Study Type/ Summary Section/ Study Report Number	Species Tested	Test Material	Results
Phase 2 Clinical Study **Mycology** Lab: (b) (4) (b) (4) Section 4.3.2.3 AN2690-ONYC-200/200A	Fungal culture and KOH testing of subungual samples for presence of *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Fungal cultures and KOH testing of samples obtained from the affected target great toenail were performed at Screening and at end-of-treatment (Day 180).	Test materials used in the clinical study: Tavaborole solution 2.5% Tavaborole solution 5% Tavaborole solution 7.5%. Daily topical dosing for 90 days followed by 3× weekly for 90 days.	• At Screening, 5% (186) of the subjects had a positive fungal culture result; 0.5% (1) had a negative fungal culture result reported as such because the organism originally isolated and thought to be a dermatophyte could not be subcultured to allow for speciation. • At Screening, 79.7% (149) of the subjects had a positive KOH result; 20.3% (78) had a negative KOH result based on the results of the central mycology laboratory. • Over 93% of subjects treated with tavaborole, across all active treatment groups, achieved negative mycology at Day 180 compared with 84% of those treated with Vehicle. • The rate of maintenance of negative mycology was similar between active and vehicle treatment groups at Day 360, 6 months after completion of dosing with 70-77% in the active treatment groups compared with a vehicle rate of 73%.

Table 1: Microbiology Studies Conducted to Support the Tavaborole Topical Solution, 5% Clinical Development Program (Cont'd)

Study Type/ Summary Section/ Study Report Number	Species Tested	Test Material	Results
Phase 3 Clinical Study Mycology Lab: (b) (4) Section 4.3.3 AN2690-ONYC-301	Fungal culture and KOH testing of subungual samples for presence of *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Mycologic testing performed at screening and at Week 52 following 48 weeks of once daily dosing.	Test materials used in the clinical study: Tavaborole Topical Solution, 5% Tavaborole Topical Solution, Vehicle	• All subjects enrolled in the clinical study showed positive fungal culture and positive KOH for *T. rubrum* or *T. mentagrophytes* at screening. • Tavaborole outperformed vehicle in the secondary efficacy analyses, with statistically significantly higher rates of negative mycology (31.1% [124/399] versus 7.2% [14/194]) observed at Week 52 in the ITT population (all p values <0.001). Similar results were observed in the PP population, with statistically significantly higher rates of negative mycology (34.6% [108/312] versus 7.7% [12/156]) also observed at Week 52 (p value < 0.001).
Phase 3 Clinical Study Mycology Lab: (b) (4) Section 4.3.3 AN2690-ONYC-302	Fungal culture and KOH testing of subungual samples for presence of *Trichophyton rubrum* and *Trichophyton mentagrophytes*. Mycologic testing performed at screening and at Week 52 following 48 weeks of once daily dosing.	Test materials used in the clinical study: Tavaborole Topical Solution, 5% Tavaborole Topical Solution, Vehicle	• All subjects enrolled in the clinical study showed positive fungal culture and positive KOH for *T. rubrum* or *T. mentagrophytes* at screening. • Tavaborole outperformed vehicle in the secondary efficacy analyses, with statistically significantly higher rates of negative mycology (35.9% [142/396] versus 12.2% [25/205]) observed at Week 52 in the ITT population (all p values <0.001). Similar results were observed in the PP population, with statistically significantly higher rates of negative mycology (38.1% [114/299] versus 12.1% [19/157]) also observed at Week 52 (p value ≤ 0.002).

Table 1: Microbiology Studies Conducted to Support the Tavaborole Topical Solution, 5% Clinical Development Program (Cont'd)

Study Type/ Summary Section/ Study Report Number	Species Tested	Test Material	Results
Clinical Susceptibility Testing			
Phase 3 Clinical Study Susceptibility Testing Lab: (b) (4) Section 4.4 AN2690-ONYC-301	Isolates of *Trichophyton rubrum* and *Trichophyton mentagrophytes* collected from subjects participating in Study AN2690-ONYC-301	Tavaborole Positive controls: ciclopirox, terbinafine Test materials used in the clinical study: Tavaborole Topical Solution, 5% Tavaborole Topical Solution, Vehicle	• The tavaborole MIC_{50} and MIC_{90} values for the subgroups of dermatophyte species, geographic distribution, sex, age, and visit were 2 µg/mL and 4 µg/mL, respectively. The MIC values ranged from 0.5-8 µg/mL for all dermatophytes. • Though 37 viable samples collected from subjects assigned to tavaborole treatment were culture-positive at Week 52, the lack of elevated MIC values shows that the occurrence of a positive culture was not due to a development of resistance to tavaborole following repeated exposure over the course of the trial. • Results for the in vitro comparator and QC strains were as expected, thus validating the methods used.

Table 1: Microbiology Studies Conducted to Support the Tavaborole Topical Solution, 5% Clinical Development Program (Cont'd)

Study Type/ Summary Section/ Study Report Number	Species Tested	Test Material	Results
Phase 3 Clinical Study Susceptibility Testing Lab (b) (4) Section 4.4 AN2690-ONYC-302	Isolates of *Trichophyton rubrum* and *Trichophyton mentagrophytes* collected from subjects participating in Study AN2690-ONYC-302	Tavaborole Positive controls: ciclopirox, terbinafine Test materials used in the clinical study: Tavaborole Topical Solution, 5% Tavaborole Topical Solution, Vehicle	• The overall tavaborole MIC_{50} and MIC_{90} values for the subgroups of dermatophyte species, geographic distribution, sex, age, and visit were both 4 µg/mL. The MIC values ranged from 1-4 µg/mL for all dermatophytes, therefore these values were within the standard error for the QC strains. • Though 39 viable samples collected from subjects assigned to tavaborole treatment were culture-positive at Week 52, the lack of elevated MIC values shows that the occurrence of a positive culture was not due to a development of resistance to tavaborole following repeated exposure over the course of the trial. • Results for the in vitro comparator and QC strains were as expected, thus validating the methods used.

ATCC, American Type Culture Collection; CLSI, Clinical and Laboratory Standards Institute; (b) (4), intent to treat; KOH, potassium hydroxide; (b) (4) MFC, minimum fungicidal concentration; MIC, minimal inhibitory concentration; MIC_{50}, minimum inhibitory concentration required to inhibit the growth of 50% of isolates tested; MIC_{90}, minimum inhibitory concentration required to inhibit the growth of 90% of isolates tested (b) (4) PP, per protocol; QC, quality control.

Source: This submission.

The methods and standard operating procedures (SOPs) for microbiologic procedures, including data management, susceptibility testing, collection and transport of specimens, organism identification, potassium hydroxide (KOH) testing were provided.

Minimum inhibitory concentrations and quality control were determined according to the methods of the Clinical and Laboratory Standards Institute with minor modifications.

Kerian Grande Roche, Ph.D.
Microbiology Reviewer

Kerry Snow, MS
Clinical Microbiology Team Leader
9 December 2013

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

/s/

KERIAN K GRANDE ROCHE
12/13/2013

KERRY SNOW
12/13/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 26 November 2013

TO: NDA 204427

FROM: Erika Pfeiler, Ph.D.
Microbiologist
CDER/OPS/NDMS

THROUGH: John Metcalfe, Ph.D.
Senior Review Microbiologist
CDER/OPS/NDMS

cc: Cristina Petruccelli Attinello
Regulatory Project Manager
CDER/OND/ODEIII/DDDP

SUBJECT: Product Quality Microbiology assessment of Microbial Limits for Tavaborole [Submission Date: 26 July 2013]

The NDA for Tavaborole does not include a microbial limits release specification for drug product release or stability; however, the applicant provides a suitable rationale for the exclusion of this testing. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.

Tavaborole Topical Solution, 5% is a topical solution for application to the nails. The drug product (b) (4) and consists of tavaborole (the active ingredient) ethanol, propylene glycol, and EDTA.

The applicant does not plan to perform microbiological testing (microbial limits or antimicrobial effectiveness testing) at release or as a part of the stability program. As a justification, the applicant cites the inherently antimicrobial formulation of the drug product, as well as successful microbiological testing performed on stability batches.

The applicant performed microbial limits and antimicrobial effectiveness testing on six lots of drug product (four primary stability lots and two supporting stability lots). Microbial limits testing was performed according to methods described in USP <61> and <62> and antimicrobial effectiveness testing was performed according to methods described in USP <51> for category 2 products. Test methods were verified to be appropriate for use with the drug product following procedures

consistent with those in USP Chapters <61> and <62>. Testing was performed at 0 and 12 months, and is scheduled to be performed at 24 or 36 months in primary stability lots. Supporting lots have at least 24 months of stability data. All tests performed to date met acceptance criteria, which were in agreement with USP <51> and USP <1111>. The application also included 3 months of in-use stability testing data, with microbial limits performed at T0 and at 3 months and antimicrobial effectiveness testing performed at 3 months, all tests met acceptance criteria.

10 October 2013 Information Request (with filing communication)

1. *You propose* (b) (4) *However, due to the nature of your product and microbiological data that you have provided in your application, you may waive microbial limits testing for product release. If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced. Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.*

2. *You describe microbial limits testing performed according to methods described in USP <61> and USP <62>. Verify the suitability of these testing methods for your drug product.*

18 November 2013 Response
The applicant elected to remove microbial limits and antimicrobial effectiveness testing for product release and stability.

ADEQUATE

Reviewer Comments – The applicant's proposal to waive microbial limits testing for product release and stability is acceptable, as the product is inherently antimicrobial, and the applicant has performed suitable microbiological testing during development.

END

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

/s/

ERIKA A PFEILER
11/26/2013

JOHN W METCALFE
11/26/2013
I concur.

Clinical Microbiology: 45-Day Filing Meeting Checklist
NDA 204427: Tavaborole
Reviewer: Kerian Grande Roche Date Review completed: 8-29-13

This review is a consult for the Division of Dermatology and Dental Products (DDDP)

NDA Number: 204427 **Applicant: Anchor Pharmaceuticals, Inc.** **Stamp Date: 7-29-13**

Drug Name: Tavaborole **NDA Type: 505 (b)(1)**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comments
1	Is the microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	✓		
2	Is the microbiology information (preclinical/nonclinical and clinical) indexed, paginated and/or linked in a manner to allow substantive review to begin?	✓		
3	Is the microbiology information (preclinical/nonclinical and clinical) legible so that substantive review can begin?	✓		
4	On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains/isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	✓		
5	Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓		
6	Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions?	✓		
7	Has the applicant submitted the clinical microbiology datasets in a format which intents to correlate baseline pathogen with clinical and microbiologic outcome?		N/A	
8	Has the applicant submitted draft/proposed interpretive criteria/breakpoint along with quality control (QC) parameters and interpretive criteria, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA/BLA studies, and in a manner to allow substantive review to begin?		N/A	

Clinical Microbiology: 45-Day Filing Meeting Checklist
NDA 204427: Tavaborole
Reviewer: Kerian Grande Roche Date Review completed: 8-29-13

	Content Parameter	Yes	No	Comments
9	Has the applicant submitted a clinical microbiology dataset in an appropriate/standardized format which intents to determine resistance development by correlating changes in the phenotype (such as *in vitro* susceptibility) and/or genotype (such as mutations) of the baseline pathogen with clinical and microbiologic outcome?	✓		
10	Has the applicant used standardized or nonstandardized methods for measuring microbiologic outcome? If nonstandardized methods were used, has the applicant included complete details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	✓		
11	Has the applicant submitted draft labeling consistent with current regulation, divisional and Center policy, and the design of the development package?	✓		
12	Has the applicant submitted annotated microbiology draft labeling consistent with current divisional policy, and the design of the development package?	✓		
13	Have all the study reports, published articles, and other references been included and cross-referenced in the annotated draft labeling or summary section of the submission?		✓	Do not see the nonclinical study report 002-NCL PP-003-01 Determination of MIC and MFC or 002-NCL-PP-015-01 Interlaboratory Study for Determination of Quality Control Isolates
14	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		✓	

IS THE MICROBIOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes___

If the NDA is not fileable from the microbiology perspective, state the reasons and provide comments to be sent to the Applicant.

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

1. Please submit all nonclinical study reports that pertain to clinical microbiology for review including 002-NCL-PP-003-01 and 002-NCL-015-01.

Clinical Microbiology: 45-Day Filing Meeting Checklist
NDA 204427: Tavaborole
Reviewer: Kerian Grande Roche Date Review completed: 8-29-13

Reviewing Microbiologist : Kerian Grande Roche
Date: 8-29-13

Kerry Snow, MS
Acting Clinical Microbiology Team Leader
29 August 2013

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

/s/

KERIAN K GRANDE ROCHE
09/05/2013

KERRY SNOW
09/05/2013

PRODUCT QUALITY MICROBIOLOGY NON-STERILE

DRUG PRODUCT FILING CHECKLIST

NDA Number: 204427 **Applicant:** Anacor Pharmaceuticals, Inc. **Letter Date:** 26 July 2013

Drug Name: Tavaborole Solution **NDA Type:** 505(b)(1) **Stamp Date:** 29 July 2013

Dosage Form: Topical Solution **Reviewer:** Erika Pfeiler, Ph.D.

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		The process does not include in-process microbiological controls.
3	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		The applicant proposes (b) (4)
4	Has the applicant submitted the results of analytical method verification studies?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable)?	X		The application contains antimicrobial effectiveness data from stability lots. The applicant states that AET will not be performed as part of release or stability testing for the drug product.
6	Is this NDA fileable? If not, then describe why.	X		

Additional Comments: This is a nonsterile product for application on the nails. The product contains tavaborole (antifungal) ethanol, propylene glycol, and EDTA. Microbial limits and AET data from 6 stability lots of drug product were included in the application. The application

[redacted] that no microbial limits or antimicrobial effectiveness testing will be performed as part of the post-approval stability protocol.

Product Quality Microbiology Information Request:

1. [redacted] However, due to the nature of your product and microbiological data that you have provided in your application, you may waive microbial limits testing for product release. If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced. Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

2. You describe microbial limits testing performed according to methods described in USP <61> and USP <62>. Verify the suitability of these testing methods for your drug product.

Erika Pfeiler, Ph.D. Date
Microbiologist

John Metcalfe, Ph.D. Date
Senior Review Microbiologist

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

/s/

ERIKA A PFEILER
08/27/2013

JOHN W METCALFE
08/27/2013
I concur.