

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204427Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 204427	Submission Date(s): 7/29/2013
Brand Name	Kerydin
Generic Name	Tavaborole Topical Solution, 5%
Primary Reviewer	An-Chi Lu, M.S., Pharm.D.
Team Leader	Doanh Tran, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Dermatology and Dental Products
Sponsor	Anacor Pharmaceuticals Inc.
Submission Type	Original NDA
Formulation; Strength(s)	Topical Solution, 5%
Indication	For the topical treatment of onychomycosis (b) (4) [REDACTED]

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1 Executive Summary

This application is for Kerydin (tavaborole) Topical Solution, 5%. Tavaborole is a new molecular entity (NME). The Sponsor has submitted this NDA via 505(b)(1) regulatory pathway, and the proposed indication for Kerydin (tavaborole) Topical Solution is for the treatment of onychomycosis. It is intended to be applied to the entire nail surface and under the tip of each nail being treated once daily for 48 weeks.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III finds NDA 204427 acceptable from a Clinical Pharmacology perspective, pending agreement on recommended labeling changes.

1.2 Phase IV Commitments/Requirements

Post Marketing Requirement (PMR) for a pharmacokinetic/safety trial of tavaborole topical solution, 5% in pediatric subjects age 12-17 years and 11 months with onychomycosis of toenails (b)(4)

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Systemic bioavailability:

Trial P06118 was a maximal use PK trial to determine the PK of tavaborole 5% solution in subjects with toenail onychomycosis following topical administration. A total of 24 subjects diagnosed with distal subungual onychomycosis involving at least 4 toenails, including at least 1 great toenail were treated with a single dose of tavaborole 5% solution (approximately 200 µL) on all 10 toenails, including up to 2 mm of the surrounding skin on Day 1. All subjects received once daily dosing for 14 consecutive days on Days 5 to 18.

After a single topical application on Day 1, the mean C_{max} (\pm standard deviation) in plasma was 3.54 ± 2.26 ng/mL, the mean AUC_{last} was 44.4 ± 25.5 ng*hr/mL, and the median T_{max} was 12 hours (range 4.03-23.9 hours). After 14 days of repeated daily applications, the mean C_{max} was 5.17 ± 3.47 ng/mL, the mean AUC_{τ} was 75.8 ± 44.5 ng*hr/mL, and the median T_{max} was 8.03 hours (range 0.47-24.0 hours).

Both the mean C_{max} and AUC increased from Day 1 to Day 18, with values of C_{max} increased from 3.54 ng/mL to 5.17 ng/mL and AUC from 44.4 ng*hr/mL to 75.8 ng*hr/mL. The accumulation ratio based on AUC was 2.2. Based on the plasma trough concentrations, it appears that steady state was reached on Day 11 after 6 days of daily dosing.

Based on the NOAEL level of 3% tavaborole solution determined in the 9-month dermal minipig toxicity study, the safety margin is 10.1 based on mean human AUC_{τ} and 4.4 based on maximum human AUC_{τ} .

Effects on QT interval:

From the review of Interdisciplinary Review Team for QT Studies Consultation, Dr. Moh Jee Ng has concluded that no significant QTc prolongation effects of tavaborole (doses of topical solution, 5% q.d. and topical solution, 5% b.i.d.) were detected. For the suprathreshold dose group, tavaborole topical solution, 5% was applied twice daily on all 10 toenails and 10 fingernails and approximately 5 mm of skin surrounding all nails for 14 days to healthy subjects. Following the suprathreshold dose, the mean C_{max} was 22.4 ± 14.3 ng/mL. Compared to the C_{max} of 5.17 ng/mL in the maximal use PK trial P06118 after 14 continuous days of once-daily dosing, the C_{max} obtained from suprathreshold dose of this TQT trial was 4.3-times higher (range: 3.3-times to 6.5-times). With the suprathreshold dose (applied to healthy subjects) achieving a C_{max} 4.3-times higher than the C_{max} observed in the maximal use PK trial, tavaborole does not prolong QTc to any clinically relevant extent.

Drug-Drug Interaction:

The drug-drug interaction potential of tavaborole was assessed in the *in vitro* inhibition and induction studies. The results indicated that tavaborole is not likely to induce the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 or inhibit the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. The I/K_i ratio is calculated to be < 0.00068 .

Pediatrics:

The sponsor did not provide any PK data for tavaborole topical solution, 5% in pediatrics. The sponsor is requesting a waiver of pediatric trials in pediatrics less than 12 years of age and deferral of pediatric trials in age range of 12-17 years and 11 months to be conducted post approval. The Division of Dermatology and Dental Products (DDDP) agrees with the waiver and deferral of pediatric trials. DDDP proposed a pharmacokinetic/safety trial in 40 pediatric subjects age 12-17 years and 11 months with onychomycosis of toenails (b) (4). This reviewer recommends that the trial includes assessment of PK under maximal use conditions in a subgroup of at least 16 evaluable subjects.

Clinical Pharmacology Briefing:

An optional intra-division level Clinical Pharmacology briefing was conducted on February 24, 2014 with the following in attendance: Hae-Young Ahn, Yow-Ming Wang, Doanh Tran, Chinmay Shukla, and An-Chi Lu.

2 Question-Based Review

2.1 General Attributes

2.1.1 What is the proposed indication for Tavaborole Topical Solution, 5%?

Tavaborole Topical Solution, 5% is proposed for the topical treatment of onychomycosis

(b) (4)

2.1.2 What is onychomycosis?

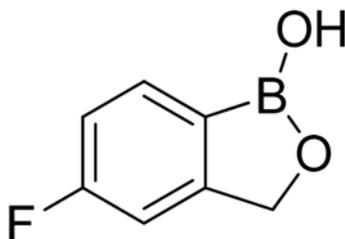
Onychomycosis is a fungal infection of the nail plate and other parts of the nail unit including the nail matrix. Dermatophytes are responsible for most finger and toenail infections, and Dermatophytic onychomycosis (tinea unguium) occurs in three distinct forms: distal and lateral subungual, proximal subungual, and superficial white. The vast majority of distal and proximal subungual onychomycosis results from *Trichophyton rubrum*. Superficial white onychomycosis is usually caused by *T. mentagrophytes*, although cases caused by *T. rubrum* have also been reported.

The prevalence in the United States and Europe is up to 10% of adult population, and is related to occlusive footwear. The disease is very common in adults, but may also occur in children.

2.1.3 What are the highlights of the physicochemical properties of Tavaborole?

Chemically, tavaborole is 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or 5-fluoro-2,1-benzoxaborol-1(3H)-ol. Tavaborole has a molecular weight of 151.93 Daltons, and is a white to off-white powder.

The molecular formula of tavaborole is $C_7H_6BF_2O_2$. The structural formula is as follows:



Formulation properties:

Tavaborole Topical Solution, 5% is an alcohol/^{(b) (4)} based solution containing 5% tavaborole (w/w). The solution is filled to a minimum label amount of 10 mL in a 12 mL, amber USP ^{(b) (4)} glass bottle with an 18-400 neck finish and an 18-400 black ^{(b) (4)} closure with a ^{(b) (4)} foam liner. Each milliliter of Kerydin contains 43.5 mg of tavaborole (5% w/w). For details of product composition see section 2.5.2.

Dosage and Route of Administration:

Apply to affected nails once daily for 48 weeks. It should be applied to the entire nail surface and under the tip of each nail being treated.

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). Tavaborole has been shown to be active against most strains of *Trichophyton mentagrophytes* and *Trichophyton rubrum*, both in vitro and in clinical infections.

2.2 General Clinical Pharmacology

2.2.1 *How was the dose/duration selected for Tavaborole Topical Solution, 5%?*

Dose selection for pivotal clinical trials and commercialization was chosen based on safety and efficacy results from Phase 2 trials.

In the Phase 2 double-blind, vehicle-controlled trial AN2690-ONYC-200/200A, three strengths of tavaborole solution, 2.5%, 5%, and 7.5%, were compared to vehicle control in subjects with onychomycosis (n=187). It was reported that patients treated with 5% achieved the highest proportion of clear nails and complete responses (clear nail plus negative fungal culture and negative KOH) at the Day 360 assessment. The 7.5% treatment group had more application site reactions (ASRs), drug holidays / dosing modifications due to ASRs, and discontinuations due to ASRs compared to the 5% treatment group.

2.2.2 *What are the design features of the clinical pharmacology and clinical trials used to support Tavaborole Topical Solution, 5%?*

The applicant has sponsored the following 12 clinical trials in support of the development of Tavaborole Topical Solution, 5%:

Clinical Pharmacology Trials:

AN2690-ONYC-101: 21 day cumulative irritation test, n =37. The medical reviewer is reviewing this trial.

AN2690-ONYC-103: Definitive repeat insult patch test (RIPT) and cumulative irritation trial of Tavaborole Topical Solution, 5% in healthy volunteers, n=279. The medical reviewer is reviewing this trial.

P05577: Absorption, metabolism, and excretion of ¹⁴C-tavaborole as a topical solution in adult males, n=6.

P06118: Maximal use Pharmacokinetic (PK) trial of Tavaborole Topical Solution, 5% in subjects with onychomycosis (14 days of dosing), n=24.

AN2690-ONYC-102: Thorough QT/QTc safety and PK trial of Tavaborole Topical Solution, 5% in healthy subjects (14 days of dosing), n=55. This reviewer has reviewed the PK portion of the result.

AN2690-ONYC-202: Open-label multiple-dose trial of safety and PK of tavaborole solution 7.5% (29 days of dosing), n=15. This PK trial was not reviewed, as tavaborole solution 7.5% is not the to-be-marketed formulation.

AN2690-ONYC-205: Open-label multiple-dose trial of safety and PK of tavaborole solution 7.5% (29 days of dosing), n=20. This PK trial was not reviewed, as tavaborole solution 7.5% is not the to-be-marketed formulation.

Phase II trials:

Uncontrolled:

AN2690-ONYC-201: Open-label rising multiple-dose multi-center trial to evaluate safety and efficacy of tavaborole solutions 5% and 7.5% in subjects with onychomycosis (180 or 360 days of dosing), n=89.

AN2690-ONYC-203: Open-label rising multiple-dose multi-center trial to evaluate safety and efficacy of tavaborole solutions 1% and 5% in subjects with onychomycosis (180 days of dosing), n=60.

Controlled:

AN2690-ONYC-200/200A: Randomized, double-blind, vehicle-controlled, multi-center trial to evaluate the safety and efficacy of topically applied tavaborole 2.5%, 5% and 7.5% solution vs. vehicle for the treatment of adult subjects with onychomycosis of the great toenail (180 days of dosing), n=187. The medical reviewer is reviewing this trial.

Phase III trials:

AN2690-ONYC-301: Randomized, double-blind, vehicle-controlled, multi-center trial to evaluate the efficacy and safety of Tavaborole Topical Solution, 5%, vs. vehicle in the treatment of onychomycosis of the toenail in adults (48 weeks of dosing), n=594. The medical reviewer is reviewing this trial.

AN2690-ONYC-302: Randomized, double-blind, vehicle-controlled, multi-center trial to evaluate the efficacy and safety of Tavaborole Topical Solution, 5%, vs. vehicle in the treatment of onychomycosis of the toenail in adults (48 weeks of dosing), n=604. The medical reviewer is reviewing this trial.

2.2.3 What trials have been conducted for bioavailability evaluation of the drug product? What is the systemic bioavailability of tavaborole topical solution, 5%?

The systemic exposure of tavaborole topical solution, 5% was evaluated in trial 18143. Trial 18143 was a maximal use PK trial to determine the pharmacokinetics of tavaborole 5% solution in subjects with toenail onychomycosis following topical administration.

A total of 24 subjects diagnosed with distal subungual onychomycosis involving at least 4 toenails, including at least 1 great toenail were treated with a single dose of tavaborole 5% solution (approximately 200 μ L) on all 10 toenails, including up to 2 mm of the surrounding skin on Day 1. All subjects received once daily dosing for 14 consecutive days on Days 5 to 18.

After a single topical application on Day 1, out of the 24 subjects, 3 subjects had all plasma tavaborole concentrations below the LLOQ (0.5 ng/mL) at the timepoints assessed (predose, 0.5, 1, 2, 4, 8, 12, 16, and 24 hours postdose), and 16 subjects had measurable concentrations at the 8-hour time point. The mean C_{max} in plasma was 3.54 ng/mL, and the median T_{max} was 12 hours.

After 14 days of repeated daily applications, on Day 18, most subjects (n=20) had measurable concentrations pre-dose, and all subjects had measurable concentrations at 12 hours post-dose. At 72 hours, about half of subjects (n=13) had measurable concentrations; at 96 hours, 6 subjects still had measurable concentrations. The mean C_{max} was 5.17 ng/mL, and the median T_{max} was 8.03 hours.

Both of the mean C_{max} and ACU increased from Day 1 to Day 18, with values of C_{max} from 3.54 ng/mL to 5.17 ng/mL and AUC from 44.4 ng*hr/mL to 75.8 ng*hr/mL. The

accumulation ratio based on AUC was 2.22. Based on the plasma trough concentrations, it appears that steady state was reached on Day 11 after 6 days of daily dosing. Table 1 shows the mean pharmacokinetic parameters of tavaborole following single dose and at steady state.

Table 1: Mean (CV, %) Plasma Pharmacokinetic Parameters of Tavaborole (SCH 900340) Following Single (Day 1) and Multiple (Day 18) Once-Daily Topical Applications of 200 µL of 5% Solution of Tavaborole to All Ten Toenails and 2 mm of Skin Surrounding Each Toenail of Onychomycosis Patients

Parameter	Day 1 (n=21) ^e	Day 18 (n=24)
Tmax ^a (hr)	12.0 (4.03-23.9)	8.03 (0.467-24.0)
Cmax (ng/mL)	3.54 (64) ^f	5.17 (67)
Cmin ^b (ng/mL)	NA	0.942 (65)
AUClast ^c (ng*hr/mL)	44.4 (57) ^{g, h}	148 (63)
AUCτ (ng*hr/mL)	NA	75.8 (59)
t½ (hr)	7.68 (27) ⁱ	28.5 (37) ^j
RA ^d	NA	2.22 (64) ^k

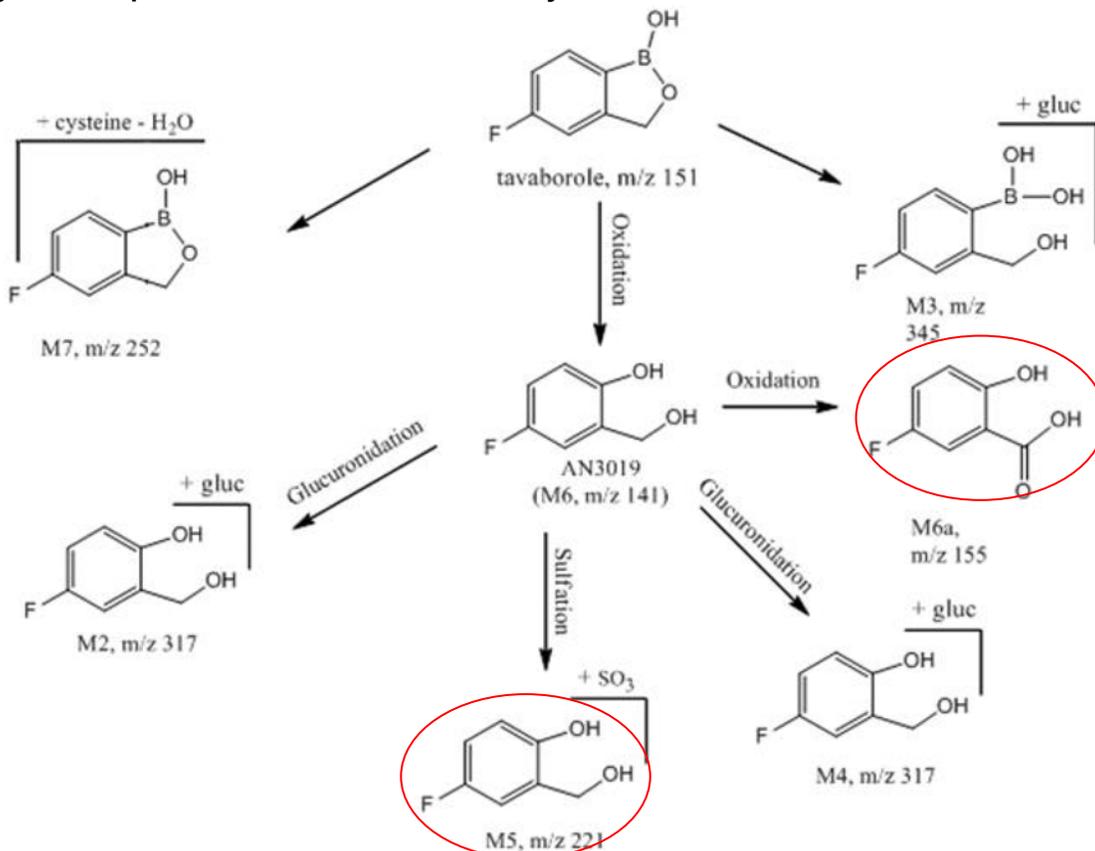
AUC24 = area under the concentration-time curve from time 0 to 24 hours; AUClast = area under the concentration-time curve from time 0 to the time of the final measurable sample; AUCτ = area under the concentration-time curve during a dosing interval τ at steady state; Cmax = maximum observed plasma concentration; Cmin = minimum observed plasma concentration; NA: not applicable; RA = accumulation ratio (index); t½ = terminal phase half-life; Tmax = time to maximum observed plasma concentration.

- a: Median (range) reported
- b: Cmin was calculated over a dosing interval of 24 hours
- c: Plasma samples were collected until 24 hours postdose on Day 1 and until 96 hours postdose on Day 18
- d: Ratio of AUCτ to AUClast on Day 1; both the AUCs were calculated over 24 hr interval
- e: Three subjects had all plasma SCH 900340 below lower limit of quantification (0.500 ng/mL) on Day 1
- f: Inclusion of 3 subjects with Cmax of 0.00 resulted in mean (CV, %) Cmax values of 3.10 (78)
- g: The last measurable time point was within 10% of 24 hour for all but one subject, thus AUClast also represents AUC24) on Day 1
- h: One subject had the last measurable concentration at 16 hr and was included in the summary statistics
- i: n=4, t1/2 could be determined only in 4 subjects
- j: n=10, t1/2 could be determined only in 10 subjects
- k: n=21

2.2.4 What is the metabolic pathway for Tavaborole Topical Solution, 5%?

The proposed biotransformation pathway for tavaborole is depicted below in Figure 1:

Figure 1: Proposed Biotransformation Pathway for Tavaborole



The proposed metabolic pathways for tavaborole were established from the results of topical administration to the skin of mice. Not all metabolites were confirmed in humans; those metabolites confirmed in humans are shown in circles in Figure 1. For humans, tavaborole metabolism was studied in the radiolabeled AME (P05577) and maximal use PK trial (P06118). In summary, tavaborole undergoes extensive metabolism. By qualitative assessment, trace levels of a sulfate conjugate (M5) and a benzoic acid metabolite (M6a) were detected at steady-state in plasma. In urine, M5 was the only metabolite identified in the radiolabeled AME (P05577) trial, and both M5 and M6a were identified after single dose and at steady state in the maximal use PK trial (P06118). Below are more details for the two trials on the metabolism of tavaborole.

In Trial P05577, six healthy adult male volunteers (19-35 years of age) were applied with a single topical application of ^{14}C -tavaborole (a total of $\sim 200\ \mu\text{L}$ containing a total of $\sim 100\ \mu\text{Ci}$ radioactivity) to all 10 toenails and 5 mm of the surrounding skin of each toe. The ratio of C_{max} for plasma tavaborole/plasma total radioactivity was approximately 0.146, indicating extensive metabolism and that the systemic exposure to tavaborole was approximately 15% of the exposure to plasma total radioactivity. The mean cumulative total radioactivity excreted in urine over a 10 day period was 17.9% of the applied dose, suggesting there is systemic absorption of this topical product. The total radioactivity

levels in all the fecal samples were less than the LLOQ (2.58 ng equiv/mL) in all the subjects, indicating excretion was primarily via the renal pathway. For metabolite profiling, there was not enough radiocarbon present in plasma or fecal samples for profiling of metabolites using liquid chromatography-mass spectrometry (LC-MS) with in-line flow scintillation analysis (FSA) or off-line microplate scintillation counter detection. In urine, M5, the sulfate conjugate metabolite of the benzyl alcohol metabolite (M6; AN3019) was the only metabolite identified. The amount of M5 excreted during 0-120 hr post-dose represented 14.6% of the administered dose applied topically. From the radiochromatogram of 0-120 hr pooled urine, three minor metabolites representing less than 1% of the dose were also observed, but could not be detected by LC-MS and thus were not identified. For further details, see Appendix for individual trial review.

In the maximal use PK trial P06118 (see above Section 2.2.3 for study design), plasma samples were pooled (0-24 hours) across all subjects on Day 1 (single dose) and Day 18 (14 days of multiple dose). Urine was collected at predose on Day 1, and at 0-24 hours as blocks post dose on Days 1 and 18.

In pooled plasma by qualitative assessment, no metabolites were detected on Day 1, and trace levels of a sulfate conjugate (M5) and a benzoic acid metabolite (M6a) were detected at steady-state on Day 18. In urine, M5 and M6a were the only metabolites detected on Day 1 and Day 18.

2.2.5 Does Tavaborole Topical Solution, 5% prolong QT intervals?

From the review of Interdisciplinary Review Team for QT Studies Consultation, Dr. Moh Jee Ng has concluded that no significant QTc prolongation effects of tavaborole (doses of topical solution, 5% q.d. and topical solution, 5% b.i.d.) were detected in the Thorough QTc Trial AN2690-ONYC-102.

In the Thorough QTc Trial AN2690-ONYC-102, a total of 55 healthy volunteers were randomized to one of eight sequences with the following four study treatments:

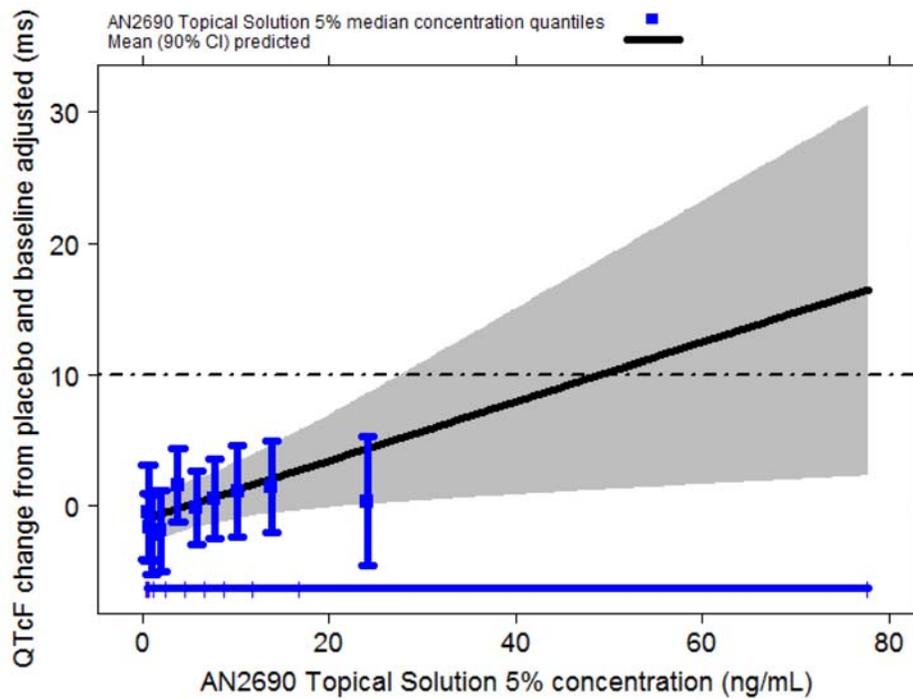
- Vehicle (V): Solution vehicle for tavaborole QD on all 10 toenails for 14 days
- Positive Control (PC): Solution vehicle for tavaborole QD on all 10 toenails for 14 days, plus a single dose of unblinded moxifloxacin 400 mg administered orally in the morning on Day 14 under fasted conditions
- Therapeutic Dose (DT): tavaborole Topical Solution, 5% QD on all 10 toenails for 14 days (nail plates only)
- Supratherapeutic Dose (DS): tavaborole Topical Solution, 5% twice daily (BID, defined as every 12 hours) on all 10 toenails and 10 fingernails and approximately 5 mm of skin surrounding all nails for 14 days

Because the TQT trials was conducted in healthy volunteers instead of subjects with onychomycosis, it is important to evaluate the tavaborole systemic exposure to ensure that the exposure achieved in the TQT trial was similar or higher than that expected following clinical use. Following the supratherapeutic dose, the mean C_{max} was 22.4 ± 14.3 ng/mL. Compared to the C_{max} of 5.17 ng/mL in the maximal use PK trial P06118

after 14 continuous days of once-daily dosing, the C_{max} obtained from suprathreshold dose of this TQT trial was 4.33-times higher (range: 3.3-times to 6.5-times).

From the review of Dr. Moh Jee Ng, as shown in Figure 2, there is a positive and significant relationship between tavorole plasma concentrations and $\Delta\Delta QTcF$ with a positive slope of 0.23 ms per ng/mL (95% CI: 0.036 – 0.41, p-value = 0.05). Dr. Ng noted that at the suprathreshold concentrations assessed in this trial, tavorole does not prolong QTc to any clinically relevant extent.

Figure 2: Observed Median-Quantile Tavorole (AN2690) Concentrations and Associated Mean (90% CI) $\Delta\Delta QTcF$ (color dots) Together with the Mean (90% CI) Predicted $\Delta\Delta QTcF$ (black line with shaded grey area)



2.3 Intrinsic Factors

2.3.1 What is the systemic drug exposure in pediatrics?

In this submission, the applicant did not provide information in pediatrics. The applicant requested a waiver of pediatric trials of subjects aged 0 to 11 years and 11 months for the reason that studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed) and requested a deferral of studies in pediatrics 12 years of age and older.

Onychomycosis (b) (4) is not prevalent in population younger than 12 years of age. The Division of Dermatology and Dental Products (DDDP) concludes that the product may not be used in a substantial number of patients in this age group and that the studies are not feasible.

DDDP recommends the applicant to conduct a pharmacokinetic/safety trial of Tavaborole topical solution, 5% in pediatric subjects age 12-17 years and 11 months with onychomycosis of toenails COPYRIGHT. There should be 40 male or female subjects 12–17 years 11 month of age with at least of 16 evaluable subjects under maximal use conditions to adequately characterize the pharmacokinetics in this age group. Subjects must have a clinical diagnosis of distal subungual onychomycosis affecting at least one great toenail (20% to 60% of the nail after the nail had been trimmed), confirmed by a central mycology laboratory to be positive for KOH wet mount and fungal culture for a dermatophyte. Subjects included in the PK subgroup should be under maximal use conditions (i.e., subjects with $\geq 50\%$ involvement of both great toenails and 4 additional affected toenails). Serial PK assessments should be performed after single dose and at steady state. Several trough samples should be obtained to assess the attainment of steady state.

2.4 Extrinsic Factors

2.4.1 What is the effect of tavaborole on the PK of other drugs?

In vitro studies for inhibition and induction indicated that tavaborole is not likely to induce the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 or inhibit the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. The I/K_i ratio is calculated to be < 0.00068 .

In the *in vitro* inhibition study, 002-NCL PK-053-01, the ability of tavaborole to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 was evaluated at concentrations from 0.1 to 100 μM in human liver microsomes. The human liver microsomes from a pool of 16 individuals were incubated with marker substrates at concentrations approximately equal to their apparent K_m , in the presence or absence of tavaborole, to evaluate tavaborole as a direct and time-dependent inhibitor of CYP activity.

Tavaborole caused 42% direct inhibition of CYP2E1 with an IC_{50} value of $>100 \mu\text{M}$, and caused time-dependent and partial NADPH-dependent inhibition of CYP2A6 activity at a concentration of tavaborole $>30 \mu\text{M}$, but no IC_{50} value was calculated due to insufficient inhibition across the range of concentrations examined.

With the estimate of the K_i value of CYP enzymes by tavaborole $>50 \mu\text{M}$, and the mean C_{max} at steady state of 5.17 ng/mL (0.034 μM) in the maximal use PK trial P06118, the I/K_i ratio is calculated to be < 0.00068 .

Table 2: In vitro evaluation of tavaborole as an inhibitor results

Enzyme	CYP Reaction	Direct Inhibition		Time-Dependent Inhibition		Potential for Time-Dependent Inhibition ^c
		Zero-Minute Preincubation		30-Minute Preincubation		
		IC ₅₀ (μM) ^a	Maximum Inhibition at 100 μM (%) ^b	IC ₅₀ (μM) ^a	Maximum Inhibition at 100 μM (%) ^b	
CYP1A2	Phenacetin O-dealkylation	>100	15	>100	5.5	No
CYP2A6	Coumarin 7-hydroxylation	>100	4.3	>100	41	Yes ^d
CYP2B6	Efavirenz 8-hydroxylation	>100	NA	>100	0.5	No
CYP2C8	Amodiaquine N-dealkylation	>100	9.5	>100	7.1	No
CYP2C9	Diclofenac 4'-hydroxylation	>100	NA	>100	NA	No
CYP2C19	S-Mephenytoin 4'-hydroxylation	>100	11	>100	5.5	No
CYP2D6	Dextromethorphan O-demethylation	>100	14	>100	8.5	No
CYP2E1	Chlorzoxazone 6-hydroxylation	>100	42	57	73	Yes ^d
CYP3A4/5	Testosterone 6β-hydroxylation	>100	5.7	>100	4.3	No
CYP3A4/5	Midazolam 1'-hydroxylation	>100	NA	>100	1.2	No

a: Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC₅₀ values. IC₅₀ values were calculated with XLFit.

b: Maximum inhibition (%) is calculated with the following formula and data for the highest concentration of test article evaluated (results are rounded to two significant figures): Maximum inhibition (%) = 100% - Percent solvent control.

c: Time-dependent inhibition was determined by comparison of IC₅₀ values with and without preincubation, by comparison of the maximum inhibition (%) with and without preincubation and by visual inspection of the IC₅₀ plot.

d: Time-dependent inhibition was found to be at least partially dependent upon the presence of NADPH-generating system.

NA = Not applicable. No value was obtained as the rates at the highest concentration of SCH 900340 evaluated (100 μM) were higher than the control rates.

In the *in vitro* induction study, DM27769, the induction potential of tavaborole on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 was evaluated. Human hepatocytes from 3 donors were incubated and treated once daily for three consecutive days with tavaborole (0.126, 1.26, and 12.6 μM), vehicle controls (DMSO 0.1% v/v), or positive controls (omeprazole 100 μM, phenobarbital 750 μM, and rifampin 10 μM). The metabolite analysis by Liquid Chromatography-Mass Spectrometry (LC-MS) was performed on the supernatant fractions (CYP1A2: Acetaminophen; CYP2B6: Hydroxybupropion; CYP2C8: N-Desethylamodiaquine; CYP2C9: 4'-Hydroxydiclofenac; CYP2C19: 4'-Hydroxymephenytoin; CYP3A4/5: 6β-Hydroxytestosterone).

Table 3 shows the induction ratios relative to vehicle control (DMSO). Using a cut-off ratio of 1.5 for presence of induction, treatment of cultured human hepatocytes with tavaborole up to 12.6 μM caused little or no change in CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A4/5 enzyme activity compared with the vehicle control.

Table 3: The effects of treating cultured human hepatocytes with tavaborole or prototypical inducers on microsomal cytochrome P450 (CYP) enzyme activity as fold increase

Treatment	Concentration	Fold Increase ^a					
		Phenacetin O-dealkylation (CYP1A2)	Bupropion hydroxylation (CYP2B6)	Amodiaquine N-dealkylation (CYP2C8)	Diclofenac 4'-hydroxylation (CYP2C9)	S-Mephenytoin 4'-hydroxylation (CYP2C19)	Testosterone 6β-hydroxylation (CYP3A4/5)
Dimethyl sulfoxide	0.1% (v/v)	1.00 ± 0.43	1.00 ± 0.69	1.00 ± 0.19	1.00 ± 0.25	1.00 ± 1.28	1.00 ± 0.45
SCH 900340	0.126 μM	1.06 ± 0.14	0.944 ± 0.044	1.06 ± 0.15	1.01 ± 0.15	1.09 ± 0.10	1.09 ± 0.10
SCH 900340	1.26 μM	0.926 ± 0.183	0.940 ± 0.175	0.981 ± 0.273	0.899 ± 0.084	1.06 ± 0.15	0.932 ± 0.167
SCH 900340	12.6 μM	1.06 ± 0.21	0.855 ± 0.144	1.00 ± 0.20	0.972 ± 0.182	1.06 ± 0.13	1.04 ± 0.14
Omeprazole	100 μM	43.8 ± 19.8	7.90 ± 1.84	2.98 ± 0.15	1.57 ± 0.20	1.59 ± 1.31	3.27 ± 1.91
Phenobarbital	750 μM	2.13 ± 0.39	11.1 ± 2.7	4.34 ± 0.43	1.83 ± 0.41	2.30 ± 1.22	9.14 ± 4.71
Rifampin	10 μM	1.97 ± 0.76	5.42 ± 2.41	5.04 ± 0.26	2.33 ± 0.31	3.67 ± 0.50	9.42 ± 4.45

a: Values are the mean ± standard deviation of three determinations (human hepatocyte preparations H920, H921 and H923). Data are shown graphically in Figure 10.

2.4.2 What other extrinsic factors (food, herbal products, smoking, alcohol use) influence the PK of Tavaborole Topical Solution, 5%?

Effects of extrinsic factors, such as herbal products, smoking, and alcohol use on the PK of Tavaborole Topical Solution, 5% were not evaluated. Since this is a topical product, an effect of food is not anticipated.

2.5 General Biopharmaceutics

2.5.1 Is the to-be-marketed formulation identical to the one used in Phase 3 efficacy and safety trials?

The to-be-marketed formulation was used in the Phase 3 safety and efficacy trials (AN2690-ONYC-301 and AN2690-ONYC-302), the Repeat Insult Patch Test (RIPT)/cumulative irritation trial (AN2690-ONYC-103), the Thorough QTc trial (AN2690-ONYC-102), and the maximal use PK trial (P06118). Including the to-be-marketed formulation, a total of three tavaborole topical solution formulations were used in the clinical trials. The second formulation was only used in one Phase 1 trial (P05577), and the third formulation was used in all other Phase 1 and Phase 2 trials. The only difference between these formulations was in the (b) (4)

2.5.2 What is the final product composition?

Table 4 shows the components and composition of Tavaborole Topical Solution, 5%.

Table 4: Composition of Tavaborole Topical Solution, 5%

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

2.6 Analytical

2.6.1 What bioanalytical methods were used to assess drug concentrations?

Two bioanalytical methods used in two trials (Maximal use PK trial P06118 and Thorough QTc Trial AN2690-ONYC-102) were assessed by this reviewer.

Maximal use PK Trial P06118:

Tavaborole concentrations in human citrate plasma were determined using a liquid chromatographic assay with mass spectrometric detection (LC-MS) after application of supported liquid-liquid extraction (SLLE).

In summary, plasma samples to determine tavaborole concentrations are centrifuged for 4 minutes at 14000 RPM. Supernatant is transferred and applied on SLLE cartridge. Elute samples by using 1-Chlorobutane/Ethanol=95:5 (v/v) and collect the eluates in glass

laboratory tubes. The eluates are then evaporated, dissolved by Milli-Q water, transferred to the wells of a tapered masterblock, and submitted for analysis.

Thorough QTc Trial AN2690-ONYC-102:

Human plasma samples containing tavaborole, tavaborole-d2 as the internal standard (I.S.), sodium citrate as the anticoagulant and 6.0% citric acid as a preservative were processed by liquid/liquid extraction. The extracts were reconstituted and analyzed by high-performance liquid chromatography using a Restek Allure PFP Propyl column. The mobile phase was nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds were detected using MS/MS in electrospray negative mode.

2.6.2 Were the bioanalytical methods adequately validated?

Maximal use PK Trial P06118:

The method for measuring tavaborole in human citrate plasma by LC-MS after application of SLLE was validated at (b) (4)

The standard curve range was from 0.5 to 50 ng/mL of human citrate plasma. Intra-run and Inter-run precision and accuracy was assessed at 4 quality control (QC) levels. Accuracy and precision at LLOQ was assessed using 5 replicates for intra-run, and 9 replicates for inter-run. A summary of precision and accuracy results is shown in Table 5.

Table 5: Precision and Accuracy Results of Tavaborole Assay in Human Citrate Plasma Validation in Trial P06118

Standard Curve Range	0.5 to 50 ng/mL human citrate plasma
Lower Limit of Quantitation (LLOQ)	0.5 ng/mL
Average Recovery of Drug	82.0 %
Intra-Batch Accuracy	1.5 ng/mL-400 ng/mL: 100-105.3% 0.5 ng/mL (LLOQ): 116.6%
Inter-Batch Accuracy	1.5 ng/mL-40 ng/mL: 92.3 – 94.7% ¹ 1.5 ng/mL-400 ng/mL: 99.7-104.7% 0.5 ng/mL (LLOQ): 114%
Intra-Batch Precision Range	1.5 ng/mL-400 ng/mL: 1.9 – 3.1% LLOQ (0.5 ng/mL): 3.9%
Inter-Batch Precision Range	1.5 ng/mL-40 ng/mL: 4.8 – 6.8% ¹ 1.5 ng/mL-400 ng/mL: 1.9 – 3.9% LLOQ (0.5 ng/mL): 4.3%

1. Values were determined in the bioanalytical report P06118/090197 Amendment 1, February 2010. Other validation values were taken from the validation report, 002-NCL PK-054-01, December 2008.

Thorough QTc Trial AN2690-ONYC-102:

The method for measuring tavaborole in human citrate plasma by high-performance liquid chromatography with tandem mass spectrometry was validated at (b) (4)

The standard curve range was from 0.5 to 50 ng/mL. Intra-day and Inter-day precision and accuracy was assessed at 3 quality control (QC) levels. Accuracy and precision at LLOQ was assessed using 6 replicates. A summary of precision and accuracy results is shown in Table 6.

Table 6: Precision and Accuracy Results of Tavaborole Assay in Human Citrate Plasma Validation in Trial AN2690-ONYC-102

Standard Curve Range	0.5 to 50 ng/mL
Lower Limit of Quantitation (LLOQ)	0.500 ng/mL
Average Recovery of Drug	72.5% (Internal standard: 72.7%)
Intra-Day Accuracy	1.5-40.0 ng/mL: range: 94.67-99.875% 0.5 ng/mL (LLOQ): range: 109.2-118.6%
Inter-Day Accuracy	1.5-40.0 ng/mL: 96-97.75% 0.5 ng/mL (LLOQ): 112.8%
Intra-Day Precision Range	1.5-40.0 ng/mL: 1.89-6.90% 0.5 ng/mL (LLOQ): 3.42-15.3%
Inter-Day Precision Range	1.5-40.0 ng/mL: 3.08-5.54% 0.5 ng/mL (LLOQ): 10.6%

3 Detailed Labeling Recommendations

The following changes are recommended for sections 5.1 and 12 of the label. Additions are noted as double underline and deletions are noted as ~~strike through~~.

7.0 DRUG INTERACTIONS

No formal drug-drug interactions studies have been conducted with tavaborole. In vitro studies have shown that tavaborole, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

12.2 Pharmacodynamics

^{(b) (4)} At therapeutic doses, Tavaborole Topical Solution, 5% is not expected to prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

Tavaborole undergoes extensive metabolism ^{(b) (4)}
^{(b) (4)} Renal excretion is the major route of elimination ^{(b) (4)}

In a clinical pharmacology trial ^{(b) (4)} of six healthy adult male volunteers who received a single topical application of 5% ¹⁴C-tavaborole solution, tavaborole conjugates and metabolites were shown to be excreted primarily in the urine.

^{(b) (4)} The pharmacokinetics of [TRADENAME] ^{(b) (4)} was investigated in 24 subjects with distal subungual onychomycosis involving at least 4 toenails (including at least 1 great toenail) following a single dose and a 2-week daily topical applications of 200 µL of a 5% solution of tavaborole to all ten toenails and 2 mm of skin surrounding each toenail. Steady state was achieved after 14 days of dosing. After a single dose, the mean (± standard deviation) peak concentration (C_{max}) of ^{(b) (4)} tavaborole was 3.54 ± 2.26 ng/mL (n=21 with measurable concentrations, range 0.618-10.2 ng/mL, LLOQ=0.5 ng/mL), and the mean AUC_{last} was 44.4 ± 25.5 ng*hr/mL (n=21). After 2-week daily dose, the mean C_{max} was ^{(b) (4)} ^{(b) (4)} -5.17 ^{(b) (4)} ± 3.47 ng/mL (n=24, range 1.51-12.8 ng/mL, ^{(b) (4)} and the mean AUC_τ was 75.8 ± 44.5 ng*hr/mL.

^{(b) (4)}

^{(b) (4)}

4 Appendix

4.1 Individual Trial Reviews

Note: Tavaborole is referred as SCH 900340 in this section.

Trial No. P06118

Title: Evaluation of the Pharmacokinetics of tavaborole in Subjects with Onychomycosis of the Toenails

Trial Initiation/Completion Dates: 7/8/2009 to 11/11/2009

Objectives:

Primary objective: To determine the pharmacokinetics of tavaborole 5% solution in subjects with toenail onychomycosis following topical administration.

Secondary objective: To evaluate the safety and tolerability of tavaborole 5% solution.

Exploratory objectives: To determine the usage amount of the drug product 5% solution in subjects with onychomycosis after a single application and during 14 days of treatment; to estimate the variability in product usage rate among these subjects; and to characterize the dose/plasma concentration/area under the concentration-time curve (AUC) relationships.

Trial Center: Single center

(b) (4)

Design of Trial:

Trial Population Demographics: Twenty-four subjects diagnosed with distal subungual onychomycosis involving at least 4 toenails, including at least 1 great toenail.

Age range: 28-82 years; **Race:** Caucasian (79%), African American (21%), Hispanic or latino (13%); **Gender:** 16 Male (67%), 8 Female (33%).

Diagnosis and main criteria for inclusion:

- Subjects could be of either sex and of any race and were to be at least 18 years, inclusive, having a Body Mass Index (BMI) between 18 and 40.5, inclusive. BMI = weight (kg)/height² (m²).
- Subjects were to have a “case definition” of distal subungual onychomycosis:
 - a) Onychomycosis of at least 4 toenails, including at least 1 great toenail;
 - b) The great toenail was to have onycholysis and at least 50-75% involvement;
 - c) Combined thickness of the nail plate and hyperkeratosis of the nail bed of each great toenail was to be 2 to 4 mm
 - d) Positive potassium hydroxide (KOH) wet mount from at least one great toenail

Investigational Products:

Tavaborole 5% solution approximately 200 µL, applied topically QD by rubber bulb dropper, Lot No. K-H09856

Trial Design:

Adult subjects with distal subungual onychomycosis involving at least 4 toenails (including at least 1 great toenail) were enrolled. On Day 1, all 24 subjects were to receive a single dose of tavaborole 5% (approximately 200 µL) on all 10 toenails, including up to 2 mm of the surrounding skin. Subjects returned on Day 5 for the multiple-dose portion of the trial with once daily dosing for 14 consecutive days on Days 5 to 18. Sample collection timepoints are shown below in Table 7.

Table 7: Timepoints of Blood Samples

Day relative to First Dose of Study Drug	Day 1	Day 5	Day 8	Day 11	Day 16	Day 17	Day 18
Blood PK sampling	Predose, 0.5, 1, 2, 4, 8, 12, 16, and 24 hours	Predose	Predose	Predose	Predose, 12 hours	Predose, 12 hours	Predose, 0.5, 1, 2, 4, 8, 12, 16, 24, 36, 48, 72, and 96 hours
Blood samples for metabolite profiling	Predose, 0.5, 1, 2, 4, 8, 12, 16, and 24 hours						Predose, 0.5, 1, 2, 4, 8, 12, 16, 24, 36, 48, 72, and 96 hours
Urine samples for metabolite profiling	Predose, 24 hours						24 hours

Adapted from Table 2 in Sponsor's Report No. 002-CLN PK-003-01

Reviewer's comments:

In the clinical pharmacology review dated 12/23/2010 under IND 71206, it was noted that "The information included in this submission appears to indicate that the design of study P06118 was conducted under maximal use conditions (i.e. maximal dose, frequency, duration, disease severity, and application areas) in diseased adult subjects with the to-be-marketed formulation. A final determination will be made at the time of NDA submission."

Key Exclusion Criteria:

- Subjects who had received any treatment listed below more recently than the indicated washout period prior to Baseline, which, in the opinion of the investigator and sponsor, would interfere with their ability to participate in the trial.

Prohibited Medications Prior to Baseline and During the Study	Washout Period Prior to Baseline
Any prescription or over-the-counter topical or oral preparations for the treatment of tinea pedis (athlete's foot), onychomycosis	4 weeks
Pedicures	4 weeks
Nail polish	2 weeks
Foot care products (lotions, creams, ointments, oils, balms)	2 weeks

Analytical Methods:

See Question-Based-Review section 2.6.1.

Analytical Method Validation:

Table 8: Tavaborole in human citrate plasma:

Assay Method	liquid chromatographic assay with mass spectrometric detection (LC-MS)
Analytical Site	(b) (4)
Compound	Tavaborole in human citrate plasma
Standard Curve Range	0.5 to 50 ng/mL human citrate plasma
Lower Limit of Quantitation (LLOQ)	0.5 ng/mL
Average Recovery of Drug	82.0%
Intra-Batch Accuracy	1.5 ng/mL-400 ng/mL: 100-105.3% 0.5 ng/mL (LLOQ): 116.6%
Inter-Batch Accuracy	1.5 ng/mL-40 ng/mL: 92.3 – 94.7% ¹ 1.5 ng/mL-400 ng/mL: 99.7-104.7% 0.5 ng/mL (LLOQ): 114%
Intra-Batch Precision Range	1.5 ng/mL-400 ng/mL: 1.9 – 3.1% LLOQ (0.5 ng/mL): 3.9%
Inter-Batch Precision Range	1.5 ng/mL-40 ng/mL: 4.8 – 6.8% ¹ 1.5 ng/mL-400 ng/mL: 1.9 – 3.9% LLOQ (0.5 ng/mL): 4.3%
Freeze-Thaw Stability	4 cycles
Bench-Top Stability	24 hours (b) (4)
Processed Stability	4 weeks for stock solutions at approximately -20 °C, 1 week for working solutions at approximately -20 °C, 3 days for both stock and working solutions at room temperature after initial storage at approximately -20 °C.
Long Term Stability	39 weeks (-20°C) <i>The trial initiated on 7/8/2009 and completed on 11/11/2009, and the sample analysis dates were on 8/12/2009 and 11/8/2009-11/9/2009. The sample storage condition was at -20 °C maintained in the frozen state until assayed. The duration from trial initiation to the last day of sample analysis was 124 days.</i>
Dilution Integrity	Up to 10-fold
Selectivity/Matrix Effect	Blank human citrate plasma samples from six different donors were spiked to the concentration level of STD B (0.5 ng/mL tavaborole and 20 ng/mL IS), five out of six blank samples the response of interfering peaks at the retention time of tavaborole was found to be less than 20% of the response found for tavaborole in STD B, and the response of interfering peaks at the retention time of the IS was found to be less than 5% of the response found for the IS at the concentration level of the IS used in the assay.
Reviewer's comments	Method acceptable

1. Values were determined in the bioanalytical report P06118/090197 Amendment 1, February 2010. Other validation values were taken from the validation report, 002-NCL PK-054-01, December 2008.

Table 9: Tavaborole in Human Urine

Assay Method	liquid chromatography atmospheric pressure ionization tandem mass spectrometry (LCAPI/MS/MS) detection
Analytical Site	(b) (4)
Compound	Tavaborole
Standard Curve Range	5.00 – 1000 ng/mL
Lower Limit of Quantitation (LLOQ)	5.00 ng/mL
Average Recovery of Drug	15 ng/mL: 70.3% 400 ng/mL: 71.3% 750 ng/mL: 66.7% Internal Standard: 73.0%
Intra-Batch Accuracy	15-750 ng/mL: 88.4-102% 5 ng/mL (LLOQ): 90.1%
Inter-Batch Accuracy	15-750 ng/mL: 93.6-99.1%
Intra-Batch Precision Range	15-750 ng/mL: 0.958-8.91% 5 ng/mL (LLOQ): 10.9%
Inter-Batch Precision Range	15-750 ng/mL: 1.76-8.38%
Freeze-Thaw Stability	3 cycles
Bench-Top Stability	Room temperature: not stable 6 hours at 4°C
Processed Stability	Processed human urine: 77 hours at 4°C
Long Term Stability	-20°C: not established (at 41 days, the accuracy for 15 ng/mL, 400 ng/mL, 750 ng/mL was 76.4%, 87.3% and 90.9%; at 95 days, it was 90.1%, 87.0%, 86.2%; at 188 days, it was 62.8%, 78.8%, 77.7%) -70°C: 188 days
Dilution Integrity	50 folds
Selectivity/Matrix Effect	Six individual lots of control matrix were fortified with the analyte at the LLOQ concentration. The mean accuracy for LLOQ samples prepared in individual lots of human urine was within $\pm 20\%$ of nominal concentration and precision was $\leq 20\%$.
<i>Reviewer's comments</i>	<i>Method acceptable</i>

Pharmacokinetic Analysis:

- AUC_{∞} : Area under the concentration-time curve from time 0 to infinity after single dosing
- AUC_{last} : Area under the concentration-time curve from time 0 to the time of the final measurable sample

- AUC_{τ} : area under the concentration-time curve during a dosing interval τ at steady state
- C_{max} : Maximum observed plasma (or serum) concentration
- T_{max} : Time to maximum observed plasma (or serum) concentration
- $t_{1/2}$: Terminal phase (elimination) half-life
- λ_z : Terminal phase (elimination) rate constant
- CL/F : Apparent total body clearance
- V_z/F : Apparent volume of distribution during the terminal phase
- C_{min} : Minimum observed plasma (or serum) concentration during a dosing interval τ at steady state
- R_A : Accumulation ratio (index)

Pharmacokinetic Results:

A total of 24 subjects were enrolled and treated in the trial, and all 24 subjects completed the trial.

Table 1 shows the mean pharmacokinetic parameters of tavaborole for this trial (See Question Based Review section 2.2.3).

On Day 1, 3 of the 24 subjects had all plasma tavaborole concentrations below the LLOQ (0.5 ng/mL) at all time points. 16 subjects had measurable concentrations at the 8-hour time point on Day 1. The median T_{max} was 12.0 hours on Day 1.

On Day 18, most subjects (n=20) had measurable concentrations pre-dose, and all subjects had measurable concentrations at 12 hours post-dose. At 72 hours, about half of subjects (n=13) had measurable concentrations; at 96 hours, 6 subjects still had measurable concentrations. The median T_{max} was 8.03 hours on Day 18. Based on the plasma trough concentrations (shown in Table 10), it appears that steady state was reached on Day 11. Figure 3 shows the individual predose (trough) plasma tavaborole concentrations following multiple once daily dose.

Table 10: Mean (CV, %) Predose and 12-hour Postdose Plasma Tavaborole (SCH 900340) Concentrations Following Multiple Once-Daily Topical Applications of 200 µL of 5% Solution of Tavaborole to All Ten Toenails and 2 mm of Skin Surrounding Each Toenail of Onychomycosis Patients

Day/ Time	Plasma SCH 900340 (ng/mL)	
	n	Mean (CV, %)
Day 5/ 0.00 hr	23	0.00 (NC)
Day 8/ 0.00 hr	21	0.820 (59)
Day 11/ 0.00 hr	22	1.24 (65)
Day 16/ 0.00 hr	24	1.51 (71)
Day 16/ 12.0 hr	23	2.80 (49)
Day 17/ 0.00 hr	22	1.20 (44)
Day 17/ 12.0 hr	24	3.67 (91)
Day 18/ 0.00 hr	22	1.40 (69)
Day 18/ 12.0 hr	24	4.16 (68)

Note: Mean values below lower limit of quantification (0.500 ng/mL) were reported as 0. CV (%) not calculated when n<3 or mean = 0.

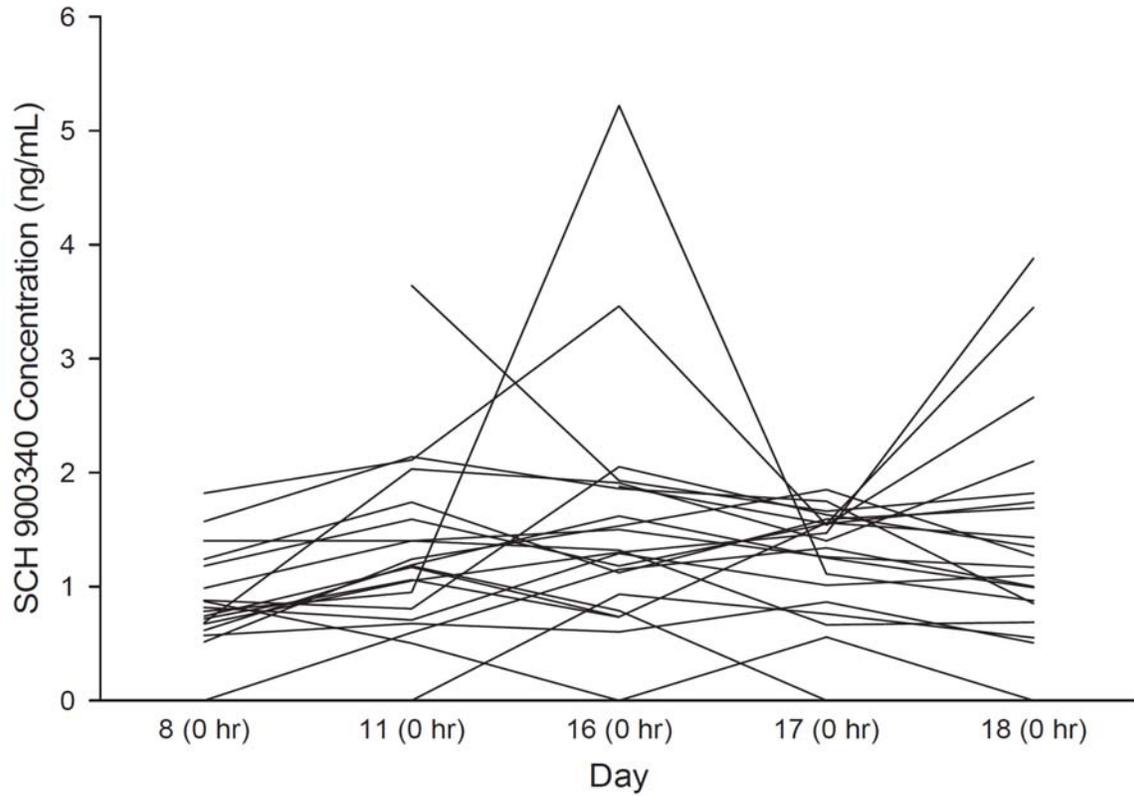
CV = coefficient of variation.

After a single topical application on Day 1, the mean C_{max} in plasma was 3.54 ng/mL. The mean C_{max} increased to 5.17 ng/mL on Day 18 following multiple daily applications. Similarly, the mean AUC_{last} of 44.4 ng*hr/mL on Day 1 increased to a mean AUC_{τ} of 75.8 ng*hr/mL on Day 18. The accumulation ratio based on AUC was 2.22. The mean half-life of 7.68 hours (range 5.72 to 10.3 hours) on Day 1 was based on 4 subjects who had available data. The mean half-life of 28.5 hours (range 14.7 to 47.9 hours) on Day 18 was based on 10 subjects who had available data. The applicant concluded that the longer half-life was probably due to more quantifiable samples on Day 18 and a longer plasma sample collection interval. The mean plasma tavaborole concentration-time profiles following single and multiple once daily topical applications of tavaborole in this trial is shown in Figure 4.

Reviewer's comments:

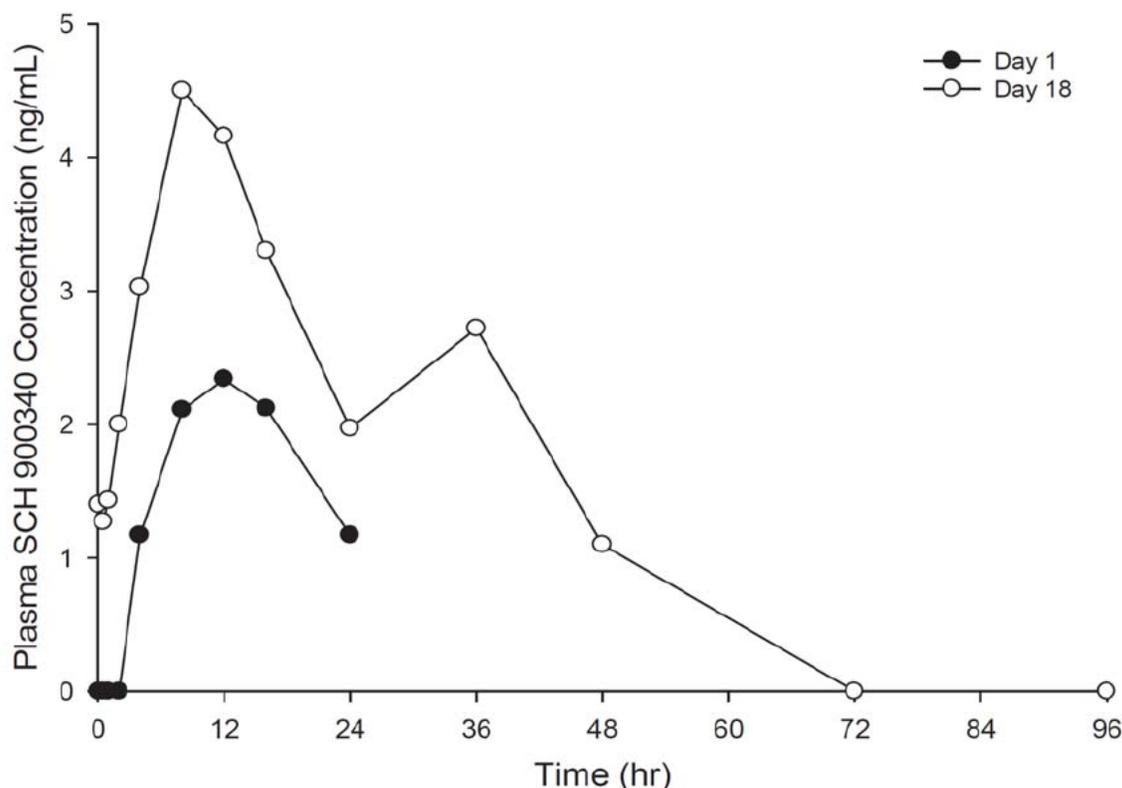
Since the sampling time is longer on Day 18 (at 36, 48, and 72 hours post dose) than on Day 1 (only till 24 hours post dose), the elimination phase of tavaborole was better captured on Day 18 thus the mean half-life calculated from Day 18 is longer than the mean half-life from Day 1. In addition, more subjects had concentrations above LLOQ due to accumulation on Day 18. Therefore, the mean half-life of 28.5 hours from Day 18 would be more representative as the true half-life of tavaborole applied topically.

Figure 3: Predose Plasma Tavaborole Concentrations Following Multiple Once-Daily Topical Applications of 200 μ L of 5% Solution of Tavaborole to All Ten Toenails and 2 mm of Skin Surrounding Each Toenail of Onychomycosis Patients (Individual Predose Profiles)



* Figure is from sponsor's clinical report.

Figure 4: Mean Plasma Tavaborole Concentrations-Time Profiles Following Single (Day 1) and Multiple (Day 18) Once-Daily Topical Applications of 200 μ L of 5% Solution of Tavaborole to All Ten Toenails and 2 mm of Skin Surrounding Each Toenail of Onychomycosis Patients (Linear: Linear)



* Figure is from sponsor's clinical report.

Metabolite profiling:

Plasma samples were pooled for 0-24 hours on Day 1 and 18 across all subjects to assess relative AUC of the parent drug and metabolites. 300 μ L of plasma from each subject was pooled on Day 1 predose to serve as control. For urine samples, except 4 subjects (Subjects 118, 122, 123, and 124) who was not collected for the first 10 hours postdose, all remaining subjects were pooled by combining 0.1% urine weight excreted from each subject during the 0-24 hour time interval on Day 1 or Day 18. 3% urine weight from each subject was pooled predose to serve as control.

For the parent drug, the pooled plasma concentration was below LLOQ on both Day 1 and Day 18. It was not detected in pooled urine sample as well. For the metabolites, trace levels of a sulfate conjugate (M5) and a benzoic acid metabolite (M6a) were detected on Day 18 in the pooled plasma. M5 and M6a were also detected as the only metabolites in the pooled urine sample in both Day 1 and Day 18. Only qualitative assessment was conducted for metabolite profiling.

Reviewer's comments:

From the plasma PK result for tavaborole, the mean C_{max} was 3.54 ng/mL on Day 1 and 5.17 ng/mL on Day 18. In addition, almost all concentrations from each individual at all

time points between 0 and 24 hours on Day 18 were above LLOQ, except 3 subjects at 0.5 and 1 hr, 2 subjects at 2 and 4 hr, and 1 subject at 8 hr post-dose. However, in the summary report for metabolite profiling, the applicant stated that the pooled parent drug plasma concentration was below LLOQ on both Day 1 and Day 18. It is not clear why tavorole concentrations of each individual on Day 18 were detectable but the pooled tavorole concentration was below LLOQ on Day 18.

For the urine concentration of tavorole, the validation report indicated that the stability at -20°C could not be established. The reason was that at 41 days, the lower QC sample exceeded 15%, however, at 95 days, all three QC samples (low, mid, and high) were below 15%, and at 188 days, all three QC samples exceeded 15%. The specimen handling and shipping instructions in the protocol stated that after urine collection, the acidified urine will be immediately frozen to -20°C, but it is not clear from the bioanalytical report on the storage condition and storage period before analysis. Therefore, the urine concentration of tavorole is not reliable and maybe there were tavorole present in the urine. However, the amount of tavorole in urine is probably not significant, and the reason is as follows. In the AME trial (Trial P05577), plasma tavaorable/plasma total radioactivity was 0.146, indicating extensive metabolism. The mean cumulative total radioactivity excreted in urine over a 10 days period was 17.9% of the administered dose. M5, the only metabolite identified in urine in this trial, represented 14.6% of the administered dose. Three other minor metabolites represented as less than 1%. Therefore, even if tavorole, the parent drug, is still in urine, it would be less than 1.7% ($17.9\% - 1\% - 14.6\% = 1.7\%$).

For the metabolites in both plasma and urine, the sponsor indicated that these metabolites were only assessed qualitatively and not quantified, and there were no bioanalytical or validation reports for assessment of metabolites in this trial.

Summary of Safety:

According to the sponsor, Treatment-emergent AEs were reported in 50% (12/24) of subjects, and the only TEAEs that were reported in more than one subject were headache (3 subjects, 13%) and oropharyngeal pain (2 subjects, 8%). All reported TEAEs were mild in severity, except for a TEAE of severe chest pain, which was serious and determined by the investigator to be unlikely related to treatment. There were 2 application site reactions reported in this trial. No deaths were reported.

Reviewer's comments: For further information on drug safety, please see review by Medical Officer Dr. Milena Lolic.

Demographic:

SCH900340 5%
Single/Multiple
Doses Combined

n=24

Sex (n,%)	
Female	8 (33)
Male	16 (67)
Race (n,%)	
White	19 (79)
Non-White	5 (21)
Black or African American	5 (21)
Ethnicity (n,%)	
Hispanic or Latino	3 (13)
Not Hispanic or Latino	21 (88)
Age (yrs)	
Mean (SD)	51.0 (12.3)
Median	51.0
Range	28 - 82
Age (n,%)	
18 - <65	23 (96)
65 or Older	1 (4)
Weight (kg)	
Mean (SD)	97.24 (21.46)
Median	94.15
Range	65.0 - 141.5
Height (cm)	
Mean (SD)	175.08 (10.04)
Median	172.95
Range	157.5 - 195.0
Elbow Breadth (cm)	
Mean (SD)	6.75 (0.81)
Median	6.85
Range	5.5 - 8.5

Applicant's Conclusion:

In this trial, following a single dose application of 5% tavaborole to all ten toenails and 2 mm of skin surrounding each toenail of subjects with distal subungual onychomycosis, the mean terminal $t_{1/2}$ of the parent compound was 7.68 hours on Day 1. Following multiple once-daily dose applications, the mean terminal $t_{1/2}$ of the parent compound was 28.5 hours on Day 18. The accumulation ratio of AUC for tavaborole was 2.22 after daily topical application of tavaborole. The terminal $t_{1/2}$ values at Day 1 and Day 18 were each difficult to assess as more than half of the pharmacokinetic profiles did not have sufficient concentrations to meet the criteria for inclusion in the terminal $t_{1/2}$ portion of the analysis and concentrations were often near the LLOQ. Tavaborole plasma concentrations appeared to be at steady-state by Day 18. Although the inter- and intra-subject variability in plasma concentrations of tavaborole remained high, generally the mean predose plasma concentrations did not appear to change from Day 11 onward. The increase of terminal half-life at steady state was most likely due to more values being

above LLOQ as a result of accumulation and a longer sampling time (24 hr on Day 1 vs 96 hr on Day 18).

At steady state, a sulfate-conjugate (M5) and a benzoic acid metabolite (M6a) were the only circulating drug-derived components detected in trace levels in human plasma. M5 was the major urinary metabolite detected in human urine. Thus it is suggested that the compound is systemically available and is slowly absorbed.

Reviewer's Comments:

The applicant's conclusion is acceptable.

Trial No. AN2690-ONYC-102

Title: A Randomized, Crossover Study in Healthy Subjects, of the Effects of Tavaborole Topical Solution, 5% on QT/QTc Intervals, with Moxifloxacin Positive Control.

Note: Tavaborole is referred as AN2690 in this section.

Trial Initiation/Completion Dates: 4/18/2012 to 8/15/2012

Objectives:

Primary objectives:

- To assess the electrocardiographic (ECG) effects of tavaborole following multiple-dose administration of Tavaborole Topical Solution, 5% relative to solution vehicle in healthy adult male and female subjects.

Secondary objectives:

- To assess the safety and tolerability of therapeutic and suprathreshold doses of Tavaborole Topical Solution, 5% when administered for 14 days to healthy adult male and female subjects.

Trial Center:

[REDACTED] (b) (4)

Supply of drugs:

Tavaborole Topical Solution, 5% (lot no. EAF-C) and solution vehicle for tavaborole (lot no. CKN-C) were supplied by Anacor (manufactured by [REDACTED] (b) (4) [REDACTED]) as 10 mL bottles, with 0.6 cc glass droppers.

Moxifloxacin hydrochloride (Avelox®) 400 mg tablets (lot no. 54025X4)

Design of Trial:

A total of 55 healthy volunteers were randomized to one of eight sequences with the following four study treatments:

- Vehicle (V): Solution vehicle for tavaborole QD on all 10 toenails for 14 days
- Positive Control (PC): Solution vehicle for tavaborole QD on all 10 toenails for 14 days, plus a single dose of unblinded moxifloxacin 400 mg administered orally in the morning on Day 14 under fasted conditions
- Therapeutic Dose (DT): Tavaborole Topical Solution, 5% QD on all 10 toenails for 14 days (nail plates only)
- Suprathreshold Dose (DS): Tavaborole Topical Solution, 5% twice daily (BID, defined as every 12 hours) on all 10 toenails and 10 fingernails and approximately 5 mm of skin surrounding all nails for 14 days

This trial included a screening period (within 20 days of admission) and four in-patient treatment periods of 16 days each, separated by three washout periods of at least 7 days each. The dosing regimens are shown in Table 11.

Table 11: Dosing Regimens

Study Treatment	Morning Dose		Evening Dose	
	Days 1-13	Day 14	Days 1-13	Day 14
Vehicle (V)	Solution vehicle for AN2690 to 10 toenails	Solution vehicle for AN2690 to 10 toenails	NA	NA
Positive Control (PC)	Solution vehicle for AN2690 to 10 toenails	Solution vehicle for AN2690 to 10 toenails	NA	NA
AND				
		Moxifloxacin 400 mg orally (following minimum 8-hour fast)		
Therapeutic Dose (DT)	AN2690 Topical Solution, 5% to 10 toenails	AN2690 Topical Solution, 5% to 10 toenails	NA	NA
Supra-therapeutic Dose (DS)	AN2690 Topical Solution, 5% to 10 toenails, and approximately 5 mm skin surrounding all nails	AN2690 Topical Solution, 5% to 10 toenails, and approximately 5 mm skin surrounding all nails	AN2690 Topical Solution, 5% to 10 toenails, and approximately 5 mm skin surrounding all nails	AN2690 Topical Solution, 5% to 10 toenails, and approximately 5 mm skin surrounding all nails

NA, not applicable.

Note: Morning and evening doses for the suprathematic dose treatment was administered twice daily approximately 12 hours apart.

PK blood samples were assessed on Day 14 of each treatment period at pre-dose (trough level; approximately 5 minutes pre-dose) and 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, and 23 hours post dose.

This trial is reviewed by the medical reviewer, Dr. Melina Lolic, and the Interdisciplinary Review Team for QT Studies (IRT-QT). This reviewer will discuss only the PK results in this trial.

Analytical Methods:

See Question-Based-Review Section 2.6.1.

Table 12: Analytical Method Validation

Assay Method	High-performance liquid chromatography with tandem mass spectrometry
Analytical Site	(b) (4)
Compound	Tavaborole in human plasma samples (sodium citrate as anticoagulant and 6% citric acid as a preservative)
Standard Curve Range	0.5 to 50 ng/mL
Lower Limit of Quantitation (LLOQ)	0.500 ng/mL
Average Recovery of Drug	72.5% (Internal standard: 72.7%)
Intra-Day Accuracy	1.5-40.0 ng/mL: range: 94.67-99.875% 0.5 ng/mL (LLOQ): range: 109.2-118.6%
Inter-Day Accuracy	1.5-40.0 ng/mL: 96-97.75% 0.5 ng/mL (LLOQ): 112.8%
Intra-Day Precision Range	1.5-40.0 ng/mL: 1.89-6.90% 0.5 ng/mL (LLOQ): 3.42-15.3%
Inter-Day Precision Range	1.5-40.0 ng/mL: 3.08-5.54% 0.5 ng/mL (LLOQ): 10.6%
Freeze-Thaw Stability ^a	4 cycles
Bench-Top Stability ^a	24 hours (human citrate plasma at room temperature)
Processed Stability	5 days
Long Term Stability	95 days (-70°C) <i>The trial initiated on 4/18/2012 and completed on 8/15/2012, and the sample analysis date was between 6/4/2012 to 9/5/2012. In the response to the information request dated 10/1/2013, the applicant indicated that the duration of pharmacokinetic plasma samples storage, from sample collection to sample analysis, did not exceed 85 days.</i>
Selectivity	Six lots were tested for specificity by extracting and analyzing one matrix blank from each lot with a freshly prepared standard curve. At 0.5 ng/mL(LLOQ), the % deviation ranges from -10.6 to 22.8% (one sample was more than 20%)
Reviewer's comments	Method acceptable

^a: values from sponsor's report IND0009736 and INT00118571, which were the same reports used for maximal use PK trial.

Protocol Deviations:

Five subjects (Subject S004, S050, S067, S072, and S103) were withdrawn from trial due to reasons such as illegal drug use or behavior issues. One subject (Subject S116) was administered the wrong study drug for 5 of 28 doses during Period 4 (tavaborole suprathapeutic treatment). The data of Subject S116 were excluded from ECG and PK analyses for the suprathapeutic treatment. Subject S116 was included in statistical analysis for the remaining treatment periods (vehicle, positive control, and therapeutic dose).

Pharmacokinetic Results:

Fifty-one (51) subjects were included in the PK-PD (ECG) Analysis Population. The four subjects (Subjects S050, S080, S099, and S103) excluded from the PK-PD Analysis Population were missing tavorole plasma concentrations. One subject (Subject S116) was included in PK analysis for therapeutic treatment but not for suprathapeutic treatment (reason see above section), and two subjects (Subjects S041 and S072) were included in PK analysis for suprathapeutic treatment but not for therapeutic treatment because they did not complete dosing. As a result, 49 subjects had data available for PK analysis of tavorole therapeutic treatment and 50 subjects had data available for PK analysis of tavorole suprathapeutic treatment.

Following multiple topical applications of tavorole solution, tavorole was absorbed into the systemic circulation from both therapeutic and suprathapeutic doses. For the therapeutic dose and suprathapeutic dose, the mean C_{max} was 1.63 ± 0.958 ng/mL and 22.4 ± 14.3 ng/mL, respectively; the mean T_{max} was 13.9 ± 5.32 hours and 10.3 ± 6.94 hours, respectively; the mean $AUC_{(0-last)}$ was 20.5 ± 13.2 ng·h/mL and 263 ± 141 ng·h/mL, respectively. The mean C_{max} ratios following suprathapeutic dose relative to therapeutic dose ranged from 9.54 to 21.0 across sequences. Corresponding mean $AUC_{(0-last)}$ ratios ranged from 9.17 to 22.3. Pharmacokinetic parameters for therapeutic and suprathapeutic doses of tavorole are summarized in Table 13. The mean tavorole plasma concentration-time profiles are shown in Figure 4. There were no significant differences in tavorole C_{max} and $AUC_{(0-last)}$ values among the eight sequences following the suprathapeutic dose with p-value >0.05 (Figure 6 and Figure 7).

The applicant did not calculate half-life by stating there were not enough data in the majority of subjects.

Table 13: Summary of Tavaborole Plasma PK Parameters in Human Subjects in Sequences 1 Through 8 Following 14 Days of Multiple Topical Applications of Tavaborole at Therapeutic and Supratherapeutic Doses (PK Analysis Population)

PK Parameter	Treatment Sequence (Seq)							
	Seq 1 (N=6)	Seq 2 (N=6-7) ^a	Seq 3 (N=6)	Seq 4 (N=6)	Seq 5 (N=6)	Seq 6 (N=5-6) ^b	Seq 7 (N=7)	Seq 8 (N=6-7) ^c
Therapeutic Dose								
	Mean (Standard Deviation)							
C _{max} (ng/mL)	1.81 (0.481)	2.04 (1.70)	1.59 (0.879)	1.29 (0.942)	1.97 (1.18)	1.80 (1.12)	1.45 (0.566)	1.11 (0.433)
T _{max} (hour)	16.1 (2.45)	14.1 (4.14)	12.9 (4.75)	10.9 (7.57)	11.1 (5.68)	14.1 (7.39)	14.4 (6.60)	14.7 (6.62)
AUC _(0-last) (ng•h/mL)	22.5 (10.6)	27.1 (18.0)	19.7 (11.0)	17.8 (13.8)	24.0 (14.8)	21.5 (18.0)	20.9 (11.9)	11.5 (6.90)
Supratherapeutic Dose								
	Mean (Standard Deviation)							
C _{max} (ng/mL)	19.8 (11.3)	24.7 (24.1)	33.4 (15.3)	23.3 (12.2)	18.8 (7.93)	21.1 (15.5)	17.0 (8.54)	21.7 (13.6)
T _{max} (hour)	14.1 (6.32)	9.96 (7.69)	14.5 (6.20)	5.45 (5.46)	5.10 (6.10)	10.1 (7.77)	18.1 (15.1)	9.77 (8.64)
AUC _(0-last) (ng•h/mL)	251 (69.8)	273 (179)	392 (197)	265 (170)	220 (96.6)	217 (94.3)	234 (113)	256 (155)
Mean C _{max} Ratio ^d	10.9	12.1	21.0	18.1	9.54	11.7	11.7	19.5
Mean AUC _(0-last) Ratio ^e	11.2	10.1	19.9	14.9	9.17	10.1	11.2	22.3

DS, supratherapeutic dose; DT, therapeutic dose; PC, positive control; PK, pharmacokinetic; Seq, sequence; V, vehicle.

Seq 1: DT, DS, V, PC; Seq 2: DS, PC, DT, V; Seq 3: V, DT, PC, DS; Seq 4: PC, V, DS, DT; Seq 5: DS, V, DT, PC; Seq 6: V, PC, DS, DT; Seq 7: DT, DS, PC, V; Seq 8: PC, DT, V, DS.

a DT (N=6) and DS (N=7).

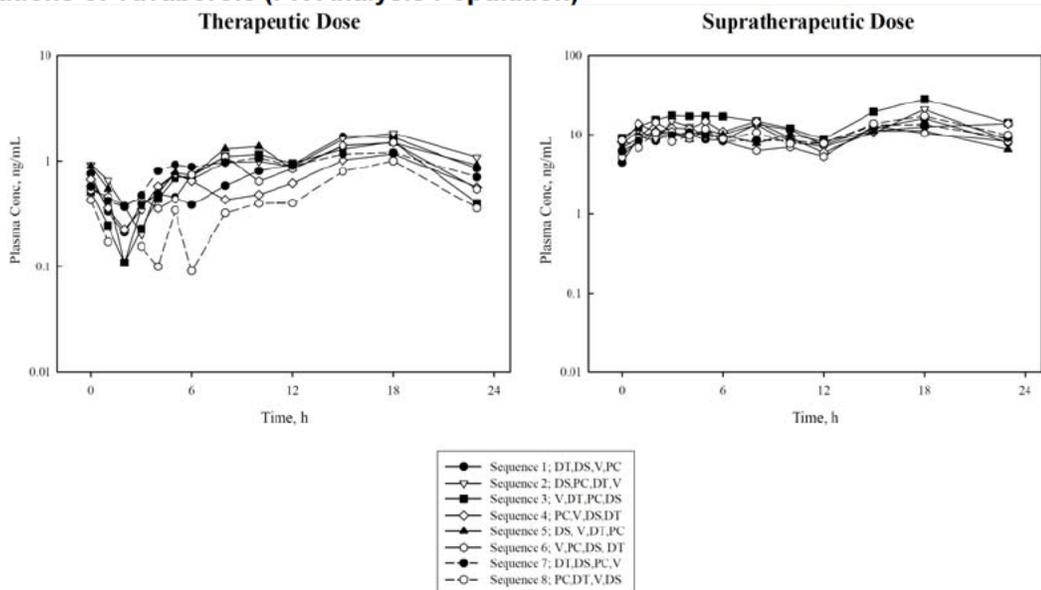
b DT (N=5) and DS (N=6).

c DT (N=7) and DS (N=6).

d AN2690 mean C_{max} at DS/AN2690 mean C_{max} at DT.

e AN2690 mean AUC_(0-last) at DS/AN2690 mean AUC_(0-last) at DT.

Figure 5: Semi-Logarithmic Plot Mean Plasma Concentration-Time Profiles of Tavaborole in Human Subjects in Sequences 1 Through 8 Following 14 Days of Multiple Topical Applications of Tavaborole (PK Analysis Population)

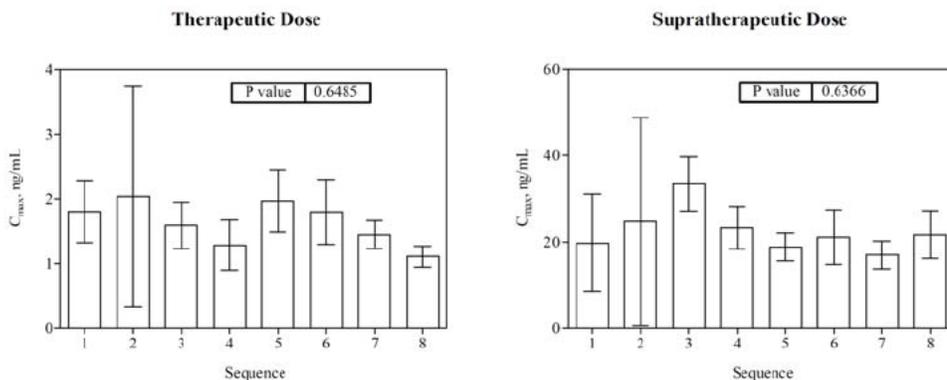


(b) (4)

Source: [Pharmacokinetics Report, Figure 2 \(Appendix 16.5\)](#)

DS, suprathematic dose; DT, therapeutic dose; PC, positive control; PK, pharmacokinetic; V, vehicle.

Figure 6: Mean and Standard Deviation C_{max} of Tavaborole in Human Subjects in Sequences 1 Through 8 Following 14 Days of Multiple Topical Applications of Tavaborole (PK Analysis Population)



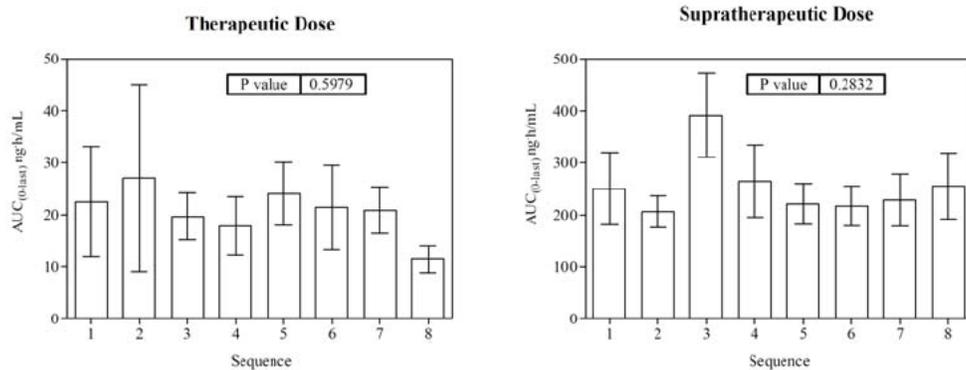
(b) (4)

Source: [Pharmacokinetics Report, Figure 3 \(Appendix 16.5\)](#)

Sequence 1: DT, DS, V, PC; Sequence 2: DS, PC, DT, V; Sequence 3: V, DT, PC, DS; Sequence 4: PC, V, DS, DT; Sequence 5: DS, V, DT, PC; Sequence 6: V, PC, DS, DT; Sequence 7: DT, DS, PC, V; Sequence 8: PC, DT, V, DS.

C_{max} , maximum observed plasma concentration; DS, suprathematic dose; DT, therapeutic dose; PC, positive control; PK, pharmacokinetic; V, vehicle.

Figure 7: Mean and Standard Deviation $AUC_{(0-last)}$ of Tavaborole in Human Subjects in Sequences 1 Through 8 Following 14 Days of Multiple Topical Applications of Tavaborole (PK Analysis Population)



Source (b) (4) Pharmacokinetics Report, Figure 4 (Appendix 16.5)

Sequence 1: DT, DS, V, PC; Sequence 2: DS, PC, DT, V; Sequence 3: V, DT, PC, DS; Sequence 4: PC, V, DS, DT; Sequence 5: DS, V, DT, PC; Sequence 6: V, PC, DS, DT; Sequence 7: DT, DS, PC, V; Sequence 8: PC, DT, V, DS

$AUC_{(0-last)}$, area under the plasma concentration-time curve from hour 0 to the last measurable concentration; DS, supratherapeutic dose; DT, therapeutic dose; PC, positive control; PK, pharmacokinetic; V, vehicle.

TQT results:

According to the review by QT-IRT reviewer Dr. Moh Jee Ng, no significant QTc prolongation effects of tavaborole (doses of tropical solution, 5% q.d. and tropical solution, 5% b.i.d.) were detected in this TQT trial.

(See review in DARRTS dated 11/12/2013).

Reviewer's comments:

Following topical administration of Tavaborole Topical Solution, 5% twice daily on all 10 toenails and 10 fingernails and approximately 5 mm of skin surrounding all nails for 14 days, the mean C_{max} was 22.4 ± 14.3 ng/mL. Compared to the C_{max} of 5.17 ng/mL in the maximal use PK trial P06118 after 14 continuous days of once-daily dosing, the C_{max} obtained from supratherapeutic dose of this TQT trial was 4.33-times higher (range: 3.3-times to 6.5-times). The dose in this TQT trial was considered appropriate. With the supratherapeutic dose achieving a C_{max} 4.3-times higher than the C_{max} observed in the maximal use PK trial, tavaborole does not prolong QTc to any clinically relevant extent.

Trial No. 002-CLN PK-005-01(P05577)

Title: Absorption, Metabolism, and Excretion of ¹⁴C- Tavaborole When Administered as a 5% Topical Solution in Healthy Adult Male Subjects

Note: Tavaborole is referred as SCH 900340 in this section.

Summary:

Six healthy adult male volunteers (19-35 years of age) were included in this study. A single topical application of ¹⁴C- tavaborole (a total of ~200 µL containing a total of ~100 µCi radioactivity) was applied to all 10 toenails and 5 mm of the surrounding skin of each toe. The ¹⁴C- tavaborole was allowed to dry and remain on the toenails and skin for 6 hours post-administration. A study center designee then wiped the solution from each toenail (and surrounding skin) with a water-wetted absorbent pad for five times with a total of five separate wipes per toe. Next, a cotton-tipped applicator was used to swipe (and dry) each toenail and surrounding skin. The cotton-tipped applicator will then be analyzed by the site for radioactivity.

At 24-hours post-administration, a study center designee wiped each toenail (and surrounding skin) with an ethanol-wetted absorbent pad five times with a total of five separate wipes per toe. Next, a cotton-tipped applicator was used to swipe (and dry) each toenail and surrounding skin. The cotton-tipped applicator was then analyzed by the site for radioactivity. Starting on Day 3, pooled urine samples were assayed for radioactivity on a daily basis.

Blood samples (17 mL) for determination of whole blood and plasma radioactivity and plasma tavaborole concentration were collected at the following times: predose at (0 hour) and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hours postdose. Blood samples (8 mL) for possible metabolite profiling were collected at the following time points: 0 (predose), 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 hours postdose. Urine (block) samples were collected prior to dose (0 hour) and then in block collections at 0 to 12, 12 to 24, 24 to 36, 36 to 48, and then every 24 hours until discharge from the study. Selected samples were analyzed, if feasible, for metabolite profiling.

The pharmacokinetic results are as follows:

Parameter	¹⁴ C-SCH900340, 5% Topical (200 µL), 100 µCi Radioactivity n=6							
	Plasma SCH 900340		Plasma Total Radioactivity		Blood Total Radioactivity		Urine Total Radioactivity	
	Units	Mean (CV%)	Units	Mean (CV%)	Units	Mean (CV%)	Units	Mean (CV%)
Tmax ^a	hours	24.0 (24.0-24.0)	hours	24.0 (24.0-24.0)	hours	24.0 (24.0-24.0) ^b	NA	NA
Cmax	ng/mL	1.35 (22)	ng equiv/g	9.24 (20)	ng equiv/g	3.17 (111) ^c	NA	NA
Ae(%Dose)	NA	NA	NA	NA	NA	NA	%	17.9 (16)
Ae(%DoseEff) ^d	NA	NA	NA	NA	NA	NA	%	29.0 (6)

Ae(%Dose) = cumulative amount excreted in urine from 0 to 240 hours postdose, expressed as a percent of the administered radioactive dose; Ae(%DoseEff) = cumulative amount excreted in urine from 0 to 240 hours postdose, expressed as a percent of the effective radioactive dose; Cmax = maximum observed plasma concentration; CV% = coefficient of variation, expressed as a percent; n = number; NA = not applicable; Tmax = time to maximum observed plasma concentration

a: Median and range reported instead of mean and CV%

b: n=3

c: Three of the six subjects had Cmax data of 0.00 ng equiv/g for blood total radioactivity.

d: The effective dose was calculated by subtracting the dose that was removed by wiping the nail and surrounding skin, beginning at 6 hours post application, from the dose administered.

Only 10 out of a total of 66 plasma samples were above the LLOQ (0.5 ng/mL). No other PK parameters for plasma tavorole were calculated. For the plasma total radioactivity and blood total radioactivity, three subjects had blood total radioactivity values less than the LLOQ (1.94 ng equiv/mL) at all times. The ratio of C_{max} for plasma tavorole/plasma total radioactivity was approximately 0.146, indicating extensive metabolism and that the systemic exposure to tavorole was approximately 15% of the exposure to plasma total radioactivity.

The mean cumulative total radioactivity excreted in urine over a 10 day period was 17.9% of the administered dose and 29.0% of the effective dose. The total radioactivity levels in all the fecal samples were less than the LLOQ (2.58 ng equiv/mL) in all the subjects. Thus, tavorole derived radioactivity was primarily excreted in the urine.

A sulfate-conjugate (M5), which was previously detected in the rat and mouse, was the only metabolite identified in urine samples in this study. Due to insufficient levels of radiocarbon, metabolite profiling was not performed on plasma and fecal samples.

Profiling and Characterization of Metabolites

Urine samples were pooled across time points (0-120 hr) and used for metabolite profiling. There was not enough radiocarbon present in plasma or fecal samples for profiling of metabolites using liquid chromatography-mass spectrometry (LC-MS) with in-line flow scintillation analysis (FSA) or off-line microplate scintillation counter detection. Urine was acidified immediately upon collection by adding approximately 40 µL of 85% H₃PO₄ per 1 mL of sample. Plasma was acidified upon separation from blood. The samples were stored at -20 ± 10°C until processing and analysis for metabolites.

Based on the relative amount (peak area contribution to total radioactivity unless otherwise stated) of each metabolite, urinary excretion was expressed as a percent of nominal dose (98 μ Ci), calculated as follows:

Amount of Metabolite (% of Dose) = Fraction of HPLC Column Recovery x % total chromatographic radioactivity (%TCR) of metabolite x Fraction of average radioactivity excreted in the collection interval achieving greater than 90% of the total drug-related material excreted by each subject.

A sulfate-conjugate (M5) of a benzyl alcohol metabolite (M6) was the only metabolite identified in human urine. The amount of M5 excreted during 0-120 hr post-dose represented 14.6% of the nominal dose applied topically. Three minor metabolites representing less than 1% of the dose were also observed in the radiochromatogram of 0-120-hr pooled urine but they could not be detected by LC-MS and thus were not identified.

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

/s/

AN-CHI LU
03/04/2014

DOANH C TRAN
03/04/2014

HAE YOUNG AHN
03/06/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 204427 Applicant: Anacor

Stamp Date: 7/29/2013

**Drug Name: Tavaborole NDA/BLA Type: Original NDA
Topical Solution, 5%**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			AME trial P05577 to characterize the absorption, metabolism, and excretion of ¹⁴ C-tavaborole following topical administration. No in vivo drug-drug interaction information was provided. In vitro inhibition/induction information was provided. CYP enzymes tested for induction were CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5, and the enzymes tested for inhibition were CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5
Criteria for Assessing Quality of an NDA					
Data					
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	X			
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	X			
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			X	
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	The applicant requested a waiver of pediatric data in children ages <input type="text" value="C"/> years and a deferral of submission of data for use of Tavaborole Topical Solution, 5% in children ages <input type="text" value="C"/> years.

10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	X			
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X			
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	X			
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
17	Was the translation from another language important or needed for publication?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology 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.

See end of filing memorandum.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

*Office of Clinical Pharmacology
New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
NDA Number	204427	Brand Name	To-be-determined
OCP Division	Division of Clinical Pharmacology 3	Generic Name	Tavaborole
Medical Division	Division of Dermatology and Dental Product	Drug Class	Antifungal agent
OCP Primary Reviewer	An-Chi Lu, M.S., Pharm.D.	Indication(s)	Onychomycosis COP
OCP Secondary Reviewer	Doanh Tran, R.Ph., Ph.D	Dosage Form	Solution, 5% w/w YRI
		Dosing Regimen	Once daily
Date of Submission	7/26/2013	Route of Administration	Topical
Estimated Due Date of OCP Review		Sponsor	Anacor
PDUFA Due Date	7/29/2014	Priority Classification	Standard
Division Due Date	3/7/2014		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	1		Safety and PK (QT/QTc) trial AN2690-ONYC-102
Patients-				
single dose:				
multiple dose:	X	3		PK trial P06118 PK trial AN2690-ONYC-202 PK trial AN2690-ONYC-205
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				

Phase 2:	X	3		AN2690- ONYC-200/200A AN2690- ONYC-201 AN2690-ONYC-203
Phase 3:	X	2		AN2690-ONYC-301 AN2690-ONYC-302
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	Systemic availability of tavaborole topical solution			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Filing Memorandum

Clinical Pharmacology Review

NDA: 204427
Compound: Tavaborole Topical Solution, 5%
Sponsor: Anacor

Date: 7/26/2013
Reviewer: An-Chi Lu

Background:

Anacor Pharmaceuticals, Inc. is submitting a New Drug Application (NDA 204-427) for Tavaborole Topical Solution, 5% under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and under the provisions of Title 21CFR§314.50. This application is subject to “The Program” under PDUFA V agreement.

The proposed new drug product, Tavaborole Topical Solution, 5%, is an antifungal agent, and is indicated for the treatment of patients with onychomycosis COPYRIGHT. The proposed dosage and administration is to apply to affected nails once daily for 48 weeks. It should be applied to the entire nail surface and under the tip of each nail being treated.

Clinical development program:

The clinical development program for Tavaborole Topical Solution included a total of 12 clinical trials, and among which 4 were conducted in healthy subjects, 6 were in subjects with distal subungual onychomycosis, 2 were in subjects with moderate to severe onychomycosis.

A total of 3 pharmacokinetics (PK) trials were conducted: 1 multiple dose maximal use PK trial in subjects with distal subungual onychomycosis (P06118) and 2 multiple dose trials using 7.5% tavaborole solution in subjects with moderate to severe onychomycosis (AN2690-ONYC-202 and AN2690- ONYC-205). The applicant conducted thorough QTc Trial AN2690-ONYC-102 in healthy subjects dosed under therapeutic and suprathreshold regimens. Both maximal use PK trial (P06118) and thorough QTc trial (AN2690-ONYC-102) used the most sensitive bioanalytical method with the LLOQ (lower limit of quantification) of 0.5 ng/mL.

Maximal use PK trial P06118

This trial was to determine the systemic PK of tavaborole following single and multiple topical once-daily doses in adult subjects with distal subungual onychomycosis involving at least 4 toenails, including at least 1 great toenail. The dosing schedule was a single 200 µL dose of Tavaborole Topical Solution, 5% on Day 1, with 14 continuous days of once-daily dosing on Study Days 5-18 following a 3-day washout. Intensive PK sampling was conducted on Day 1 (single-dose PK) and Day 18 (multiple-dose PK). This trial also

analyzed pharmacodynamic measures of 6 β -hydroxycortisol (6 β -OHC) and free cortisol (FC) in 24-hour urine samples to evaluate the effect of tavorole administration on CYP3A4 activity.

The mean (%CV) plasma PK parameters for tavorole following single (Day 1) and multiple (Day 18, after 14 daily doses) topical applications are shown below:

Parameter	Day 1 (n=21) ^a	Day 18 (n=24)
C _{max} (ng/mL)	3.54 (64)	5.17 (67)
T _{max} ^b (h)	12.0 (4.03-23.9)	8.03 (0.467-24.0)
AUC _{last} (Day 1) or AUC _τ (Day 18) ^c (ng•h/mL)	44.4 (57)	75.8 (59)
t _{1/2} (h)	7.68 (27) ^d	28.5 (37) ^d
R _A	NA	2.22 (64) ^e

AUC_{last}, area under the concentration-time curve from time 0 to the time of the final measurable sample; AUC_τ, area under the concentration-time curve during a dosing interval τ at steady state; C_{max}, maximum observed plasma concentration; NA, not applicable; R_A, accumulation ratio (index); t_{1/2}, terminal-phase half-life; T_{max}, time to maximum observed plasma concentration.

^a Three subjects had all concentrations below LLOQ on Day 1.

^b Median (range) reported.

^c AUCs calculated over a 24-hour interval.

^d n = 4 for Day 1 and n = 10 for Day 18; other subjects did not have sufficient concentrations to meet the criteria for inclusion in the terminal t_{1/2} analysis.

^e n = 21.

Source: Study P06118 CSR, Table 11

Based on the trough concentrations from Study Day 11 (Dosing Day 7) to Day 18 (Dosing Day 14) of 1.20-1.51 ng/mL, mean tavorole plasma concentrations has reached steady state during a 2-week once-daily dosing period.

Thorough QTc Trial AN2690- ONYC-102

This trial was a randomized 4-arm crossover study in healthy subjects to assess the ECG effects of tavorole following multiple-dose administration of Tavorole Topical Solution, 5% relative to vehicle. Subjects were randomized to one of eight sequences with four treatments: vehicle (once daily to all 10 toenails for 14 days), positive control (moxifloxacin 400 mg taken once orally on Day 14), therapeutic dose (Tavorole Topical Solution, 5% once daily to all 10 toenails for 14 days), and Supratherapeutic Dose (Tavorole Topical Solution, 5% twice daily to all 10 toenails and 10 fingernails and approximately 5 mm of surrounding skin for 14 days). Fifty-five healthy volunteers were enrolled and evaluated for ECG analysis, and 51 subjects were evaluable for PK analysis.

The applicant reported that the therapeutic and supratherapeutic tavorole dose groups had no clinically relevant changes in heart rate, QRS duration, cardiac repolarization, and QTc prolongation. PK exposure (C_{max} and AUC_{0-last}) increased with the increase in tavorole dose. Mean C_{max} values ranged from 17.0 ng/mL to 33.4 ng/mL following supratherapeutic dose and 1.11 ng/mL to 2.04 ng/mL following therapeutic dose. Compared to the mean C_{max} of 5.17 ng/mL observed under maximal use conditions after

14 days of daily dose, the C_{max} obtained from supratherapeutic dose of this TQT trial was 3.3-times to 6.5-times higher.

Dose Selection:

Dose selection for pivotal clinical trials and commercialization was chosen based on safety and efficacy results from collective data of three Phase 2 trials: AN2690-ONYC-200/200A, AN2690-ONYC-201, and AN2690-ONYC-203.

Specific population:

Pediatric: The applicant requested a waiver of pediatric data in children ages (b) (4) years and a deferral of submission of data for use of Tavaborole Topical Solution, 5% in children ages (b) (4) years. A protocol synopsis for the trial in pediatric patients aged (b) (4) years was submitted, and the submission of final study report is planned to be in January 2022.

Clinical vs. to-be-marketed formulation:

A total of three tavaborole topical solution formulations were used in the clinical trials. The to-be-marketed formulation was used in the Phase 3 safety and efficacy trials (AN2690-ONYC-301 and AN2690-ONYC-302), the Repeat Insult Patch Test (RIPT)/cumulative irritation trial (AN2690-ONYC-103), the Thorough QTc trial (AN2690-ONYC-102), and the maximal use PK trial (P06118). The second formulation was only used in one Phase 1 trial (P05577), and the third formulation was used in all other Phase 1 and Phase 2 trials. The only difference between these formulations was in the (b) (4).

Method validation:

Tavaborole assay:

Tavaborole concentrations in human citrate plasma were determined using a liquid chromatographic assay with mass spectrometric detection (LC-MS) after application of supported liquid-liquid extraction (SLLE) in the maximal use PK trial P06118. The long term stability of tavaborole in human citrate plasma stored at approximately -20°C was reported to be 39 weeks. The trial initiated on 7/8/2009 and completed on 11/11/2009, and the sample analysis dates were on 8/12/2009 and 11/8/2009-11/9/2009. The method validation report and bioanalysis report for trial P06118 are available for review.

For the Thorough QTc Trial AN2690-ONYC-102, acidified human plasma containing AN2690 are stable for (b) (4). The samples were stored in a freezer (b) (4). The trial initiated on 4/18/2012 and completed on 8/15/2012, and the sample analysis date was between 6/4/2012 to 9/5/2012. The method validation report and bioanalysis report for trial AN2690-ONYC-102 are available for review.

For both of the multiple dose PK trials using 7.5% tavaborole solution in subjects with moderate to severe onychomycosis AN2690-ONYC-202 and AN2690-ONYC-205, long-term storage stability for tavaborole in human plasma was (b) (4). Trial was initiated on 4/26/2006 and completed on 5/9/2007 for Trial AN2690-ONYC-

202, and initiated on 3/14/2007 and completed on 5/11/2007 for Trial AN2690-ONYC-205. The applicant stated that a total of (b) (4) of long-term storage stability was required to cover the storage of the human plasma samples at (b) (4).

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 204427 is fileable.

Comments for sponsor:

For the Thorough QTc Trial AN2690-ONYC-102, provide the duration of pharmacokinetic plasma samples storage, from sample collection to sample analysis, to ensure that it is within the available long-term stability of (b) (4)

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/s/

AN-CHI LU
09/06/2013

DOANH C TRAN
09/06/2013