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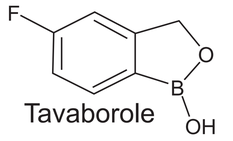

SAFETY AND EFFICACY OF TAVABOROLE (FORMERLY AN2690), A NOVEL BORON-BASED MOLECULE, IN PHASE 2 TRIALS FOR THE TOPICAL TREATMENT OF TOENAIL ONYCHOMYCOSIS

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INTRODUCTION

Onychomycosis is a fungal infection of the nail unit 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.

Current treatment options include oral (PO) and topical drugs. Although PO therapies can provide better efficacy, limitations include drug interactions and systemic adverse effects such as hepatotoxicity and cardiotoxicity. Currently approved topical agents are limited by their relatively lower efficacy, need for adjunctive debridement and removal of prior applications. The difficulty in treating onychomycosis may result from the deep-seated nature of the infection within the anatomically complex nail unit (nail plate, nail bed, and nail matrix) and the inability of some drugs to effectively reach all compartments of the nail unit.

There is a clear need for therapeutic options that are more effective than current topical treatments and safer than systemic (PO) treatments.

AN2690 (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) is a novel oxaborole that inhibits protein synthesis by inhibition of aminoacyl-tRNA synthetase (AARS) via a novel oxaborole-tRNA trapping mechanism.[1] AN2690 demonstrates broad-spectrum antifungal activity against dermatophytes, yeasts, molds, and other filamentous fungi with minimum inhibitory concentration (MIC) values for relevant species in the low microgram-per-milliliter range.[2] 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),[3] making this compound an excellent candidate for topical treatment.

A study of maximum use human exposure concluded that safety margins are ≥10× (range 10× to 285×) across a full range of nonclinical toxicity studies.[2]

INTRODUCTION

To summarize the safety and efficacy data from three Phase 2 trials of tavaborole in the topical treatment of toenail onychomycosis.

TABLE 1. Overview of Tavaborole Phase 2 Studies

	201	203	200
Location	Mexico	US	Mexico and US
Type	Open-label	Open-label	Double-blind dose-ranging
Objectives	Cohorts 1 and 2: Safety and efficacy of 5% and 7.5% concentrations, respectively Cohort 3: Safety and efficacy of 5% solution when dosed daily over a longer period	Safety and efficacy of lower doses and less frequent dosing	Safety and efficacy of various concentrations relative to vehicle Select appropriate concentration for Phase 3
No. of Patients	89	60	187
Dosing	Cohorts 1 and 2: 30 pts dosed QD with 5% for 6 mos 30 pts dosed QD with 7.5% for 6 mos Cohort 3: 29 pts dosed QD for 12 mos	30 pts dosed QD with 1.0% for 6 mos 30 pts dosed QD with 5.0% for 30 d then TIW for 5 mos	Vehicle (63 pts), 2.5% (33 pts), 5% (31 pts), 7.5 (60 pts) QD for 3 mos, then TIW for 3 mos
Dosing Instructions	One or more drops of solution sufficient to cover the affected toenail(s)	One or more drops of solution sufficient to cover the great toenail and all other affected toenails	Apply number of drops sufficient to cover area with thin layer on, under, and around each nail bed being treated
Treatment Duration	6 months for cohorts 1 and 2 12 months for cohort 3	6 months	6 months
Endpoint at 6 months*	Negative culture PLUS at least 2mm clear nail growth or an ISGA of clear or almost clear	Negative culture PLUS at least 2mm clear nail growth or an ISGA of clear or almost clear	Negative culture PLUS at least 2mm clear nail growth or an ISGA of clear or almost clear
Patient Population	Adults with distal, subungual onychomycosis of one great toenail with 20-60% involvement and with demonstrated history of toenail growth of the targeted great toenail	Adults with distal, subungual onychomycosis of at least one great toenail with 20-60% involvement and with demonstrated history of toenail growth of the targeted great toenail	Adults with distal, culture- and KOH-positive subungual onychomycosis of the great toenail with 20% to 60% involvement and with demonstrated history of toenail growth of the targeted toe

METHODS

The key design elements of three Phase 2 clinical trials are shown in Table 1.

Study Designs

Two studies were open-label (Studies 201 & 203), and one was a double-blind, vehicle-controlled dose-ranging trial (Study 200). Mycological assessments (KOH wet mounts and fungal cultures) and clinical assessments (Investigator Static Global Assessment [ISGA] and clear nail growth) were assessed in all studies.

METHODS (CONT)

Dosing

Across the 3 trials, vehicle or tavaborole solution at concentrations of 1%, 2.5%, 5%, or 7.5% was topically administered for 180 or 360 days. In the open-label trials, subjects were instructed to apply one or more drops to cover the affected toenail(s).

In the double-blind trial, patients were instructed to apply the test article on, around, and under the nail plate.

Assessments

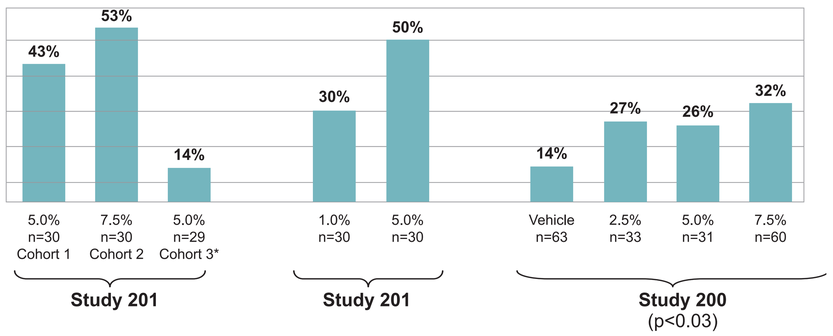
Samples for mycology testing were collected from the area under the tip of the nail.

Treatment response at Day 180 (Studies 203 and 200) or 360 (Study 201, Cohorts 1 & 2) was defined as (a) ≥2 mm of new clear nail growth or an ISGA of clear or almost clear, plus (b) negative fungal culture.

For Study 201 Cohort 3, the primary efficacy endpoint was treatment response at Day 360 defined as (a) clear nail unit, plus (b) negative fungal culture (note that neither clear nail growth nor ISGA of almost clear was considered toward measurement of treatment success in this cohort).

Safety assessments included collection of adverse events (AE), application site reactions, laboratory tests, physical examinations, and vital signs.

FIGURE 1. Subject Response after 6 Months of Treatment



Primary efficacy endpoint of treatment response at Day 180 was defined as (a) ≥2 mm of new clear nail growth or an ISGA of clear or almost clear, plus (b) negative fungal culture.

*For Study 201 Cohort 3, the primary efficacy endpoint was treatment response at Day 360. Six month data for (a) ≥2 mm of new clear nail growth or an ISGA of clear or almost clear, plus (b) negative fungal culture are presented in this figure. The efficacy endpoints for Study 201 Cohort 3 were all anomalously low relative to other tavaborole treatment groups.

RESULTS

To summarize the safety and efficacy data from three Phase 2 trials of tavaborole in the topical treatment of toenail onychomycosis.

Efficacy

Figure 1 shows subject response after 6 months of treatment. In the studies with treatment duration of 180 days, comparable efficacy was seen at Day 180 with concentrations of 2.5%, 5%, and 7.5%.

Figure 2 provides representative photographs of patients who cleared following treatment for 6 months and follow-up for an additional 6 months.

Mycology

Figure 3 shows the time course to achievement of negative culture over time. In most treatment cohorts, >90% of patients achieved negative culture status within the first 2 weeks of treatment and maintained negative culture status for the duration of treatment. Figure 4 shows the time course to achievement of mycological cure over time. Figure 5 shows mean clear nail growth over time.

Safety

Tavaborole was well-tolerated. Most AEs were mild and most were not considered related to study drug. Treatment-emergent AEs occurring in ≥5% of subjects in any dose group regardless of relatedness to study drug were influenza, pharyngitis, tinea pedis, upper respiratory tract infection, tooth abscess, gastroenteritis, and peripheral edema. All 13 serious AEs were considered unrelated to study drug; no serious AE occurred in more than 1 subject. One subject died from an unrelated traumatic head injury.

Topical irritation was the most common adverse effect seen the trials. Application site reactions were generally mild to moderate and reversible.

References

1. Rock FL et al (2007) An antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site. Science 316:1759-61.
2. Data on file. Anacor Pharmaceuticals, Inc.
3. Baker SJ et al (2007) In vitro nail penetration of AN2690, effect of vehicle and coefficient of efficacy. Presented at American Academy of Dermatology 65th Annual Meeting. 2-6 Feb 2007, Washington, DC. Poster available at http://www.anacor.com/pdf/poster_1800.pdf

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FIGURE 2. Patient Photos Showing Clinical Clearance: From Baseline Through 6 Months of Treatment and 6 Months of Follow Up

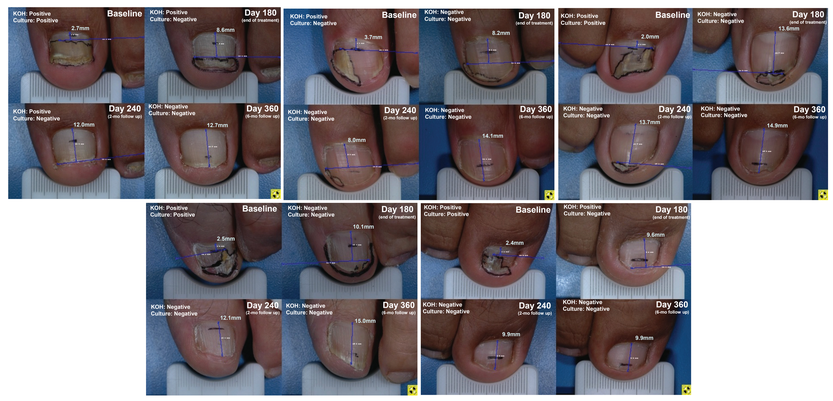


FIGURE 3. % of Patients Achieving Negative Culture Status Over Time

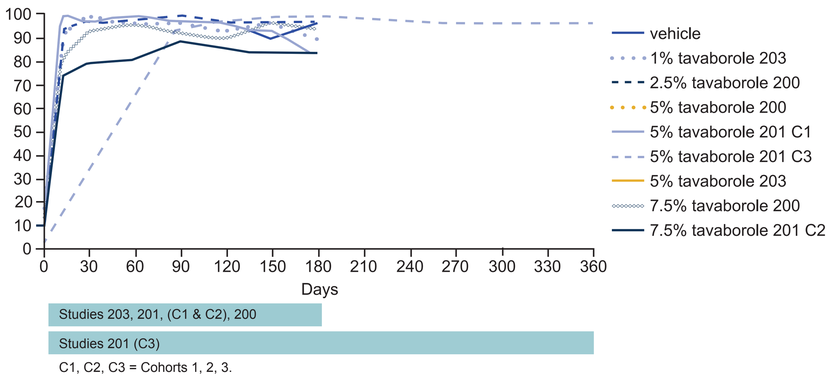


FIGURE 4. % of Patients Achieving Mycological Cure Over Time

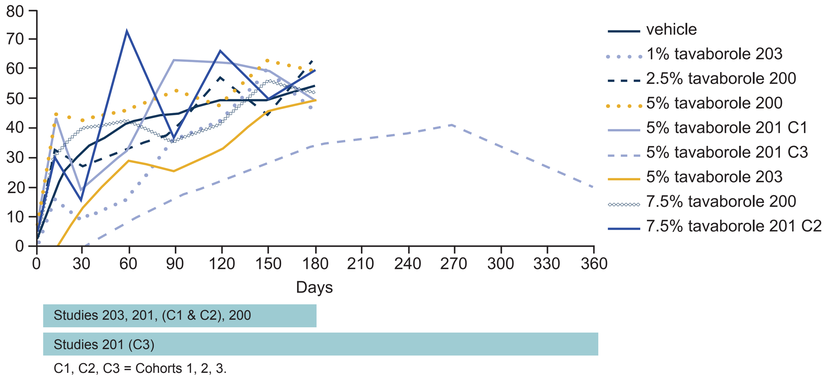
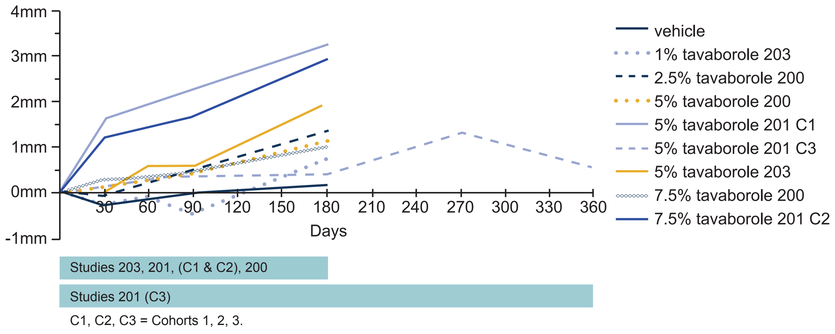


Figure 5. Mean Clear Nail Growth Over Time



CONCLUSIONS

- Tavaborole is a new boron-based molecule well-suited for the treatment of onychomycosis, with a unique mechanism of action, excellent nail penetration, and antifungal activity.
- In the Phase 2 clinical studies of topical tavaborole solution, all concentrations demonstrated a therapeutic effect and a good safety profile.
- In the double-blind, vehicle-controlled trial of 187 patients, tavaborole was significantly more efficacious than vehicle alone ($p<0.03$).
- Across all trials, local irritation was the most common adverse effect.
- Tavaborole Solution, 5% is currently being evaluated in pivotal Phase 3 trials.