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-RNA 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 micromolar-per-milliliter range.2 AN2690 penetrates through the nail plate and achieves concentrations greater than the minimum fungicidal concentrations (MFCs) determined in vitro. The depth 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.4

METHODS

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

Table 1. Overview of Tavaborole Phase 2 Studies

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<thead>
<tr>
<th>Location</th>
<th>201</th>
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<tbody>
<tr>
<td>Mexico</td>
<td>US</td>
<td>Mexico and US</td>
<td></td>
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<tr>
<td>Type</td>
<td>Topical</td>
<td>Double-blind dose-ranging</td>
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**Objectives**

- Cohort 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

**Ant. of Patients**

- Cohort 1: 60
- Cohort 2: 60
- Cohort 3: 60

**Dosing**

- Cohort 1: 30 pts dosed QD with 5% for 6 mos
- Cohort 2: 27% 26%
- Cohort 3: 5.0%

**Dosing instructions**

- 1% tavaborole (vehicle) and 2% tavaborole for 3 mos, then TIW for 6 mos
- Cohort 1: n=30
- Cohort 2: n=30
- Cohort 3: n=30

**Treatment Duration**

- 6 mos
- (2-mo follow up)
- (6-mo follow up)

**Endpoints & assessments**

- Negative culture
- Negative culture or almost clear
- Negative culture or clear
- Negative culture or clear or almost clear

**Patient Population**

- Adults with distal subungal onychomycosis of one great toenail with greater than 20% involvement and with demonstrated history of failed treatment

**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, larynx edema, 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 injury.

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

**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.