EFFECTIVENESS AND SAFETY OF TAVABOROLE, A NOVEL BORON-BASED MOLECULE FOR THE TREATMENT OF ONYCHOMYCOsis: RESULTS FROM TWO PHASE 3 STUDIES

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INTRODUCTION

Onychomycosis is a fungal infection of the nail unit often caused by dermatophytes, which are ubiquitous in the environment. Approximately 14% of the population and as many as 50% of people aged >70 years are afflicted with onychomycosis. Additionally, it has been reported that there is a 20% genetic susceptibility to T. rubrum infection of the nail with a high rate of relapse.

Current treatment options include oral (PO) and topical drugs. Limitations with PO therapies 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.

Difficulty in treating onychomycosis may be due to the deep-seated nature of the infection within the anatomical 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.

Tavaborole (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) is a novel, small, boron-based molecule that inhibits protein synthesis by inhibition of aminocycl-IRNA synthetase (AARS) via a novel oxaborole-IRNA trapping mechanism. Tavaborole demonstrates broad-spectrum antifungal activity against dermatophytes, yeasts, molds, and other filamentous fungi with penetration of the nail plate while retaining its antifungal activity against pathogenic dermatophytes in the presence of keratin.

METHODS

Study Designs

Two identical Phase 3, randomized, double-blind, vehicle-controlled, multi-center, parallel-group studies were conducted. Study 301 enrolled 593 subjects at 33 sites in the US and Mexico; Study 302 enrolled 604 subjects at 42 sites in the US and Canada.

Eligibility

Subjects 18 years and older (no upper age limit) with 20% to 60% involvement of the great toenail (“target great toenail” [TGT]) were randomized 2:1 to Tavaborole Topical Solution, 5% or Vehicle once a day for 48 weeks. To be eligible for inclusion, an affected TGT had to include 3 mm or more of proximal clear nail (measured from the proximal nail fold to the most proximal visible mycotic border) and ≤3 mm distal toenail plate thickness with positive potassium hydroxide (KOH) wet mount and positive fungal culture for dermatophyte.

Intervention

Subjects applied Tavaborole Topical Solution, 5% or Vehicle to the TGT and all other affected toenails once daily (QD) for 48 weeks. Nail debridement was not performed. Removal of product was not required.

Assessments

All subjects were evaluated at Screening, Baseline (Day 1), and at Weeks 2, 6, 12, 18, 24, 30, 36, 42, 48 and Week 52. Each evaluation included a clinical assessment of disease involvement of the TGT. Samples for KOH wet mount and fungal culture were obtained at screening, Weeks 12, 24, 36, 48 and 52, and, if applicable, at Week 60 and/or the Early Termination Visit, as well as any visit at which the TGT was first observed to be Completely Clear Nail (CN) or Almost CN.

Endpoint Definitions

Completely CN: No clinical evidence of onychomycosis as evidenced by a normal toenail plate, no onycholysis, and no subungual hyperkeratosis

Almost CN: No more than minimal evidence of onychomycosis as evidenced by a toenail plate that is dystrophic or discolored over <10% of the distal aspect, with minimally evident onycholysis and subungal hyperkeratosis

Negative Mycology: Negative KOH wet mount and negative fungal culture

RESULTS

In Studies 301 and 302, respectively, enrolled subjects had an age range of 18-88 and 20-81 years; 81.3% and 82.7% were male; and 78.9% and 89.5% were white.

Efficacy

Tavaborole met the primary endpoint and all secondary endpoints in both studies (p<0.001; Table 1). Notably, at week 52, 26.1% and 27.5% of subjects treated with tavaborole in Studies 301 and 302, respectively, achieved Completely CN or Almost CN. In a post hoc analysis conducted, Negative Culture was demonstrated in 87.0% and 85.4% of subjects, respectively.

Illustrative cases of Complete Cure at Week 52 (Figure 1) and Almost CN with Negative Mycology at Week 52 (Figure 2) are shown below.

Safety

Tavaborole was well tolerated with the majority of AEs reported as mild and not considered related to study drug. None of the serious adverse events (SAEs) reported were considered treatment-related.

The rate of treatment discontinuations as a result of AEs was low:

- Study 301: 2.5% for tavaborole, 1.5% for vehicle
- Study 302: 0.8% for tavaborole, 0.5% for vehicle

The incidence of treatment-related AEs was comparable to vehicle. Treatment-related AEs occurring in at least 1% of subjects across both studies included exfoliation, erythema, and dermatitis, all occurring at the application site (Table 2).

CONCLUSIONS

In two Phase 3 studies, once-daily treatment of Tavaborole Topical Solution, 5% was significantly more effective than Vehicle in the treatment of onychomycosis of the toenail in adults meeting primary and secondary endpoints at Week 52 (p<0.001):

- 7-9% of subjects achieved Completely CN and negative mycology
- 26-28% of subjects achieved Completely CN or Almost CN
- 15-18% of subjects achieved Completely CN or Almost CN and negative mycology
- 31-36% of subjects achieved negative mycology
- 85-87% of subjects achieved negative fungal culture at Week 52.

Treatment-related AEs were comparable to Vehicle.

The majority of treatment-related AEs reported in the Tavaborole group were application site AEs of mild to moderate severity.

References


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