ORIGINAL ARTICLE

Efficacy and safety of tavaborole topical solution, 5%, a novel boron-based antifungal agent, for the treatment of toenail onychomycosis: Results from 2 randomized phase-III studies

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Background: Onychomycosis, a fungal nail infection, can impact quality of life.

Objective: We sought to evaluate the efficacy and safety of tavaborole topical solution, 5% for treatment of toenail onychomycosis.

Methods: In 2 phase-III trials, adults with distal subungual onychomycosis affecting 20% to 60% of a target great toenail were randomized 2:1 to tavaborole or vehicle once daily for 48 weeks. The primary end point was complete cure of the target great toenail (completely clear nail with negative mycology) at week 52. Secondary end points included completely or almost clear nail, negative mycology, completely or almost clear nail plus negative mycology, and safety.

Results: Rates of negative mycology (31.1%-35.9% vs 7.2%-12.2%) and complete cure (6.5% and 9.1% vs 0.5% and 1.5%) significantly favored tavaborole versus vehicle ($P \leq .001$). Completely or almost clear nail rates also significantly favored tavaborole versus vehicle (26.1%-27.5% vs 9.3%-14.6%; $P < .001$). Rates of completely or almost clear nail plus negative mycology (15.3%-17.9% vs 1.5%-3.9%) were significantly greater for tavaborole versus vehicle ($P < .001$). Application-site reactions with tavaborole included exfoliation (2.7%), erythema (1.6%), and dermatitis (1.3%).

Limitations: Duration of follow-up is a limitation.

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Writing and editorial assistance was provided by Callie Grimes of Peloton Advantage, LLC, Parsippany, NJ, and was supported by Anacor Pharmaceuticals, Inc. Diane Nelson of Anacor Pharmaceuticals, Inc, provided critical review and revision of the manuscript.

Disclosure: Ms Baldwin and Dr Zane are employees of Anacor Pharmaceuticals, Inc. Dr Elewski has received honoraria and grants while serving as a consultant and investigator with the following companies: Anacor Pharmaceuticals, Inc; Valeant Pharmaceuticals International Inc, Bridgewater, NJ; and Meiji Seika Pharma Co, Ltd, Tokyo, Japan. Dr Aly was consultant and investigator for Anacor Pharmaceuticals, Inc. Dr González Soto was an investigator for the following companies: Anacor Pharmaceuticals, Inc; Pfizer, New York, NY; and Eli Lilly, Indianapolis, IN. Dr Rich was the principal investigator for onychomycosis studies with the following companies: Anacor Pharmaceuticals, Inc; Topica Pharmaceuticals, Los Altos, CA; Valeant Pharmaceuticals International Inc; and Viamet Pharmaceuticals Inc, Durham, NC. Dr Pollak has received grants and honoraria while serving as advisory board member, investigator, and speaker for the following companies: Anacor Pharmaceuticals, Inc; Valeant Pharmaceuticals International Inc; and Topica Pharmaceuticals. Drs Weisfeld and Wiltz were principal investigators for Anacor Pharmaceuticals, Inc. The authors were fully responsible for the content, editorial decisions, and opinions expressed in the current article. No author received an honorarium related to the development of this manuscript.

Accepted for publication April 6, 2015.

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Published online May 5, 2015.

0190-9622

http://dx.doi.org/10.1016/j.jaad.2015.04.010

Conclusion: Tavaborole demonstrates a favorable benefit-risk profile in treatment of toenail onychomycosis. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2015.04.010.)

Key words: antifungal agents; arthrodermataceae; nails; onychomycosis; randomized controlled trial; tavaborole.

Tavaborole topical solution, 5% (Anacor Pharmaceuticals, Inc, Palo Alto, CA) is a novel, boron-based pharmaceutical approved by the Food and Drug Administration (FDA) in July 2014 for the treatment of toenail onychomycosis caused by *Trichophyton rubrum* and *T mentagrophytes*.[1] Tavaborole represents a new class of pharmaceutical antifungal agents with a novel chemical structure and mechanism of action (Fig 1).[2-5] Tavaborole targets fungal cytoplasmic leucyl-transfer ribonucleic acid (tRNA) synthetase, a member of a family of aminoacyl-tRNA synthetase enzymes essential for protein synthesis.[5] These enzymes maintain and translate genetic code within DNA, and possess a proofreading mechanism that corrects enzymatic mistakes that occur on a separate, active editing site. Tavaborole binds to the editing site via its boron atom to trap leucyl tRNA, preventing its catalytic turnover and inhibiting protein synthesis. Tavaborole demonstrates broad-spectrum antifungal activity and more than 1000-fold greater selectivity for the fungal leucyl-tRNA synthase than the mammalian leucyl-tRNA synthetase[6]; *T rubrum* and *T mentagrophytes* isolates collected from clinical trial patients have not demonstrated resistance after repeated exposure to tavaborole.[1]

The low molecular weight of tavaborole allows a high amount of penetration through full-thickness human nail plates.[7] Ex vivo permeation studies have demonstrated tavaborole penetration through multiple layers of nail polish (data on file, Anacor Pharmaceuticals, Inc; TER-002-14, ANA-005, 2013). Phase-I trials showed favorable safety and low systemic exposure in patients with toenail onychomycosis,[8] and phase-II trials provided evidence of improved clear nail growth and negative fungal cultures.[9] The objective of the 2 phase-III trials described herein was to evaluate the efficacy and safety of tavaborole versus vehicle in adults with distal subungual toenail onychomycosis.

CAPSULE SUMMARY

- Tavaborole topical solution, 5% is approved for treatment of toenail onychomycosis.
- Tavaborole was significantly more effective than vehicle in treating toenail onychomycosis in 2 phase-III trials; incidence of treatment-related application-site reactions was low.
- The favorable benefit-risk profile makes tavaborole a reasonable therapeutic option for toenail onychomycosis.

METHODS

Study treatment and patients

Study treatments included tavaborole and vehicle, which were applied topically to the affected nails once daily for 48 weeks by the patient. Patients were instructed to apply a sufficient amount of study treatment on, under, and around the infected target great toenail (TGT) and infected nontarget toenails with a thin, even layer.

Patients 18 years of age or older with distal subungual toenail onychomycosis involving 20% to 60% of at least 1 TGT were eligible if they had a positive potassium hydroxide (KOH) wet mount and positive culture for dermatophytes, greater than or equal to 3-mm clear nail measured from the proximal nail fold to the most proximal visible mycotic border, and distal TGT thickness 3 mm or less. Patients were excluded if they had proximal subungual or superficial white onychomycosis, severe disease, dermatophytoma, exclusively lateral disease, yellow/brown spikes, coinfection with nondermatophyte fungi, anatomic abnormalities of the toes or toenails, active tinea pedis (involving the sides or back of the foot, interdigital, or plantar) requiring treatment, history of chronic moccasin-type tinea pedis (involving the sides or back of the foot), history of other significant chronic fungal disease, psoriasis, lichen planus, known immunodeficiency, significant peripheral vascular disease, known structural heart disease, or uncontrolled diabetes (hemoglobin A1C $\geq$8%). Patients who used topical antifungals on the toenails within 4 weeks or systemic antifungals within 24 weeks were also excluded. Recent use of other topical agents on the toe or toenails, systemic corticosteroids, or immunomodulatory agents was not permitted.

Study design

Two phase-III, multicenter, randomized, double-blind, vehicle-controlled, parallel-group trials of