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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Conclusion: Tavaborole demonstrates a favorable benefit-risk profile in treatment of toenail onychomycosis. (J Am Acad Dermatol 2015;73:62-9.)

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

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.

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.

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

Abbreviations used:

AE: adverse event
FDA: Food and Drug Administration
KOH: potassium hydroxide
TEAE: treatment-emergent adverse event
TGT: target great toenail
tRNA: transfer ribonucleic acid

identical design were conducted: 1 at 27 sites in the United States and Mexico from December 2010 to November 2012 (study 1; NCT01270971) and the other at 32 sites in the United States and Canada from February 2011 to January 2013 (study 2; NCT01302119). Both studies were conducted in accordance with ethical principles originating in the Declaration of Helsinki and in compliance with the principles of Good Clinical Practice and all applicable regulatory requirements. The study protocol was approved by an institutional review board/independent ethics committee at each site, and all patients provided written informed consent.

Patients were screened 4 to 10 weeks before randomization. Eligible patients were randomized 2:1 to receive tavaborole or vehicle, and applied study treatment to the TGT and all other affected toenails once daily for 48 weeks. Nail debridement was not permitted.

Disease involvement was assessed at screening, baseline (day 1), week 2, week 6, and every 6 weeks thereafter. At these visits, nail trimming of the TGT was limited to within 1 mm distal to the hyponychium or distal groove if needed. Patients were encouraged not to trim the TGT. All other toenails were also evaluated for the presence of onycholysis and subungual hyperkeratosis. Subungual samples were obtained from the TGT at screening and every 12 weeks during treatment and sent to a central mycology laboratory for KOH wet mount examination with calcofluor white stain and fungal culture to identify pathogenic fungi including dermatophyte species. After study treatment was completed at week 48, follow-up efficacy assessments were made at week 52.

Efficacy

The primary efficacy end point was complete cure of the TGT defined as completely clear nail and negative mycology at week 52. Secondary end points included completely or almost clear nail of the TGT, negative mycology of the TGT, and completely or almost clear nail plus negative mycology, each determined at week 52. Completely clear nail was defined as no clinical evidence of onychomycosis based on a normal toenail plate, no onycholysis, and no subungual hyperkeratosis. Almost clear nail was defined as no more than minimal evidence of onychomycosis based on a toenail plate that was dystrophic or discolored on 10% or less of the distal aspect, with minimally evident onycholysis and subungual hyperkeratosis. Negative mycology was defined as negative KOH wet mount and negative fungal culture.

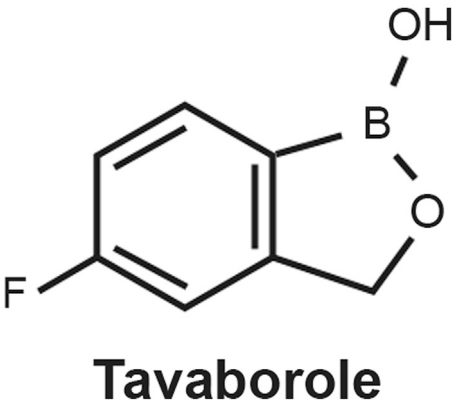

Fig 1. Tavaborole chemical structure. Tavaborole is a novel, boron-based pharmaceutical approved for the treatment of toenail onychomycosis caused by *Trichophyton rubrum* and *T mentagrophytes*.[1] Tavaborole inhibits leucyl-tRNA-synthetase, resulting in inhibition of fungal protein synthesis and termination of fungal cell growth.[5]

Safety

Safety assessments were conducted at each visit, as was a physical examination evaluating the frequency and severity of application-site reactions: burning/stinging, induration/edema, oozing/crusting, pruritus, erythema, and scaling. Adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs, vital signs, laboratory parameters, and electrocardiographic parameters were monitored throughout the study.

Statistics

Efficacy parameters were evaluated in the intent-to-treat population, which included all randomized patients who received study treatment. Safety parameters were evaluated in all randomized patients who received at least 1 dose of study treatment and had at least 1 postbaseline assessment. Comparisons between treatment groups for the primary and secondary efficacy end points were made using the Cochran-Mantel-Haenszel test stratified by analysis. A last-observation-carried-forward approach was used to impute missing efficacy data. Two-sided hypothesis testing was conducted using a significance level of .05. AEs were classified using the *Medical Dictionary for*

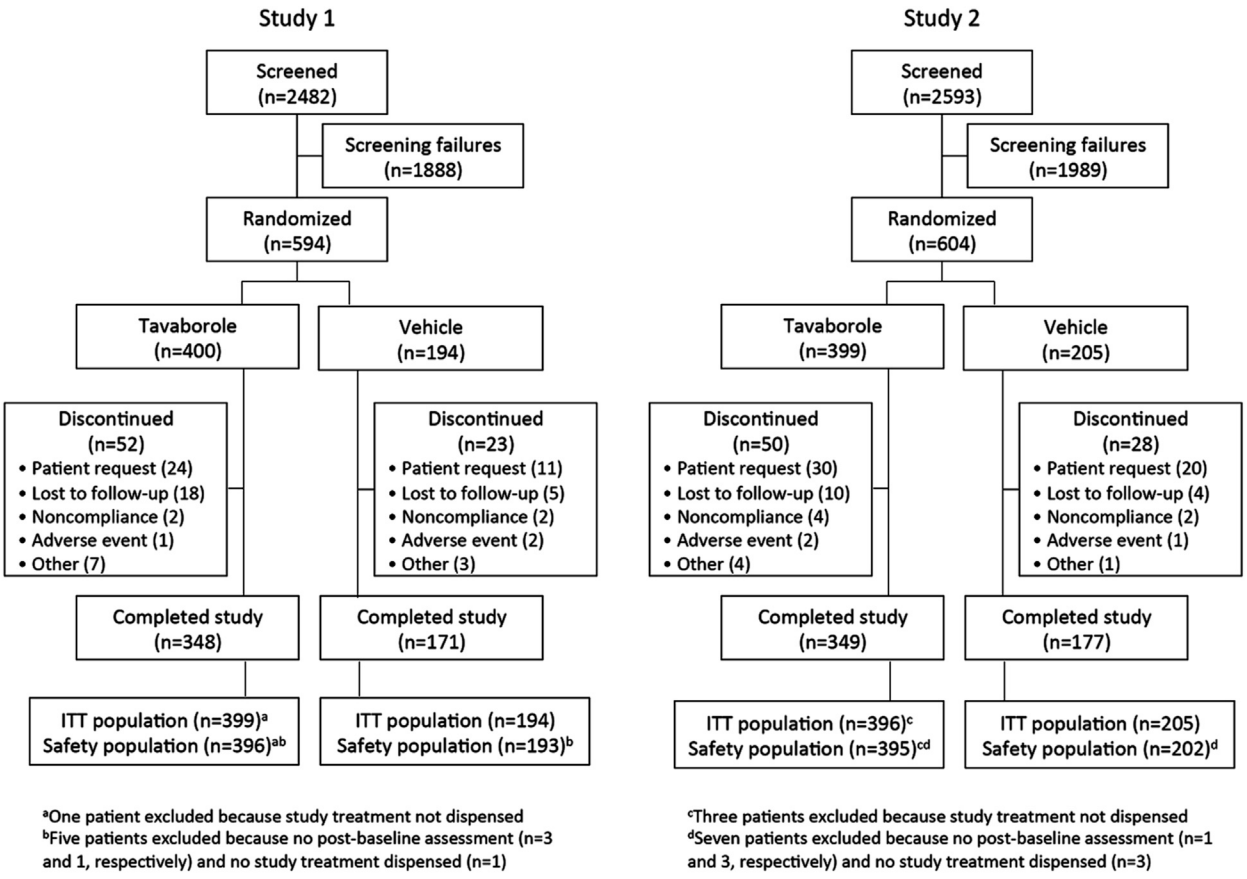

Fig 2. Toenail onychomycosis. Patient disposition. *ITT*, Intent-to-treat.

Regulatory Activities (Version 13.1, http://www.meddra.org). All safety parameters were summarized descriptively by treatment group.

RESULTS

Patients

The disposition of patients (study 1, N = 594; study 2, N = 604) is depicted in Fig 2. Demographic and clinical characteristics of the intent-to-treat population were similar between treatment groups and generally consistent across the 2 trials (Table I).

Efficacy

Tavaborole was significantly more effective than vehicle for all primary and secondary efficacy end points, and produced higher rates of negative culture and negative KOH at week 52 versus vehicle (Table II). A significantly greater proportion of patients achieved complete cure of the TGT at week 52 with tavaborole versus vehicle in study 1 (6.5% vs 0.5%; $P = .001$) and study 2 (9.1% vs 1.5%; $P < .001$). Rates of completely or almost clear nail at week 52 with tavaborole were 26.1% and 27.5% in study 1 and study 2, respectively, versus 9.3% and 14.6% with vehicle (both $P < .001$). Negative mycology rates with tavaborole were 31.1% and 35.9% in study 1 and study 2, respectively, versus 7.2% and 12.2% with vehicle (both $P < .001$). Photographs illustrating a case with complete cure and a case of almost clear nail with negative mycology are shown in Fig 3.

The onset of tavaborole clinical activity was evident by week 24 and generally increased through the end of treatment at week 48 and the final efficacy assessment at week 52 (Fig 4). Complete cure of the TGT was observed as early as week 24 in study 2 and at week 30 in study 1. Negative culture rates ranged from 95% at week 24 to 87% at week 52 in study 1 and 94% at week 24 to 85% at week 52 in study 2. Negative KOH rates mirrored negative mycology data.

Safety

The incidence of TEAEs with tavaborole versus vehicle was similar in study 1 (64.4% vs 69.9%, respectively) and study 2 (57.5% vs 54.0%, respectively) (Table III). Most TEAEs in patients receiving tavaborole (95.5%) or vehicle (93.4%) were reported as mild or moderate in severity. The most common treatment-related application site TEAEs with tavaborole in the 2 trials combined

Table I. Demographics and baseline characteristics of the intent-to-treat population

Characteristic	Study 1		Study 2	
	Tavaborole (n = 399)	Vehicle (n = 194)	Tavaborole (n = 396)	Vehicle (n = 205)
Age, y				
Mean (SD)	53.6 (12.5)	53.4 (12.3)	55.5 (11.5)	55.4 (11.0)
Range	18-88	19-81	20-81	27-81
Gender, n (%)				
Male	324 (81.2)	158 (81.4)	323 (81.6)	174 (84.9)
Female	75 (18.8)	36 (18.6)	73 (18.4)	31 (15.1)
Race				
White	316 (79.2)	152 (78.4)	355 (89.6)	183 (89.3)
Black	19 (4.8)	12 (6.2)	21 (5.3)	14 (6.8)
American Indian/Alaska Native	0 (0)	0 (0)	2 (0.5)	1 (0.5)
Asian	2 (0.5)	0 (0)	11 (2.8)	2 (1.0)
Native Hawaiian/Pacific Islander	0 (0)	0 (0)	2 (0.5)	1 (0.5)
Other	62 (15.5)	30 (15.5)	5 (1.3)	4 (2.0)
Country				
United States	340 (85.2)	164 (84.5)	315 (79.5)	165 (80.5)
Canada	—	—	81 (20.5)	40 (19.5)
Mexico	59 (14.8)	30 (15.5)	—	—
No. of nontarget toenails ≥10% affected by onychomycosis				
Mean (SD)	3.4 (2.8)	3.8 (2.7)	3.3 (2.8)	3.3 (2.6)
Range	0-9	0-9	0-9	0-9

Table II. Efficacy end points at week 52

End point	Study 1			Study 2		
	Tavaborole (n = 399) n (%)	Vehicle (n = 194) n (%)	*P* value	Tavaborole (n = 396) n (%)	Vehicle (n = 205) n (%)	*P* value
Primary end point						
Complete cure of TGT*	26 (6.5)	1 (0.5)	.001	36 (9.1)	3 (1.5)	<.001
Secondary end points						
Completely CN or almost CN of TGT	104 (26.1)	18 (9.3)	<.001	109 (27.5)	30 (14.6)	<.001
Negative mycology of TGT	124 (31.1)	14 (7.2)	<.001	142 (35.9)	25 (12.2)	<.001
Completely or almost CN plus negative mycology of the TGT	61 (15.3)	3 (1.5)	<.001	71 (17.9)	8 (3.9)	<.001
Other end points						
Negative culture of TGT	347 (87.0)	93 (47.9)	—	338 (85.4)	105 (51.2)	—
Negative KOH of TGT	128 (32.1)	17 (8.8)	—	147 (37.1)	35 (17.1)	—
Completely CN or almost CN of TGT with negative culture	98 (24.6)	11 (5.7)	—	100 (25.3)	19 (9.3)	—

CN, Clear nail; *KOH*, potassium hydroxide wet mount; *TGT*, target great toenail.
*Completely CN and negative mycology.

were exfoliation (2.7%), erythema (1.6%), and dermatitis (1.3%). The majority of TEAEs were considered not related or unlikely related to study treatment. The incidence of treatment-related TEAEs was higher with tavaborole versus vehicle in study 1 (8.8% vs 2.6%, respectively) and study 2 (3.3% vs 0.5%, respectively) and was attributed to a higher rate of application-site reactions with tavaborole versus vehicle in study 1 (7.3% vs 0.5%, respectively) and study 2 (3.0% vs 0%, respectively). Rates of discontinuations as a result of AEs occurred at similar rates between treatment groups (Table III).

There were no deaths in either study. Serious AEs were reported in 19 patients (2.4%) who received tavaborole and 10 patients (2.5%) who received vehicle; none were considered treatment-related. Results of clinical laboratory and vital assessments

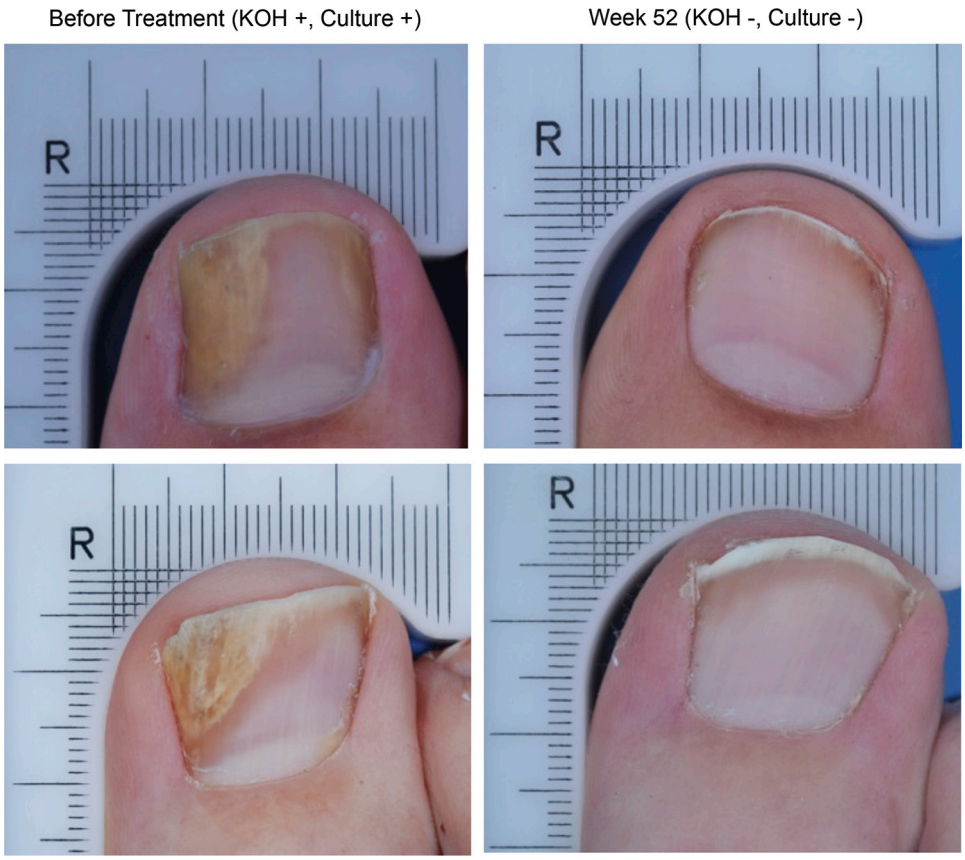

Fig 3. Toenail onychomycosis. Illustrative cases of complete cure of the target great toenail (*top*) and almost clear nail with negative mycology (*bottom*) after treatment with tavaborole for 48 weeks. *KOH*, Positive potassium hydroxide wet mount.

did not identify any safety signals, and no drug-related effects were observed on the electrocardiograms.

DISCUSSION

These findings from 2 phase-III trials demonstrate that once-daily tavaborole, without adjunctive debridement, is effective, safe, and well tolerated in the treatment of toenail onychomycosis. Tavaborole was significantly more effective than vehicle for all primary and secondary end points at week 52, with 26% to 28% of patients achieving completely or almost clear nail; 31% to 36% achieving negative mycology; 7% to 9% achieving complete cure; and 15% to 18% achieving completely or almost clear nail and negative mycology. The primary efficacy end point of complete cure (0% involvement of the nail plate and negative mycology) was chosen to enhance objectivity and is currently a regulatory standard for assessing the efficacy of antifungal agents for the treatment of toenail onychomycosis. The safety and efficacy of tavaborole was demonstrated in both adult and geriatric patients with a varied degree of disease severity, as the phase-III clinical trials enrolled patients aged 18 to 88 years with up to 60% clinical involvement of the TGT. Complete cure rates may not reflect the full clinical benefit of tavaborole. Although completely clear nail represents a definitive clinical cure, an almost clear nail (≤10% affected) represents a clinically meaningful and successful outcome for many patients, and is likely the most realistically achievable outcome considering the residual nail defects that remain after the infection is cured.

The number of TEAEs reported with tavaborole was low. Treatment-related TEAEs were localized to the application site; the most common were exfoliation, dermatitis, and erythema (1.3%-2.7%). Rates of discontinuations as a result of TEAEs were low and comparable with vehicle. Thus, tavaborole offers a favorable safety and tolerability profile. Tavaborole is a clear, colorless solution that is easy to apply, dries quickly, and does not require adjunctive debridement or removal of prior applications.

The clinical efficacy and safety of tavaborole is supported by its ability to penetrate the nail plate, owing to its small size (152 d), hydrophilicity, and ability to retain pharmacologic antifungal activity in the presence of keratin.[6] In ex vivo nail studies,

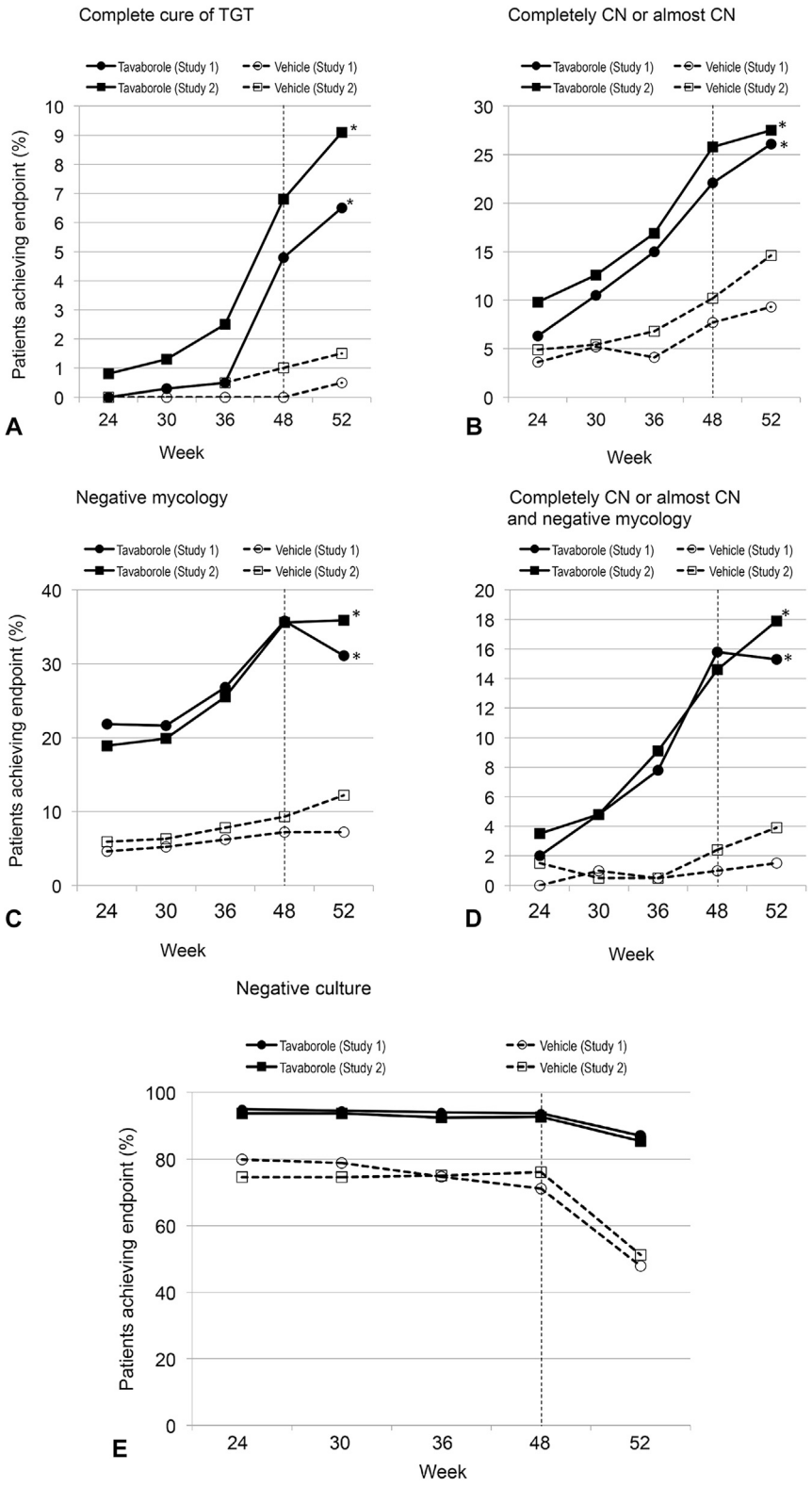

Fig 4. Tavaborole efficacy in toenail onychomycosis. Change in efficacy end points over time from weeks 24 to 52. Each panel shows the percentage of patients achieving the end point at the indicated time point: complete cure (**A**); completely clear nail (*CN*) or almost CN (**B**); negative mycology (**C**); completely or almost CN plus negative mycology (**D**); and negative culture (**E**). *$P \leq .001$ for tavaborole vs vehicle at week 52 for each of the end points assessed. Vertical lines indicate end of treatment at 48 weeks. Negative mycology was defined as negative potassium hydroxide wet mount and negative fungal culture. *TGT*, Target great toenail.

Table III. Summary of adverse events

Adverse event	Study 1		Study 2	
	Tavaborole (n = 396) n (%)	Vehicle (n = 193) n (%)	Tavaborole (n = 395) n (%)	Vehicle (n = 202) n (%)
Patients with ≥1 TEAEs	255 (64.4)	135 (69.9)	227 (57.5)	109 (54.0)
Most common TEAEs*				
Tinea pedis	42 (10.6)	35 (18.1)	53 (13.4)	25 (12.4)
Nasopharyngitis	23 (5.8)	10 (5.2)	27 (6.8)	16 (7.9)
Upper respiratory tract infection	20 (5.1)	8 (4.1)	18 (4.6)	12 (5.9)
Back pain	17 (4.3)	3 (1.6)	7 (1.8)	2 (1.0)
Ingrowing nail	14 (3.5)	1 (0.5)	6 (1.5)	0 (0)
Sinusitis	12 (3.0)	5 (2.6)	6 (1.5)	5 (2.5)
Hypertension	11 (2.8)	8 (4.1)	11 (2.8)	4 (2.0)
Influenza	11 (2.8)	10 (5.2)	2 (0.5)	0 (0)
Headache	10 (2.5)	5 (2.6)	11 (2.8)	7 (3.5)
Muscle strain	8 (2.0)	1 (0.5)	10 (2.5)	6 (3.0)
Most common application site TEAEs†				
Exfoliation	16 (4.0)	1 (0.5)	5 (1.3)	0 (0)
Dermatitis	8 (2.0)	0 (0)	2 (0.5)	0 (0)
Erythema	7 (1.8)	0 (0)	6 (1.5)	0 (0)
Pain	5 (1.3)	1 (0.5)	3 (0.8)	0 (0)
Hematoma	2 (0.5)	1 (0.5)	3 (0.8)	2 (1.0)
Discontinuations as a result of TEAEs	1 (0.3)	2 (1.0)	2 (0.5)	1 (0.5)

TEAE, Treatment-emergent adverse event.
*Occurring in ≥3% of patients in any treatment group.
†Occurring in ≥1% of patients in any treatment group.

tavaborole effectively penetrated the nail plate and achieved concentrations above the minimum fungicidal concentration.[6,8] Tavaborole application once daily for 28 days to the toenails of patients with onychomycosis resulted in nail drug concentrations substantially above the minimum concentration required to inhibit 90% of isolates (minimal inhibitory concentration$_{90}$) of *T rubrum*.[8] Tavaborole nail concentrations were 20 times higher than the minimum fungicidal concentration against the dermatophytes 3 months after the end of treatment. Tavaborole demonstrated nail penetration 40-fold greater than ciclopirox after 14 days of application in a human cadaver fingernail model.[10]

In conclusion, these studies demonstrate that tavaborole, a novel, first-in-class, boron-based pharmaceutical approved by the FDA for the treatment of toenail onychomycosis, has a favorable benefit-risk profile and is an attractive option for the treatment of onychomycosis of the toenail as a result of dermatophytes.

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