

Clinical Trial Designs for Topical Antifungal Treatments of Onychomycosis and Implications on Clinical Practice

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PRACTICE POINTS

- Despite similar overall designs, notable differences in the study designs of phase 3 clinical trials investigating tavaborole, efinaconazole, and ciclopirox for the treatment of onychomycosis are likely to have had an effect on the reported results, making the efficacy of these agents difficult to compare.
- The primary difference between studies for tavaborole, efinaconazole, and ciclopirox include the age range of participants, the range of mycotic nail involvement, the presence/absence of tinea pedis, and the nail trimming/debridement protocols used.
- Without head-to-head investigations, there is room for prescribing clinicians to interpret study results for these agents differently.

There currently are 3 topical agents approved by the US Food and Drug Administration (FDA) to treat onychomycosis: tavaborole, efinaconazole, and ciclopirox. The phase 3 clinical trial designs for these treatments and their notable differences make it difficult for clinicians to interpret the data into clinical practice. For example, the primary end point predominantly used to assess efficacy in all the trials is complete cure, defined as no involvement of the nail plus mycologic

cure; also, a notable number of patients fail to achieve a complete cure despite clear improvement in the nail. Despite close similarities in the end points and overall design of the clinical trials used for these agents, differences in design are notable, including the age range of participants, the range of mycotic nail involvement, the presence/absence of tinea pedis, and the nail trimming/debridement protocols used. The differences in clinical trial designs for the 3 FDA-approved topical agents and the lack of head-to-head studies makes efficacy interpretation and comparison inappropriate. This article reviews the phase 3 clinical trials that led to FDA approval of these agents, focusing on their similarities and differences.

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Onychomycosis is a fungal nail infection primarily caused by dermatophytes.¹ If left untreated, the infection can cause nail destruction and deformities,¹ resulting in pain and discomfort,² impaired foot mobility,³ and an overall reduced quality of life.¹ Onychomycosis is a chronic condition that requires long treatment periods due to the slow growth rates of toenails.¹ To successfully cure the condition, fungal eradication must be achieved.

Prior to the US Food and Drug Administration (FDA) approval of tavaborole and efinaconazole, ciclopirox was the only approved topical treatment for onychomycosis.⁴ The recent approval of tavaborole and efinaconazole has increased treatment options available to patients and has started to pave the way for future topical treatments. This article discusses the 3 approved topical treatments for onychomycosis and focuses on the design of the phase 3 clinical trials that led to their approval.

Topical Agents Used to Treat Onychomycosis

Tavaborole, efinaconazole, and ciclopirox have undergone extensive clinical investigation to receive FDA approval. Results from pivotal phase 3 studies establishing the efficacy and safety of each agent formed the basis for regulatory submission. Although it may seem intuitive to compare the relative performance of these agents based on their respective phase 3 clinical trial data, there are important differences in study methodology, conduct, and populations that prevent direct comparisons. The FDA provides limited guidance to the pharmaceutical industry on how to conduct clinical trials for potential onychomycosis treatments. Comparative efficacy and safety claims are limited based on cross-study comparisons. The details of the phase 3 trial designs are summarized in the Table.

Tavaborole—Tavaborole is a boron-based treatment with a novel mechanism of action.⁵ Tavaborole binds to the editing domain of leucyl-transfer ribonucleic acid

synthetase via an integrated boron atom and inhibits fungal protein synthesis.⁶ Two identical randomized, double-blind, vehicle-controlled, parallel-group, phase 3 clinical trials evaluating tavaborole were performed.⁵ The first study (registered at www.clinicaltrials.gov with the identifier NCT01270971) included 594 participants from 27 sites in the United States and Mexico and was conducted between December 2010 and November 2012. The second study (NCT01302119) included 604 participants from 32 sites in the United States and Canada and was conducted between February 2011 and January 2013.

Eligible participants 18 years and older had distal subungual onychomycosis (DSO) of the toenails affecting 20% to 60% of 1 or more target great toenails (TGTs), tested positive for fungus using potassium hydroxide (KOH) wet mounts and positive for *Trichophyton rubrum* and *Trichophyton mentagrophytes* on fungal culture diagnostic tests, had distal TGT thickness of 3 mm or less, and had 3 mm or more of clear nail between the proximal nail fold and the most proximal visible mycotic border.⁵ Those with active tinea pedis requiring treatment or with a history of chronic moccasin-type tinea pedis were excluded. Participants were randomized to receive either tavaborole or vehicle (2:1). Treatments were applied once daily to all infected toenails for a total of 48 weeks, and nail debridement (defined as partial or complete removal of the toenail) was not permitted. Notably, controlled trimming of the nail was allowed to 1 mm of the leading nail edge. Regular assessments of each toenail for disease involvement, onycholysis, and subungual hyperkeratosis were made at screening, baseline, week 2, week 6, and every 6 weeks thereafter until week 52. Subungual TGT samples were taken at screening and every 12 weeks during the study for examination at a mycology laboratory, which performed KOH and fungal culture tests. A follow-up assessment was made at week 52.⁵

The primary end point was complete cure of the TGT at week 52, with secondary end points of completely

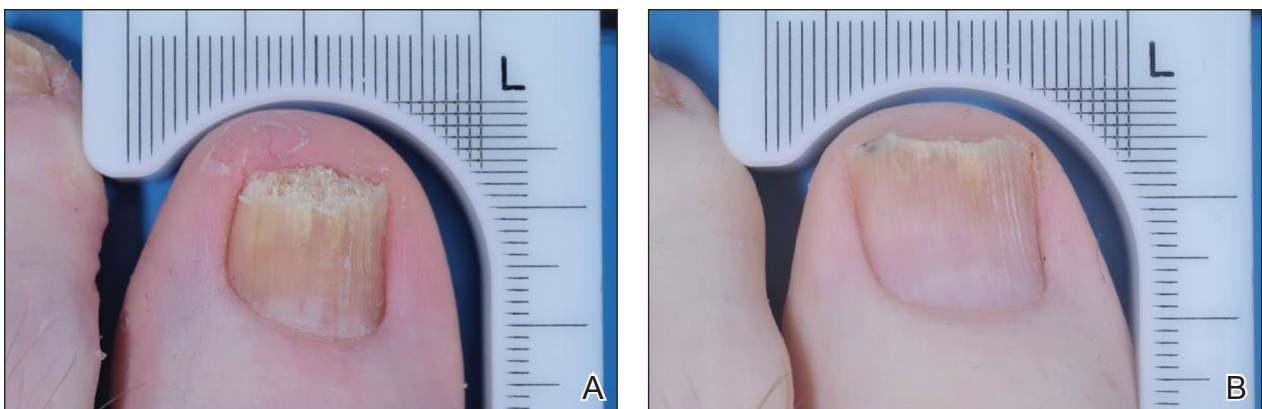


FIGURE 1. Illustrative case of toenail onychomycosis before (A) and at week 52 (B) in tavaborole phase 3 clinical trials. Almost clear nail with negative mycology was achieved at week 52 after 48 weeks of treatment with tavaborole.

or almost clear TGT nail ($\leq 10\%$ dystrophic nail), completely or almost clear TGT nail ($\leq 10\%$ dystrophic nail) plus negative mycology, and negative mycology of TGT.⁵ Examples of TGTs in participants who achieved complete cure and almost clear nails with negative mycology before and after treatment with tavaborole are shown in Figure 1. An example of a patient considered to have treatment failure is shown in Figure 2. This patient showed marked improvement in nail appearance and had a negative culture result but had a positive KOH test, which demonstrates the stringency in which topical agents are judged in onychomycosis trials.⁵

Efinaconazole—Efinaconazole is a topical triazole antifungal specifically indicated to treat onychomycosis. Two identical randomized, vehicle-controlled, double-blind, multicenter trials were performed to assess the safety and efficacy of efinaconazole solution 10%.⁷ The first study (NCT01008033) involved 870 participants

and was conducted at a total of 74 sites in Japan (33 sites), Canada (7 sites), and the United States (34 sites) between December 2009 and September 2011. The second study (NCT01007708) had 785 participants and was conducted at 44 sites in Canada (8 sites) and the United States (36 sites) between December 2009 and October 2011.

Participants aged 18 to 70 years with a clinical diagnosis of DSO affecting 1 or more TGT were eligible to participate.⁷ Other eligibility criteria included an uninfected toenail length 3 mm or more from the proximal nail fold, a maximum toenail thickness of 3 mm, positive KOH wet mounts, and positive dermatophyte or mixed dermatophyte/candida cultures. Dermatophytes included *T rubrum* and *T mentagrophytes*. Those with severe moccasin-type tinea pedis were excluded. Participants were randomized to receive efinaconazole or vehicle (3:1). Once-daily treatments were self-applied to nails for

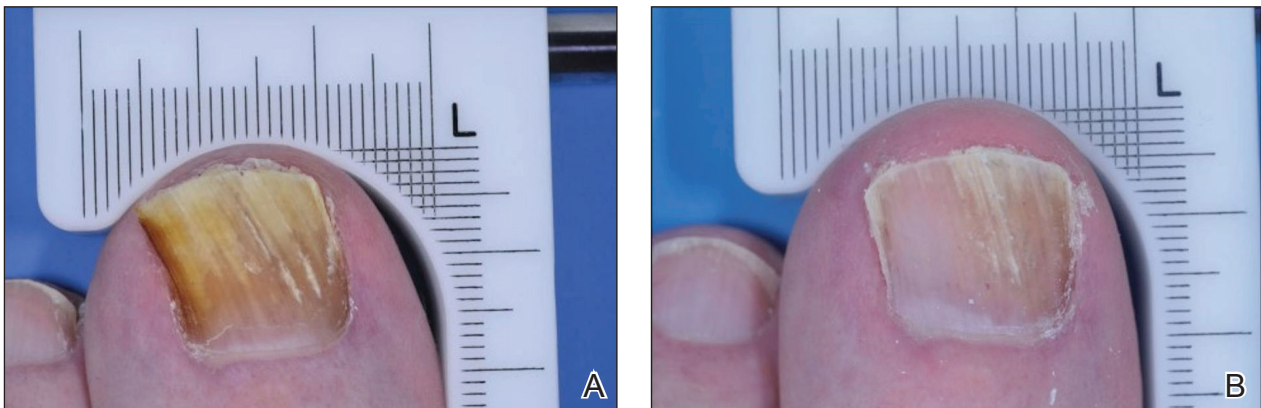


FIGURE 2. Clinical example of a treatment failure from the tavaborole phase 3 clinical trials. A patient before treatment (A) and at week 52 (B) who achieved an almost completely clear nail plus negative culture but positive potassium hydroxide preparation results after 48 weeks of treatment with tavaborole.

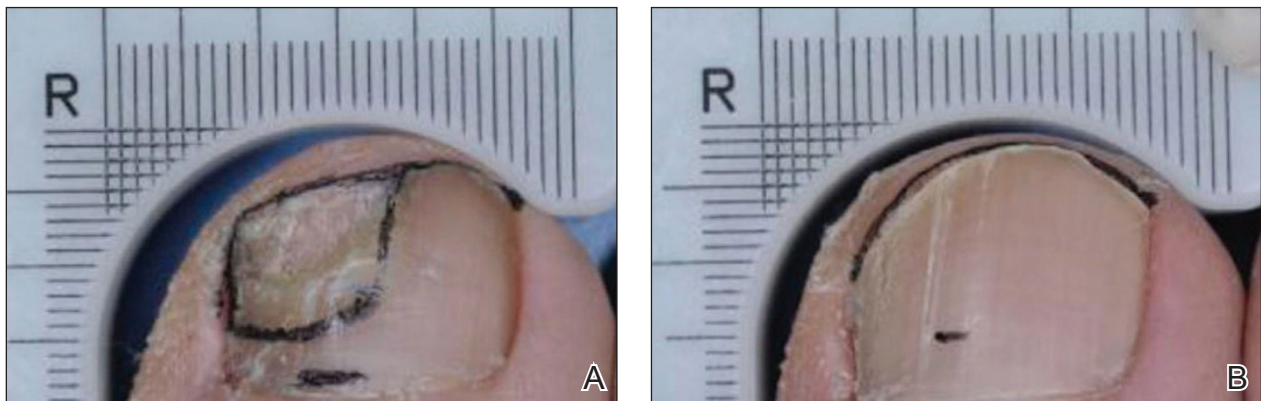


FIGURE 3. Representative clinical example of an onychomycosis patient before (A) and after treatment with efinaconazole for 48 weeks (B) with a trimmed nail, achieving complete cure. Reprinted from the *Journal of the American Academy of Dermatology*, Copyright 2013, with permission from Elsevier.⁷

Summary of Phase 3 Clinical Trials for US Food and Drug Administration–Approved Topical Therapies for Onychomycosis

Clinicaltrials.gov Identifier	Study Population	Mean Age (Range), y	Participant Race	Randomization	Mycotic Area Involvement	Presence of Tinea Pedis	Nail Trimming	Debridement	Treatment Application	Treatment Period/Final Assessment
Tavaborole solution 5% ⁵										
NCT01270971;	Study 1: 594;	Study 1: 53 (18–88);	Study 1 (tavaborole vs vehicle): white, 79.2% vs 78.4%; black, 4.8% vs 6.2%; Asian, 0.5% vs 0%; other, 15.5% vs 15.5%; study 2	2:1	20%–60%	Active tinea pedis requiring treatment excluded, history of chronic moccasin-type tinea pedis excluded	Trimming limited by investigator to no closer than 1 mm from the hyponychium	Not permitted	Treatment applied once daily on, around, and under the infected TGT and other infected non-TGTs in a thin even layer using a glass dropper	48 wk/52 wk
NCT01302119	study 2: 604	55 (20–81)	(tavaborole vs vehicle): white, 89.6% vs 89.3%; black, 5.3% vs 6.8%; Asian, 2.8% vs 1.0%; other, 2.3% vs 2.9%							
Efinaconazole solution 10% ⁷										
NCT01008033;	Study 1: 870;	Study 1: 52 (18–71);	Study 1 (efinaconazole vs vehicle): white, 64.8% vs 65.4%; black, 5.5% vs 3.3%; Asian, 28.8% vs 29.4%; other, 0.9% vs 1.9%; study 2	3:1	20%–50%	Severe moccasin-type tinea pedis excluded	Trimming not specifically controlled by the protocol	Not permitted	Treatment applied once daily via brush applicator to the clean dry nail plate surface, the lateral and proximal nail folds, the hyponychium, and the undersurface of the nail plate	48 wk/52 wk
NCT01007708	study 2: 785	51 (18–71)	(efinaconazole vs vehicle): white, 90.9% vs 81.6%; black, 5.9% vs 10.4%; Asian, 1.9% vs 3.0%; other, 2.2% vs 5.0%							
Ciclopirox nail lacquer topical solution 8% ⁸										
N/A	Study 1: 223;	Study 1: 49 (18–70);	Study 1 (ciclopirox vs vehicle): white, 94.6% vs 91.9%; black, 0.9% vs 1.8%; Hispanic, 3.6% vs 6.3%; other, 0.9% vs 0%; study 2 (ciclopirox vs vehicle): white, 86.6% vs 88.1%; black, 3.4% vs 5.1%; Asian, 3.4% vs 0%; Hispanic, 5.0% vs 5.1%; other, 1.7% vs 1.7%	1:1	20%–65%	Tinea pedis not excluded	Trimming allowed	Performed every month	Treatment applied once daily to the entire nail plate including 5 mm of the proximal nail fold, hyponychium, and ventral surface using a brush applicator; repeated daily for 7 d before removing lacquer	48 wk/12–24 wk after treatment ^a
	study 2: 237	50 (19–70)								

Abbreviations: TGT, target toenail; N/A, not available.

^aParticipants who were clinically cured only.

48 weeks. Clinical assessments were made at baseline and every 12 weeks until week 48, with a follow-up assessment at week 52. No nail trimming protocol was provided.⁷

The primary end point of the efinaconazole phase 3 trials was complete cure at week 52, with secondary end points including mycologic cure, treatment success ($\leq 5\%$ mycotic nail), and complete or almost complete cure (negative culture and KOH, $\leq 5\%$ mycotic nail). An example of a complete cure from baseline to week 52 is shown in Figure 3.⁷

Ciclopirox—Ciclopirox was the first topical therapy to be approved for the treatment of onychomycosis. Ciclopirox is a broad-spectrum antifungal agent that inhibits metal-dependent enzymes, which are responsible for the degradation of toxic peroxides in fungal cells. The safety and efficacy of ciclopirox nail lacquer topical solution 8% also was investigated in 2 identical phase 3 clinical trials.⁸ The first study was conducted at 9 sites in the United States between June 1994 and June 1996 and included 223 participants. The second study was conducted at 9 sites in the United States between July 1994 and April 1996 and included 237 participants.

Eligible participants were required to have DSO in at least one TGT, positive KOH wet mount with positive dermatophyte culture, and 20% to 65% nail involvement.⁸ Those with tinea pedis were not excluded. Participants were randomized to receive once-daily treatment with ciclopirox or vehicle (1:1) (applied to all toenails and affected fingernails) for 48 weeks. The product was to be removed by the patient with alcohol on a weekly basis. Trimming was allowed as necessary, and mechanical debridement by the physician could be performed monthly. Assessments were made every 4 weeks, and mycologic examinations were performed every 12 weeks. Participants who were clinically cured were assessed further in a 12- to 24-week posttreatment follow-up period.⁸

The primary end point of complete cure and secondary end points of treatment success (negative culture and KOH, $\leq 10\%$ mycotic nail), mycologic cure, and negative mycologic culture were assessed at week 48.⁸

Phase 3 Clinical Trial Similarities and Differences

The phase 3 clinical trials used to investigate the safety and efficacy of tavaborole,⁵ efinaconazole,⁷ and ciclopirox⁸ were similar in their overall design. All trials were randomized, double-blind, vehicle-controlled studies in patients with DSO. Each agent was assessed using a once-daily application for a treatment period of 48 weeks.

Primary differences among study designs included the age range of participants, the range of mycotic nail involvement, the presence/absence of tinea pedis, and the nail trimming/debridement protocols used. Differences were observed in the patient eligibility criteria of these trials. Both mycotic area and participant age range were inconsistent for each agent (eTable). Participants with

larger mycotic areas usually have a poorer prognosis, as they tend to have a greater fungal load.⁹ A baseline mycotic area of 20% to 60%,⁵ 20% to 50%,⁷ and 20% to 65%⁸ at baseline was required for the tavaborole, efinaconazole, and ciclopirox trials, respectively. Variations in mycotic area between trials can affect treatment efficacy, as clinical cures can be reached quicker by patients with smaller areas of infection. Of note, the average mycotic area of involvement was not reported in the tavaborole studies but was 36% and 40% for the efinaconazole and ciclopirox studies, respectively.^{5,8} It also is more difficult to achieve complete cure in older patients, as they have poor circulation and reduced nail growth rates.^{1,10} The participant age range was 18 to 88 years in the tavaborole trials, with 8% of the participants older than 70 years,⁵ compared to 18 to 71 years in both the efinaconazole and ciclopirox trials.^{7,8} The average age of participants in each study was approximately 54, 51, and 50 years for tavaborole, efinaconazole, and ciclopirox, respectively. Because factors impacting treatment failure can increase with age, efficacy results can be confounded by differing age distributions across different studies.

Another important feature that differed between the clinical trials was the approach to nail trimming—defined as shortening of the free edge of the nail distal to the hyponychium—which varies from debridement in that the nail plate is removed or reduced in thickness proximal to the hyponychium. In the tavaborole trials, trimming was controlled to within 1 mm of the free edge of the nail,⁵ whereas the protocol used for the ciclopirox trials allowed nail trimming as necessary as well as moderate debridement before treatment application and on a monthly basis.⁸ Debridement is an important component in all ciclopirox trials, as it is used to reduce fungal load.¹¹ No trimming control was provided during the efinaconazole trials; however, debridement was prohibited.⁷ These differences can dramatically affect the study results, as residual fungal elements and portions of infected nails are removed during the trimming process in an uncontrolled manner, which can affect mycologic testing results as well as the clinical efficacy results determined through investigator evaluation. Discrepancies regarding nail trimming approach inevitably makes the trial results difficult to compare, as mycologic cure is not translatable between studies.

Furthermore, somewhat unusually, complete cure rate variations were observed between different study centers in the efinaconazole trials. Japanese centers in the first efinaconazole study (NCT01008033) had higher complete cure rates in both the efinaconazole and vehicle treatment arms, which is notable because approximately 29% of participants in this study were Asian, mostly hailing from 33 Japanese centers. The reason for these confounding results is unknown and requires further analysis.

Lastly, the presence or absence of tinea pedis can affect the response to onychomycosis treatment. In

the tavaborole trials, patients with active interdigital tinea pedis or exclusively plantar tinea pedis or chronic moccasin-type tinea pedis requiring treatment were excluded from the studies.⁵ In contrast, only patients with severe moccasin-type tinea pedis were excluded in efinaconazole trials.⁷ The ciclopirox studies had no exclusions based on presence of tinea pedis.⁸ These differences are noteworthy, as tinea pedis can serve as a reservoir for fungal infection if not treated and can lead to recurrence of onychomycosis.¹²

Conclusion

In recent years, disappointing efficacy has resulted in the failure of several topical agents for onychomycosis during their development; however, there are several aspects to consider when examining efficacy data in onychomycosis studies. Obtaining a complete cure in onychomycosis is difficult. Because patients applying treatments at home are unlikely to undergo mycologic testing to confirm complete cure, visual inspections are helpful to determine treatment efficacy.

Despite similar overall designs, notable differences in the study designs of the phase 3 clinical trials investigating tavaborole, efinaconazole, and ciclopirox are likely to have had an effect on the reported results, making the efficacy of the agents difficult to compare. It is particularly tempting to compare the primary end point results of each trial, especially considering tavaborole and efinaconazole had primary end points with the same parameters; however, there are several other factors (eg, age range of study population, extent of infection, nail trimming, patient demographics) that may have affected the outcomes of the studies and precluded a direct comparison of any end

points. Without head-to-head investigations, there is room for prescribing clinicians to interpret results differently.

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