Potential role of tavaborole for the treatment of onychomycosis

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ABSTRACT Systemic antifungal treatments are believed to be more effective than topicals for the treatment of onychomycosis; however, they are associated with more risks of adverse events. Tavaborole is the first member of a new class of antifungals that has been developed as a new topical nail solution for the treatment of toenail onychomycosis caused by dermatophytes. During Phase I–III clinical trials, tavaborole 5.0% nail solution showed a favorable safety and efficacy profile. Tavaborole 5.0% received US FDA market approval on 8 July 2014.

Onychomycosis is a fungal infection of the fingernails or toenails caused by dermatophytes, non-dermatophytes molds (NDMs) and/or yeasts. Single or multiple infectious agents may be identified as causative [1–8]. The prevalence and etiology of onychomycosis vary with geography and climate [9,10]. Indeed, in cooler western countries, onychomycosis is primarily caused by dermatophytes (80–90%), followed by yeasts (5–17%) and NDMs (2–3%). However, in warmer southern Europe, fewer onychomycosis-related infections are caused by dermatophytes (40–68%) and more are caused by yeasts (21–55%). These proportions change again in Asian and Middle Eastern countries with similar proportions of infections caused by dermatophytes (40–48%) and yeasts (43–46%), and an increase in NDM-related infections (8–11%) are observed. Finally, in warm and humid countries in Africa, onychomycosis-related infections are predominantly caused by yeasts (84%). The prevalence of onychomycosis is estimated to be around 3.8% in tropical Asian countries, between 10 and 12% in North America and up to 29.6% in European countries [9–11].

The prevalence of onychomycosis may be on the rise as recent studies reported an increase in the number of onychomycosis cases observed over the past few decades [11–13]. This change may be due to an increase in patient populations at higher risk of infection [11]. These populations include patients with compromised blood circulation (elderly, vascular disease and diabetes) and/or immune response (genetic predisposition, psoriasis, organ transplant patients and HIV-positive patients) [9,11].

Treatment of onychomycosis is recommended to avoid medical complications and to improve the patient’s quality of life [14]. The dermatology community generally agrees that before treating clinically diagnosed onychomycosis, a mycological confirmation of the diagnosis is required. Ideally, onychomycosis treatment should result in complete cure, which is generally defined as both mycological and clinical cure. Physicians’ primary treatment objective is the eradication of the infectious organism causing the disease (i.e., mycological cure) whereas patients’ primary objective is improvement in the appearance of the nail (i.e., clinical cure). The current treatments for onychomycosis include nail avulsion and debridement, topical and systemic antifungal therapies and the newer laser therapy. These interventions can be used as monotherapy or combination therapy [15,16].
Guidelines for laser therapy have yet to be published, but several treatment guidelines have been published for the other modes of treatment [11,17–19]. Their recommendations are generally based on the safety and efficacy of the interventions as well as the type and the severity of onychomycosis [11,17–19]. Indeed, onychomycosis has several clinical presentations classified based on the pattern of nail involvement and extent of invasion [20]. These presentations include distolateral subungal onychomycosis (DLSO), proximal subungal onychomycosis (PSO), superficial onychomycosis (SO) and total dystrophic onychomycosis (TDO), which is the final stage of all patterns of invasion [20]. The general consensus is that systemic antifungals should be used as a first line of therapy with the exception of: cases of SO, when systemic treatments are contraindicated due to medical conditions or risk of drug interactions; and in early cases of DLSO, which can be defined as no matrix involvement, less than 50% nail surface affected and only few digits are infected. In these cases, topical antifungals should be used [11,17–19]. Topicals can be combined with nail avulsion or debridement when the presence of dermatophytoma or spikes makes drug penetration suboptimal [11,17–19].

Overview of the market
Several effective systemic therapies are available, but all are associated with risks of adverse events [15]. Topical antifungals are safer than systemic antifungals, but they are less effective [15]. Poor nail permeability and inactivation by keratin are some of the factors limiting the efficacy of current topical antifungals [16,21]. Several technologies, such as Transfersome® (IDEA AG, Munich, Germany), are presently being developed to improve nail penetration [16]. Furthermore, the effect of keratin on antifungal activity is now a part of preclinical investigations designed to test prospective antifungals for the treatment of onychomycosis.

Topical antifungals currently used for the treatment of onychomycosis include ciclopirox 8% nail lacquer (available worldwide), amorolfin 5% nail lacquer (unavailable in North America) and efinaconazole 10% nail solution (recently licensed in Canada and the USA) [22,23]. A Transfersome formulation containing 1.5% of the antifungal terbinafine (TDT-067) underwent Phase II testing and is currently under investigation in a Phase II/III study [24,25]. Phase III testing is also in progress regarding luliconazole 10% nail solution [26]. Tavaborole underwent Phase III testing and received US FDA approval on 8 July 2014 [27,28].

Introduction to the compound
Tavaborole (AN2690), is the first antifungal benzoxaborole developed by Anacor Pharmaceuticals Inc. for the topical treatment of onychomycosis. Tavaborole is a broad-spectrum antifungal and its activity against the dermatophyte *Trichophyton rubrum* is not inhibited by nail keratin [29]. Tavaborole has better nail penetration than ciclopirox and amorolfin [29,30].

Chemistry
Tavaborole is an antifungal of the oxaborole class of boron-containing compounds (Figure 1B) [31]. These compounds were designed from a previous class of borinic acid quinolone ester compounds (Figure 1A) with antibacterial properties and they were specifically selected based on their antifungal properties. The broad-spectrum antifungal activity of these compounds was optimized by the addition of a 5-fluoro group and their hydrophilicity optimized by the substitution of a 1-phenyl group for a 1-hydroxy group (Figure 1C). This optimal compound, 1-hydroxy-5-fluoro-1,3-dihydro-2,1-benzoxaborole has also been shown to maintain its activity in presence of keratin [29] and to have better *in vitro* nail penetration than other oxaboroles at a 10% concentration in ethanol and ciclopirox 8% nail lacquer [30]. This compound, AN2690, was selected for future drug development for the topical treatment of onychomycosis and was subsequently named tavaborole.

Further studies using normal human nails from cadavers were performed to adjust the tavaborole 10% formulation to achieve optimal nail penetration [30]. Nail penetration was tested with four different formulations [30]. Three of these formulations were nail lacquers: 70% ethanol, 20% poly (vinyl methyl ether alt maleic acid monobutyl ester) producing a durable water insoluble film, 56% ethanol, 14% water, 15% poly (2-hydroxyethyl methacrylate) 5% dibutyl sebacate producing a less durable water soluble film and 55% ethanol, 15% ethyl acetate, 15% poly (vinyl acetate), and 5% dibutyl sebacate producing a less durable water insoluble film, which can be peeled off [30]. The last formulation was a simple solvent vehicle, 20% propylene glycol, 70% ethanol [30]. There
were no statistically significant differences in nail penetration between these formulations; thus, the simple solvent vehicle was selected for further comparison with ciclopirox 8% nail lacquer. The weight-normalized concentration of tavaborole in all parts of the nail was significantly higher (p ≤ 0.002) than the weight-normalized concentration of ciclopirox after a 14-day treatment.

**Pharmacodynamics**

Among all of the antifungal treatments for onychomycosis, the mechanism of action of tavaborole is unique. Indeed, the three systemic antifungals usually prescribed (terbinafine, itraconazole and amorolfine) inhibit the synthesis of ergosterol, an important component of the fungal cell membrane required for membrane integrity and fungal growth, whereas the other approved topical antifungal (ciclopirox) impairs microbial metabolism. The novel antifungal properties of tavaborole are due to its specific targeting of an enzyme involved in fungal protein synthesis. Indeed, protein synthesis requires the involvement of a family of enzymes called aminoacyl-tRNA synthetases. These enzymes catalyze the specific attachment of amino acids to their tRNAs. As similar amino acids can be mistakenly charged, these enzymes evolved to include an editing site for the recognition and release of these mischarged amino acids. Tavaborole forms, via its boron atom, a covalent adduct with the tRNA for leucine within the editing site of the LeuRS. The enzyme is then locked in an inactive form, which results in the interruption of protein synthesis. Based on the analysis of crystal structures, small differences between the editing domain of the human and fungal LeuRS contribute to the fungal specificity of this mechanism of action.

**Pharmacokinetics & metabolism**

To determine the extent of systemic exposure, topical tavaborole 7.5% solution was applied daily for 28 days to all toenails of 15 participants with moderate to severe onychomycosis. The daily volume applied was at least 0.25 ml of solution. Two sets of blood samples were collected. The first set was collected before participants received a dose at 0, 1, 14, 15 and 28 days. The second set was collected 0.25, 0.5, 1, 2, 3, 4, 6 and 8 h after receiving a dose on days 0, 14 and 28. The level of tavaborole was under the detectable level (25 ng/ml) in all samples.

Accumulation in the toenail was also assessed during and after application of tavaborole 7.5% solution once daily for 28 days in a Phase I clinical trial with 15 participants with moderate to severe toenail onychomycosis. In these participants with a combined thickness of the nail plate and the nail bed >3 mm, a concentration of 29 μg of tavaborole per mg of nail was achieved after 28 days. This concentration corresponds to about 5000-times the MIC and 600-times the minimum fungicidal concentration (MFC) of tavaborole for T. rubrum. 5 months after the last dose, tavaborole was still detected at a concentration of 0.10 μg/mg, which corresponds to 17-times the minimum inhibitory concentration to eradicate 90% of the infection (MIC) and twice the MFC for T. rubrum. Thus, high levels of tavaborole are achieved in the toenail following daily application and tavaborole remains in the toenail for an extended period of time.

**Clinical efficacy**

- **Phase I/II study**

An open-label multidose study examined 15 participants with onychomycosis affecting at least 80% of both great toenails and a combined thickness of the nail plate and nail bed of >3 mm for each great toenail. Participants were potassium hydroxide (KOH) positive for onychomycosis of at least one great toenail and must have had a clinical diagnosis of onychomycosis in at least...
six additional toenails. Tavaborole 7.5% was applied once daily to all 10 toenails and surrounding skin for 28 days and efficacy was evaluated by fungal culture or KOH from samples of both great toenails. After a 4-month follow-up period, 17 of the 26 toenails (65%) were culture negative and eight of the 26 great toenails (31%) were KOH negative. In addition, an average of 1.2 mm of clear nail growth was observed between day 84 and day 150 in the last 2 months of the follow-up period (36) (Tables 1 & 2).

- **Phase II studies**
Several Phase II studies have been performed to evaluate the safety and efficacy of tavaborole (40) (Table 2). A double-blind vehicle-controlled randomized clinical trial (Phase II 200) included 187 adult participants with DLSO affecting 20–60% of the great toenail. The inclusion criteria required the target toenail to be positive for dermatophytes by KOH and culture at baseline and to have demonstrated nail growth capability. Three solutions of tavaborole (2.5, 5.0 and 7.5%) were tested in comparison to vehicle. Participants were treated once daily for the first 3 months and three-times weekly for the following 3 months. The primary efficacy outcome was the rate of participants achieving negative culture and at least 2 mm of clear nail growth or an investigator static global assessment (ISGA) of clear or almost clear. After 6 months of treatment, the three concentrations of tavaborole tested resulted in significantly higher efficacy rates compared with vehicle (p < 0.03) (40).

In a nonrandomized open-label study (Phase II 201), 89 participants were recruited in three arms (Table 2) (40). Participants in the two parallel arms (Cohorts 1 and 2) were required to have DLSO (confirmed by KOH) affecting 20–60% of the great toenail with demonstrated nail growth capability. Participants in these arms were treated once daily for 6 months with tavaborole 5.0 or 7.5% solution. While in the third arm (Cohort 3), participants were required to have DLSO confirmed by KOH and culture affecting 20–60% of the great toenail and demonstrated nail growth capability and these participants were treated once daily for 12 months with tavaborole 5.0% solution. The efficacy outcome was defined as negative culture and at least 2 mm of clear nail growth for 28 days and efficacy was evaluated by fungal culture or KOH from samples of both great toenails.

### Table 1. Minimum inhibitory concentration of tavaborole, amorolfin and efinaconazole compared with ciclopirox.

<table>
<thead>
<tr>
<th>Infectious organism</th>
<th>Minimum inhibitory concentration (μg/ml)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tavaborole</td>
<td>Ciclopirox</td>
</tr>
<tr>
<td><strong>Dermatophytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichophyton rubrum</td>
<td>1–8</td>
<td>0.03–1</td>
</tr>
<tr>
<td>Trichophyton mentagrophytes</td>
<td>2–8</td>
<td>0.03–0.5</td>
</tr>
<tr>
<td>Trichophyton tonsurans</td>
<td>2–4</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Epidermophyton floccosum</td>
<td>≤0.5</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>Microsporum audouinii</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Microsporum canis</td>
<td>2</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>Microsporum gypseum</td>
<td>2</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td><strong>Nondermatophyte molds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>0.25</td>
<td>0.25–0.50</td>
</tr>
<tr>
<td>Fusarium solani</td>
<td>≤0.5</td>
<td>≥4</td>
</tr>
<tr>
<td><strong>Yeasts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida albicans</td>
<td>1.0</td>
<td>0.06–0.5</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>≤0.5</td>
<td>0.13–0.5</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>1</td>
<td>0.13–0.25</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>≤0.5</td>
<td>0.13–0.5</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>≤0.5</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>0.25</td>
<td>≤0.031</td>
</tr>
<tr>
<td>Malassezia furfur</td>
<td>1</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Malassezia pachydermatis</td>
<td>1</td>
<td>≤0.5</td>
</tr>
<tr>
<td>Malassezia sympodialis</td>
<td>1</td>
<td>≤0.5</td>
</tr>
</tbody>
</table>
**Table 2. Clinical efficacy of Phase I and II studies.**

<table>
<thead>
<tr>
<th>Study details</th>
<th>Phase I</th>
<th>Phase II 200</th>
<th>Phase II 201</th>
<th>Phase II 203</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>USA</td>
<td>Mexico and USA</td>
<td>Mexico</td>
<td>USA</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Open-label, single group</td>
<td>Randomized, double-blind, vehicle-controlled, multicenter</td>
<td>Multicenter, open-label</td>
<td>Multicenter, open-label</td>
</tr>
<tr>
<td><strong>Eligibility criteria</strong></td>
<td>Great toenail, &gt;80% nail involvement, combined thickness &lt;3 mm, KOH positive</td>
<td>DLSO great toenail, 20–60% nail involvement, combined thickness &lt;3 mm, KOH positive and culture positive for dermatophytes, capable of nail growth</td>
<td>DLSO great toenail, 20–60% nail involvement, combined thickness &lt;3 mm, KOH positive, culture positive (5.0% for 12 months only), capable of nail growth</td>
<td>DLSO great toenail, 20–60% nail involvement, combined thickness &lt;3 mm, KOH positive and culture positive for dermatophytes, capable of nail growth</td>
</tr>
<tr>
<td><strong>Treatment Arm</strong></td>
<td>Tavaborole 7.5%</td>
<td>Vehicle</td>
<td>Tavaborole 5.0%</td>
<td>Tavaborole 5.0%</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>q.d.</td>
<td>q.d. (3 mo)/t.i.w.</td>
<td>q.d. (3 mo)/t.i.w.</td>
<td>q.d. (3 mo)/t.i.w.</td>
</tr>
<tr>
<td><strong>Duration of treatment</strong></td>
<td>1 mo</td>
<td>6 mo</td>
<td>6 mo</td>
<td>6 mo</td>
</tr>
<tr>
<td><strong>Participants (n)</strong></td>
<td>15</td>
<td>63</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td><strong>Efficacy rate (%)</strong></td>
<td>N/A</td>
<td>14</td>
<td>27*</td>
<td>26*</td>
</tr>
</tbody>
</table>

Ref. [36,39] [40,41] [40,42] [40,42–44] [40,42]

* †p < 0.05 compared with vehicle (0.0%).

**Efficacy** is defined as negative fungal culture and (≥2 mm of new clear nail growth or investigator static global assessment of clear or almost clear).

**The primary efficacy end point of this arm was treatment response at day 360; however, 6 months data are presented here.**

* d: Days; DLSO: Distal subungual onychomycosis; mo: Months; q.d.: Once daily; t.i.w.: Three-times weekly.
Table 3. Clinical efficacy of Phase III studies.

<table>
<thead>
<tr>
<th>Study details</th>
<th>Phase III 301</th>
<th>Phase III 302</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Mexico and the USA</td>
<td>Canada and the USA</td>
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<tr>
<td>Design</td>
<td>Randomized, double-blind, vehicle-controlled, multicenter</td>
<td></td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>DLSO great toenail, 20–60% nail involvement, at least 3 mm of clear nail from proximal nail fold, KOH positive</td>
<td></td>
</tr>
<tr>
<td>Treatment arm</td>
<td>Tavaborole 5%</td>
<td>Vehicle</td>
</tr>
<tr>
<td></td>
<td>q.d.</td>
<td>q.d.</td>
</tr>
<tr>
<td>Participants (n)</td>
<td>399</td>
<td>194</td>
</tr>
<tr>
<td>Duration of treatment/end point</td>
<td>48 weeks/52 weeks</td>
<td>48 weeks/52 weeks</td>
</tr>
<tr>
<td>Complete cure rate (%)</td>
<td>6.5*</td>
<td>9.1*</td>
</tr>
<tr>
<td>Negative mycology (%)</td>
<td>31.1*</td>
<td>35.9*</td>
</tr>
<tr>
<td>Clear or almost clear nail (%)</td>
<td>26.1*</td>
<td>27.5*</td>
</tr>
<tr>
<td>Ref.</td>
<td>[45,46]</td>
<td>[27,45]</td>
</tr>
</tbody>
</table>

*p ≤ 0.001 compared with vehicle (0.0%).

Complete cure rate is defined as the proportion of participants with completely clear nail and mycological cure.

Clear or almost clear nail is defined as the proportion of participants with ≤10% clinical nail involvement.

DLSO: Distalateral subungual onychomycosis; mo-month; q.d.: Once daily.

Safety & tolerability

- Preclinical toxicity studies

Tavaborole was tested against five cytochrome P450 isoforms: CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. At a concentration of 10 μM, tavaborole did not significantly inhibit any of these enzymes [47]. These data combined with the negligible systemic absorption of topically applied tavaborole suggest that there is little risk of drug–drug interactions associated with this intervention.

In vitro and in vivo animal experiments demonstrated that there was no genetic toxicity associated with tavaborole [48]. Tavaborole 10% solution and its vehicle were not primary irritants or contact sensitizers. Local skin irritation was observed in mini pigs after daily application in a dose-dependent manner [47,49]. Moreover, eye irritation likely due to the vehicle was observed in rabbits [47]. Thus, contact with the eyes should be avoided. Reduced fetal body weight was observed in rabbits following topical application of tavaborole 10% solution, but not with the tavaborole 5% solution used in the Phase III studies [49].

- Clinical studies

The safety information released for the Phase III studies reports that none of the serious adverse events were related to tavaborole and that the treatment with tavaborole 5% solution was associated with a low rate of discontinuation due to adverse events (0.8–2.9 vs 0.5–1.5% for vehicle).

The treatment-related adverse events observed included the following application site reactions: exfoliation (2.7%), erythema (1.6%) and dermatitis (1.3%) [45]. Mild to moderate, reversible application site reactions were also reported as the most common adverse events in Phase II studies [38, 40, 50]. In the Phase I study conducted using tavaborole 7.5% solution, no laboratory abnormalities were observed for routine hematology and serum chemistry [36]. Taken together, these data show that tavaborole 5.0% solution is a safe topical treatment for onychomycosis.

Regulatory affairs

Tavaborole received FDA approval on 8 July 2014 [28].

Conclusion

Tavaborole is a safe topical treatment for onychomycosis with a novel mechanism of action. Its efficacy for mild to moderate toenail DLSO caused by dermatophytes is comparable to other approved topical antifungals. It is also worth noting that Anacor Pharmaceuticals Inc. is currently developing a second benzoxaborole compound, AN2718, for the treatment of skin and nail fungal infections [51].

Financial & competing interests disclosure

AK Gupta is an advisory board member, consultant, investigator and speaker for Valeant Pharmaceuticals International Inc. AK Gupta was involved in preclinical studies of tavaborole for Anacor Pharmaceuticals Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.
EXECUTIVE SUMMARY

Mechanisms of action
- Tavaborole is a boron-containing antifungal targeting the fungal LeuRS enzyme involved in the protein synthesis.

Pharmacokinetic properties
- The level of systemic tavaborole is not detectable after daily topical application of a 7.5% solution over 28 days.
- Tavaborole accumulates in the toenail at a concentration superior to its minimum inhibitory concentration and is still detectable several months after its application.

Clinical efficacy
- Tavaborole is more efficacious than vehicle for the treatment of toenail distolateral subungual onychomycosis caused by dermatophytes.
- No clinical trials have been performed for onychomycosis caused by Candida spp.

Safety & tolerability
- Preclinical and clinical data suggest that tavaborole is a safe topical treatment for onychomycosis.

Drug interactions
- Tavaborole does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4.
- Topically applied tavaborole has negligible systemic absorption.

Dosage & administration
- In Phase III studies, tavaborole 5.0% nail solution was applied once daily for 48 weeks.

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