Safety, Pharmacokinetics, and Efficacy of Efinaconazole 10% Topical Solution for the Treatment of Onychomycosis in Pediatric Patients

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SYNOPSIS

- Onychomycosis—a chronic fungal nail infection—can occur in children, ranging in prevalence from 0.35% – 5.5% worldwide[1]
- Onychomycosis has been reported to be responsible for approximately 15% of all nail dystrophies in children[2]
- Treatment of onychomycosis is challenging, and can require systemic antifungals for prolonged periods of time; however, parents and healthcare practitioners are hesitant to use long-term systemic treatments in children[3]
- Efinaconazole 10% topical solution (Jublia® Ortho Dermatologics, Bridgewater, NJ) is an azole antifungal indicated for the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*

OBJECTIVE

- To evaluate efinaconazole 10% topical solution in pediatric patients with onychomycosis

METHODS

- This phase 4, multicenter, open-label study evaluated safety, pharmacokinetics (PK), and efficacy of efinaconazole 10% topical solution in pediatric patients with distal lateral subungual onychomycosis
- Efinaconazole was administered once daily for 48 weeks, with a 4-week posttreatment follow up at week 52
- Participants were aged 6 – 16 years with culture-positive mild-to-severe onychomycosis affecting ≥20% of at least 1 great toenail
- The PK subset was patients 12 – 16 years with moderate-to-severe onychomycosis affecting ≥50% of each great toenail and onychomycosis in ≥4 additional toenails
- The primary objective of this study was evaluation of safety and PK
  - Safety included adverse events (AEs) and serious AEs (SAEs)
  - PK assessments included area under the concentration time curve from 0 to 24 hours ($AUC_{0\text{-}24}$), maximum plasma concentration (C_{max}), and time to C_{max} (T_{max}); PK parameters were assessed based on blood samples collected on days 28 and 29 (predose and up to 24 hours postdose)
- Efficacy assessments included mycologic cure, complete cure, and clinical efficacy

RESULTS

Study Population

- A total of 62 patients were enrolled in the study; of these, 12 (19.4%) patients did not complete the study (withdrawal by parent/guardian, n=6; lost to follow-up, n=5; participant request, n=1)
- Sixty participants administered ≥1 dose of study drug (safety population), 17 of whom had PK data on days 28 and 29 (PK population)
- In the safety population, mean age was 13.4 years (range: 6 – 16 years), 66.7% were male, and 88.3% were white
- In the PK population, mean age was 14.1 years (range: 12 – 16 years), 64.7% were male, and 100% were white

Safety

- A summary of all treatment-emergent AEs (TEAEs) is shown in **Table 1**
- All TEAEs were mild or moderate and none led to study discontinuation
- The only treatment-related TEAE was ingrowing nail, with 8 events in 2 participants (**Table 1**)
- No treatment-related SAEs were reported
- No safety signals or trends associated with local skin reactions were observed

TABLE 1. Treatment-Emergent Adverse Event Summary (Safety Population)

	Efinaconazole Solution (n=60)
Number of TEAEs, No.	99
Participants with ≥1 TEAE, n (%)	38 (63.3)
Participants with ≥1 treatment-emergent SAE, n (%)	1 (1.7)[a]
Most common TEAEs (>5% in safety population), n (%)	
Nasopharyngitis	18 (30.0)
Headache	6 (10.0)
Influenza	5 (8.3)
Tinea pedis	4 (6.7)
Contusion	4 (6.7)
Nail injury	4 (6.7)
Ingrowing nail	4 (6.7)
Treatment-related TEAE, n (%)	
Ingrowing nail	2 (3.3)

[a]The SAE of pneumonia was deemed unrelated to treatment; the moderate event resolved with hospitalization and did not require a change in study drug application.
SAE, serious adverse event, TEAE, treatment-emergent adverse event.

Pharmacokinetics

- The final PK analysis population comprised 15 patients; 2 patients were not included (samples arrived thawed from facility [n=1] and statistical outlier [n=1])
- The concentration-time profiles for efinaconazole and the H3 metabolite were relatively stable, with only minor fluctuations during the 24-hour dosing interval (**Figure 1**)
- Systemic exposure to efinaconazole was low (**Table 2**)
- Based on mean $AUC_{0\text{-}24}$ in molar amounts, exposure to the H3 metabolite was approximately 5-fold higher than that observed for efinaconazole (0.169 versus 0.0327 nmol*h/mL)

FIGURE 1. Mean Efinaconazole and H3 Metabolite Plasma Concentration-Time Profiles After Topical Administration of Efinaconazole Solution on Day 28 (PK Analysis Population)

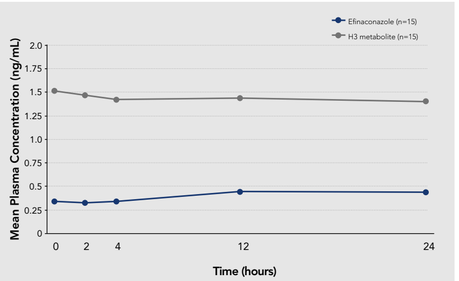


TABLE 2. Mean Pharmacokinetic Parameters of Efinaconazole and H3 Metabolite After Topical Administration of Efinaconazole Solution on Day 28 (PK Analysis Population)

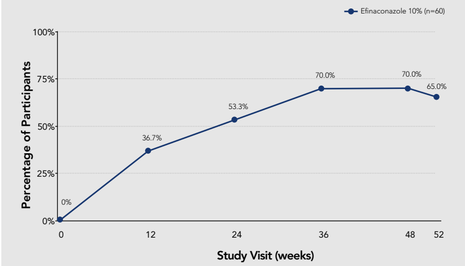
	Efinaconazole (n=15)	H3 Metabolite (n=15)
T_{max}, median (range), h	12.0 (0.00 – 24.5)	4.05 (0.00 – 24.5)
C_{max}, mean (SD), ng/mL	0.549 (0.375)	1.65 (1.31)
$AUC_{0\text{-}24}$, mean (SD), ng*h/mL	11.4 (7.68)[a]	38.1 (30.4)[b]

[a]n=11; [b]n=13.
$AUC_{0\text{-}24}$, area under the concentration time curve from 0 to 24 hours; C_{max}, maximum plasma concentration; SD, standard deviation; T_{max}, time to maximum plasma concentration.

Efficacy

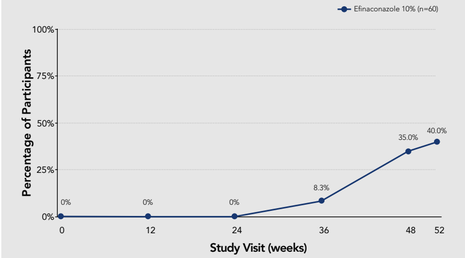
- By week 52, 65.0% of patients achieved mycologic cure, with a 36.7% mycologic cure rate observed as early as week 12 (**Figure 2**)
- A total of 40.0% of patients had complete cure by week 52 (**Figure 3**), and half of patients achieved clinical efficacy by study end (**Figure 4**)

FIGURE 2. Mycologic Cure (Safety Population, LOCF)



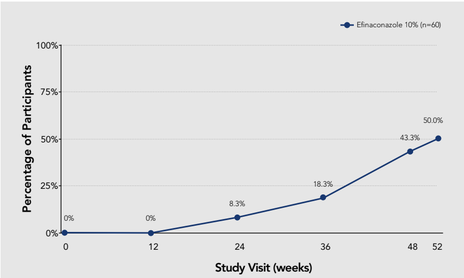
Mycologic cure was defined as negative potassium hydroxide (KOH) and negative fungal culture.
LOCF, last observation carried forward.

FIGURE 3. Complete Cure (Safety Population, LOCF)



Complete cure was defined as 0% clinical involvement of the target toenail and mycologic cure (negative KOH and negative fungal culture).
LOCF, last observation carried forward.

FIGURE 4. Clinical Efficacy (Safety Population, LOCF)



Clinical efficacy was defined as affected target great toenail area <10%.
LOCF, last observation carried forward.

CONCLUSIONS

- Efinaconazole 10% topical solution administered once daily for a year was well tolerated in this pediatric population
- The systemic exposure to efinaconazole in this pediatric population was comparable to that previously reported in adults (C_{max}, 0.67 ng/mL; $AUC_{0\text{-}24}$, 12.15 ng*h/mL)[4]
- Efinaconazole was efficacious in pediatric patients, with improved mycologic cure (65%) and complete cure (40%) rates compared with adults from two 1-year studies (mycologic cure: 53.4–55.2%; complete cure: 15.2–17.8%)[4]

REFERENCES

1. Gupta AK, et al. *Pediatr Dermatol*. 2018;35(5):552-559.
2. Rodriguez-Pazos L, et al. *Mycoses*. 2011;54(5):450-453.
3. Eichenfield LF, Friedlander SF. *J Drugs Dermatol*. 2017;16(2):105-109.
4. Prescribing Information. JUBLIA® (efinaconazole) topical solution, 10%. Ortho Dermatologics.

AUTHOR DISCLOSURES

LE has served as investigator and consultant for Ortho Dermatologics. BE has provided clinical research support (research funding to University) for Abbvie, Anaptys- Bio, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Incyte, Leo, Lilly, Merck, Menlo, Novartis, Pfizer, Regeneron Sun, Ortho Dermatologics, Vanda; and as consultant (received honorarium) from Boehringer Ingelheim, Celgene, Leo, Lilly, Menlo, Novartis, Pfizer, Sun, Ortho Dermatologics, Verrica. JS is a consultant for Ortho Dermatologics, Bausch Health, Regeneron, Sanofi, and Pfizer. TR has served as consultant for Ortho Dermatologics. AG has served as consultant, speaker, and investigator for Ortho Dermatologics. RP is an employee of Bausch Health US, LLC and may hold stock and/or stock options in its parent company. TL is an employee of Ortho Dermatologics and may hold stock and/or stock options in its parent company.

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