A phase II, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study to investigate the efficacy and safety of 4 dose regimens of oral albaconazole in patients with distal subungual onychomycosis

Bárður Sigurgeirsson, MD, PhD,[a] Koen van Rossem, MD, PhD,[b] Steven Malahias, BS,[b] and Kerry Raterink, MS[b]
Kópavogur, Iceland, and Research Triangle Park, North Carolina

Background: Onychomycosis is effectively treated with terbinafine and itraconazole. However, frequent repeated dosing is required, and hepatic and cardiac adverse events may occur.

Objectives: Evaluate efficacy and safety of albaconazole, a novel triazole, for once-weekly treatment of distal subungual onychomycosis of the great toenail.

Methods: This double-blind, phase II study randomized 584 patients to receive albaconazole 100 to 400 mg or placebo weekly for 24 or 36 weeks. Effective treatment was measured as mycologic cure and clear or almost clear nail at week 52.

Results: All treatment groups achieved greater effective treatment rates (21%-54%) compared to placebo (1%; $P < .001$ for all groups) at week 52. Effective treatment was attained at week 24 in $\geq 5\%$ of patients in most groups. Most adverse events were mild or moderate, and treatment-related adverse events were all $\leq 3\%$. No treatment-related hepatic or cardiac serious adverse events were observed.

Limitations: The follow-up period was likely too short to detect maximal efficacy; cure rates were increasing at study end. The efficacy and tolerability of albaconazole were not compared with other available treatments, and the global change in target toenail scale was subjective.

Conclusions: Albaconazole was well tolerated at all doses and resulted in high cure rates for onychomycosis. (J Am Acad Dermatol 2013;69:416-25.)

Key words: albaconazole; dermatophyte; nail fungus; onychomycosis; phase II study; triazole.

Onychomycosis is a fungal nail infection that represents a significant health burden, with an estimated prevalence ranging from 2% to 48% globally.[1-12] Topical antifungal agents have only limited use, and onychomycosis is often treated systemically with terbinafine or triazoles (itraconazole and fluconazole).[1,13] Oral terbinafine administered daily for 12 weeks is considered the criterion standard, with high mycologic (46%-82%) and clinical cure rates (53%-70%) and lower relapse rates compared to other agents.[1,13-17]

Albaconazole is a broad-spectrum azole antifungal discovered at Palau Pharma SA (Barcelona, Spain) that has in vitro activity against yeasts and a

From the Dermatology Centre,[a] University of Iceland, Kópavogur, and Stiefel, a GSK company,[b] Research Triangle Park.

Supported by Stiefel, a GSK company.

Dr Sigurgeirsson was a sponsored investigator on this study and a member of an advisory board that assisted in the planning and design of the study. He also has served as a consultant and investigator for and received honoraria from Arpedia, Celtic, deCode, Galderma, Novartis, Prostrakan, Stiefel, TLT, Topica, and Vertex. Dr van Rossem, Mr Malahias, and Ms Raterink are employees of Stiefel, a GSK company. The registration number for this trial is NCT00730405.

Accepted for publication March 2, 2013.

Reprint requests: Bárður Sigurgeirsson, MD, PhD, Department of Dermatology, University of Iceland, Hudlæknastöðin, Smaratorg 1, 201 Kópavogur, Iceland. E-mail: bsig@hudlaeknastodin.is.

Published online May 24, 2013.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2013.03.021

broad range of filamentous fungi and dermatophytes, including organisms that are most commonly associated with onychomycosis.[18,19]

Its long half-life in humans (mean half-life = 70.5 hours after single oral doses of 240 mg) may allow for weekly dosing. A previous study found that albaconazole 100 and 350 mg per week for 12 weeks was significantly better than placebo in treating distal subungual onychomycosis; however, cure rates were not yet considered optimal (Stiefel data on file). The purpose of this dose-ranging study was to assess the efficacy and safety of 4 once-weekly dose regimens of albaconazole in patients with distal subungual onychomycosis. We also sought a suitable dose regimen for subsequent pivotal phase III studies.

CAPSULE SUMMARY

- Onychomycosis can be effectively treated with terbinafine and triazoles, but current therapies require daily dosing.
- This trial shows that once-weekly treatment with albaconazole, a novel triazole, yielded high effective treatment rates (up to 54%) with a favorable safety profile.
- Albaconazole could provide an alternative to current therapies for onychomycosis.

METHODS

Study design

This was a phase II, double-blind, placebo-controlled, dose-ranging, multicenter, parallel group study. Twenty-six centers in the United States, 3 in Canada, and 1 in Iceland participated in this study, which was approved by the institutional review boards of all institutions and was conducted in accordance with the Declaration of Helsinki. Patients were assigned to 1 of 4 once-weekly albaconazole capsule dose regimens: 100 mg (36 weeks), 200 mg (36 weeks), 400 mg (36 weeks), 400 mg (24 weeks plus 12 weeks of placebo), or placebo-matched capsules (36 weeks). Assuming a dropout rate of 20% and a placebo response rate of 10%, 110 subjects per group would detect a 20% difference between active and placebo groups, with >90% power and a 2-sided 5% type I error rate. The study had 3 phases: pretreatment (up to 10 weeks); treatment (baseline to week 36; visits occurred every 4 weeks until week 30, with an additional visit at week 36); and follow-up (weeks 40-52; visits every 4 weeks).

Pharmacokinetic (PK) blood and nail samples were obtained and electrocardiograms (ECGs) performed according to the schedule in Fig 1. During pretreatment, the following information was obtained and tests conducted: informed consent, demographics, medical history, physical examination, clinical assessment of toenails and fingernails and mycologic assessment of target toenail, clinical laboratory tests, pregnancy test, 12-lead ECG, vital signs, and concomitant medication use.

Global change in target toenail condition was assessed by visual examination at weeks 12, 24, 30, 36, 44, and 52 using the following rating scale: 0 = cleared; 1 = much improved; 2 = minimally improved; 3 = unchanged; 4 = minimally worse; and 5 = much worse. Culture and potassium hydroxide (KOH) microscopy of the target toenail were performed at screening and every visit from week 12 through the end of the study. The percentage of affected target nail, measurement of clear growth of target nail, and number of affected nails were determined at every visit, including screening and baseline.

Patients

Participants ranged in age from 19 to 74 years, and all patients had distal subungual onychomycosis affecting at least 1 great toenail (target toenail) with $\geq 25\%$ nail involvement, ≥ 2 mm of unaffected toenail at the proximal end, and microscopic (KOH/calcofluor) and culture confirmation of dermatophytes. Baseline and laboratory screening parameters were within normal ranges. Eligible patients had alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin levels that were ≤ 1.5 times the upper normal limit at screening, and baseline ECG findings were within normal ranges, unless considered to be clinically insignificant by the investigator. Exclusion criteria were: females who were pregnant, trying to become pregnant, or who were breastfeeding; receipt of an investigational drug within 4 weeks before the first dose of the study product, an investigational systemic drug treatment for onychomycosis within 6 months before the first dose of the study product, or topical onychomycosis treatment within 3 months before the first dose of the study product; scheduled receipt of any other investigational drug during the study; receipt of any known substrate of the 3A4 isozyme of cytochrome P450 (CYP3A4) with QT prolongation potential; the concomitant use of prohibited medications (see Supplemental Table I, available online at http://www.jaad.org); a history of any condition that could possibly affect drug absorption (eg, gastrectomy), uncontrolled diabetes, clinically significant peripheral vascular disease or circulatory impairment, or any major illness within 30 days before screening; or ECG abnormalities deemed clinically relevant.