Long-term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis

Lawrence F. Eichenfield, MD,[a,b] Robert S. Call, MD,[c] Douglass W. Forsha, MD,[d] Joseph Fowler, Jr, MD,[e] Adelaide A. Hebert, MD,[f] Mary Spellman, MD,[g] Linda F. Stein Gold, MD,[h] Merrie Van Syoc, BS,[i] Lee T. Zane, MD,[j] and Eduardo Tschen, MD, MBA[k]

San Diego and Palo Alto, California; Richmond, Virginia; West Jordan, Utah; Louisville, Kentucky; Houston, Texas; Detroit, Michigan; New York, New York; and Albuquerque, New Mexico

Background: Long-term topical treatment is often required for atopic dermatitis (AD), a chronic inflammatory skin disease.

Objective: To assess the long-term safety results from a multicenter, open-label, 48-week safety study (AD-303) of patients (N = 517) ≥2 years of age with mild to moderate AD who continued crisaborole treatment, a topical phosphodiesterase-4 inhibitor, after completing a 28-day phase 3 pivotal study (AD-301, AD-302).

Methods: Global disease severity was assessed in patients every 4 weeks, and if assessed as mild or greater, a 28-day treatment period with crisaborole applied twice daily was initiated. Adverse events (AEs), including treatment-emergent AEs (TEAEs), and serious AEs were analyzed.

Results: During the pivotal studies and AD-303, 65% of patients reported ≥1 TEAE, most of which were mild (51.2%) or moderate (44.6%) and considered unrelated to treatment (93.1%). The frequency and severity of TEAEs were consistent. The most frequently reported treatment-related AEs (overall, 10.2%) were dermatitis atopic (3.1%), application-site pain (2.3%), and application-site infection (1.2%). Nine patients (1.7%) discontinued the long-term study because of TEAEs.

Limitations: Long-term efficacy was not analyzed.

Conclusion: Crisaborole ointment had a low frequency of treatment-related AEs over 48 weeks of treatment of patients with AD. (J Am Acad Dermatol 2017;77:641-49.)

Key words: atopic dermatitis; crisaborole; eczema; long-term safety; ointment; PDE4; phosphodiesterase-4; topical treatment.

From the Division of Pediatric Dermatology, Rady Children's Hospital, San Diego[a]; Departments of Dermatology and Pediatrics, University of California, San Diego[b]; Clinical Research Partners, Richmond[c]; Jordan Valley Dermatology and Research Center, West Jordan[d]; Dermatology Specialists Research, Louisville[e]; Department of Dermatology, UTHealth McGovern Medical School—Houston[f]; Paid consultant to Anacor Pharmaceuticals Inc, Palo Alto[g]; Henry Ford Health System, Detroit[h]; Pfizer Inc, New York[i]; Anacor Pharmaceuticals Inc, acquired by Pfizer Inc, New York[j]; and Academic Dermatology Associates, Albuquerque.[k]

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Please visit http://www.jaad.org for a complete list of investigators for Study AD-303.

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Correspondence to: Lawrence F. Eichenfield, MD, Pediatric Dermatology, Rady Children's Hospital—San Diego, 8010 Frost St, San Diego, CA 92123. E-mail: leichenfield@rchsd.org.

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Atopic dermatitis (AD), a chronic inflammatory skin disease characterized by eczematous lesions, an impaired epidermal barrier, and intense pruritus, is estimated to affect 15%-30% of children and 2%-10% of adults in industrialized countries.[1,2] Given the chronic and recurrent nature of AD, long-term treatment is often necessary.[1-3] The American Academy of Dermatology; American Academy of Allergy, Asthma, and Immunology; and American College of Allergy, Asthma, and Immunology treatment guidelines for AD recommend topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI).[3,4] Despite the favorable efficacy of TCS, AD treatment guidelines recommend limiting long-term use of high-dose TCS and restricting application sites to avoid cutaneous adverse events (AEs) (eg, atrophy, telangiectasia) and side effects associated with systemic absorption (eg, hypothalamic-pituitary axis suppression).[3-5] TCI are approved in the United States for short-term and noncontinuous long-term treatment,[3,4] but a boxed warning is included for the potential for lymphoma or other malignancies with long-term use,[3,4,6,7] despite recent reports refuting an increased risk for malignancy.[8-11] No new topical treatments have been approved in the United States in >15 years for the treatment of AD. A novel topical therapeutic agent with the ability to mitigate the signs and symptoms of AD with reduced safety concerns would be useful for long-term disease management.

Phosphodiesterase-4 (PDE4), an intracellular enzyme involved in proinflammatory cytokine production, has been identified as a novel therapeutic target to control the underlying inflammation associated with AD.[12-14] PDE4 is overactive in inflammatory cells of patients with AD, leading to degradation of cyclic adenosine monophosphate and subsequent production of proinflammatory cytokines.[15-18] Crisaborole ointment, 2% (Pfizer Inc, New York, NY), a treatment for mild to moderate AD, inhibits PDE4-dependent cyclic adenosine monophosphate degradation, which regulates nuclear factor kappa B and nuclear factor of activated T-cell signaling pathways to enhance the cellular control of inflammation.[13,14,19,20] Results of preclinical studies have shown that crisaborole effectively penetrates the skin to inhibit cytokine release at the site of inflamed skin and is noncarcinogenic.[21-24] In addition, crisaborole is rapidly and substantially metabolized to its inactive metabolites, thus limiting systemic exposure of the patient to active PDE4 inhibition and potential off-target side effects.[25]

Phase 1 and phase 2 trials have demonstrated a favorable safety profile for crisaborole ointment and improvement in global and lesional disease severity.[25-28] Two identically designed, 28-day, vehicle-controlled, pivotal phase 3 studies demonstrated that crisaborole ointment significantly improved global disease severity and all measured signs and symptoms of AD in patients ≥2 years of age with mild to moderate AD.[29] In addition, 28-day treatment with crisaborole ointment did not result in any serious treatment-related AEs, and most AEs were mild to moderate and were considered unrelated to treatment.[29] To assess the long-term safety of crisaborole ointment, crisaborole- and vehicle-treated patients from the phase 3 trials were enrolled in an open-label, single-arm, 48-week extension study (AD-303). The extent of drug exposure, AEs, and use of rescue therapy were assessed in children, adolescents, and adults with mild to moderate AD.

CAPSULE SUMMARY

- Current topical treatments for atopic dermatitis are associated with long-term treatment safety concerns.
- A 48-week phase 3 safety study with crisaborole ointment, a nonsteroidal, anti-inflammatory, phosphodiesterase-4 inhibitor, demonstrated a low frequency of treatment-related adverse events.
- Crisaborole ointment represents a potential long-term option to improve the management of atopic dermatitis.

METHODS

Study design and oversight

A multicenter, open-label, long-term safety study was conducted in the United States over 48 weeks in patients with mild to moderate AD after they completed a 28-day phase 3 pivotal study (AD-301, NCT02118766; AD-302, NCT02118792) (Fig 1). Institutional review board approval was obtained for the protocol, informed consent/assent forms, and all relevant supporting data. The study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice and all country-specific regulatory requirements. In accordance with the International Council on Harmonization technical requirements for the registration of pharmaceuticals for human use guidelines for the assessment of clinical safety for long-term treatment, the enrolled patient population size was large enough to ensure that a minimum of 100 and 300 patients completed 12 and 6 months of follow-up, respectively.[30]