Crisaborole: a New Option for the Treatment of Atopic Dermatitis
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Atopic dermatitis, one of the most common inflammatory skin disorders, remains a difficult condition to manage. Approximately 20-30% of children and 5-10% of adults have atopic dermatitis, with more than 80% of patients developing symptoms before 5 years of age. Topical application of emollients is of limited benefit, while more effective treatments may have significant adverse effects. Frequent or sustained use of topical glucocorticoids can produce thinning of the skin and place patients at risk for adrenal suppression, increased infections, and growth suppression. Topical calcineurin inhibitors such tacrolimus or pimecrolimus, while generally well tolerated, carry a black box warning for a potential association with rare cases of malignancy.

On December 14, 2016, the Food and Drug Administration (FDA) approved crisaborole 2% ointment for the treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. Crisaborole is the first of several novel anti-inflammatory treatment options for this condition to come to market. Dupilumab, a new monoclonal antibody for atopic dermatitis, is currently under priority review by the FDA.

Mechanism of Action
Crisaborole, 5-(4-cyanophenoy)-1,3-dihydro-1-hydroxy-[2,1]benzoxaborole, belongs to the class of drugs known as benzoxaboroles. These agents are boron-based small molecules that are potent inhibitors of phosphodiesterase 4 (PDE4). Intracellular PDE4 converts cyclic adenosine monophosphate (cAMP) to 5′-AMP and is predominantly found in immune cells, including B cells, T cells, neutrophils, monocytes, macrophages, and eosinophils. Inhibition of PDE4 prevents degradation of cAMP. The resulting increase in cAMP activates protein kinase A, which negatively modulates the signaling pathways that promote release of Th1 and Th2 cytokines involved in initiating and sustaining inflammation, pruritus, and epidermal hyperplasia. Benzoxaborole PDE4 inhibitors have been shown in cell culture to suppress release of tumor necrosis factor-alpha (TNFα), interleukin-23 (IL-23), IL-22, IL-17, IL-14, IL-13, IL-4, and interferon-ɤ. The low molecular weight of crisaborole results in effective penetration of the epidermis and dermis, while the inclusion of boron mimics the phosphate in cAMP, allowing the drug to effectively target and inhibit intracellular PDE4.

Pharmacokinetics
Topical administration of PDE4 inhibitors allows rapid absorption into the skin, but limits systemic exposure. The small fraction of a crisaborole 2% ointment dose that is systemically absorbed is highly bound (97%) to plasma proteins. It undergoes extensive hepatic metabolism via hydrolysis and subsequent oxidation to two inactive metabolites. These metabolites then undergo renal excretion. Crisaborole does not produce clinically significant induction or inhibition of cytochrome P450 enzymes.

The pharmacokinetic profile of crisaborole was evaluated in a premarketing study of 33 children 2 to 17 years of age with mild to moderate atopic dermatitis. The 2% ointment was applied in a dose of approximately 3 mg/cm² twice daily for 8 days. Plasma samples were evaluated on the last day of the study. The mean maximum plasma concentration (Cmax) was 127 ± 196 ng/mL, with an area under the concentration time curve (AUC) from 0 to 12 hours of 949 ± 1240 ng·hr/mL, demonstrating the low systemic exposure following topical application.

Additional pharmacokinetic data are available from a multicenter, open-label phase 2a safety and
tolerability study by Tom and colleagues, conducted in 23 adolescents ranging from 12 to 17 years of age (mean age 15 ± 1.5 years). These patients had lesions covering 10-35% of their body surface area (BSA), excluding the scalp, and Investigator Status Global Assessment (ISGA) scores of 2 or 3. The ISGA is a 5-point assessment of disease severity, ranging from 0 (clear) to 4 (severe), with scores of 2 or 3 indicating mild and moderate atopic dermatitis, respectively. Crisaborole was applied in a surface area-based dosage twice daily for 28 days. Dosing cards were used to provide the correct dose and to document application sites. Plasma samples were collected on days 1, 2, 4, 6, 8, and 9, following administration of the morning dose in the clinic to ensure accurate timing.

Twenty-two patients completed the study. The mean for C\text{max} on days 1 and 8 were 105 ± 160 and 94.6 ± 189 ng/mL, respectively. Median time to reach C\text{max} was 2.37 hrs, with a range of 1-24 hrs) on day 1. The median time to C\text{max} on day 8 was 2.17 hrs (1-7.93 hrs). Mean AUC values were also similar on days 1 and 8, at 448 ± 527 and 462 ± 506 ng·hr/mL, with a resulting day 8 to day 1 ratio of 1.43-fold. Elimination half-life was 7.2 ± 2.3 hrs on day 1 and 11.9 ± 8.3 hrs on day 8.

Similar results were found in a phase Ib study published by Zane and colleagues in the July/August 2016 issue of Pediatric Dermatology. This open-label pharmacokinetic, safety, and tolerability study enrolled 34 patients ranging from 2 to 17 years of age; all with lesions involving ≥ 25% BSA. The methodology for the pharmacokinetic assessment was similar to the previous study. The mean C\text{max} of 111 ± 113 ng/mL on day 1 occurred at a median time of 3.00 hrs (range 3-12 hrs). The AUC for 0-12 hours was 759 ± 730 ng·hr/mL. Results for day 8 included a mean C\text{max} of 127 ± 196 ng/mL, a median time to C\text{max} of 3.00 hrs (range 3-24 hrs), and an AUC of 949 ± 1240 ng·hr/mL. This larger study confirms the limited systemic accumulation of crisaborole 2% ointment in children and adolescents after short-term use, confirming the earlier pharmacokinetic data.

Clinical Experience

Crisaborole ointment was evaluated in multiple clinical trials prior to FDA approval last year, ranging from proof-of-concept studies to large phase 3 randomized, vehicle-controlled trials. The results of many of these manufacturer-sponsored trials have been published in peer-reviewed journals, allowing readers access to a significant amount of premarketing data. The following section presents a summary of these studies in chronologic order of the date of publication.

In 2015, Murrell and colleagues published the results of a phase 2a proof-of-concept study of crisaborole in adults with atopic dermatitis. This randomized, double-blind, 6-week study compared crisaborole 2% ointment to the vehicle (ointment without the active drug) in 25 adults with mild to moderate atopic disease. Patients used the study ointment on one target lesion, and monitored symptoms on both their target lesion and one additional comparable lesion that was not treated. The primary endpoint for the study was the change from baseline in the Atopic Dermatitis Severity Index (ADSI) score at day 28. Seventeen patients (68%) documented a greater decrease in ADSI score in the crisaborole-treated lesion compared to the vehicle, while five patients (20%) had a greater decrease in the vehicle-treated lesion. Twenty-nine adverse effects were reported in 11 patients; 90% were classified as mild and unrelated to the study medication. No serious or severe reactions were reported. This study provided preliminary evidence of the efficacy and safety of crisaborole 2% ointment and support for further research.

Stein Gold and colleagues conducted a larger phase 2 randomized dose-ranging study of crisaborole ointment in two strengths, 0.5% and 2% in adolescents with mild to moderate atopic dermatitis. A total of 68 patients 12-17 years of age were randomized to either once or twice-daily treatment. Each patient treated two lesions, one with the 0.5% product and another with the 2% product. At study completion on day 29, all dosing regimens had produced improvements in ADSI scores, as well as in all five signs and symptoms of atopic dermatitis: erythema, excoriation, exudation, lichenification, and pruritus. The greatest improvement was seen with the 2% ointment applied twice daily, with a 71% improvement in ADSI from baseline. Sixty-two percent of patients in this group had total or partial clearance of their target lesions (an ADSI ≤ 2). The only adverse effect reported in this study was mild application site irritation in four patients. No patients discontinued treatment.

Tom and colleagues found a significant decrease in ISGA scores and severity of atopic dermatitis symptoms in the 23 adolescents in their phase 2a pediatric pharmacokinetic, safety, and tolerability study. Treatment success was defined as an ISGA of ≤ 1 or a decrease of 2 points or more from baseline. The signs and symptoms evaluated were identical to the previous study. The mean ISGA score decreased from 2.43 ± 0.51 at baseline to 1.35 ± 1.03 on day 29, a mean change of -1.08 ± 0.85. Eight patients (35%) met the criteria for treatment success. Mean scores for all signs and symptoms decreased from 1.87 at
baseline to 0.57 at day 29 (mean change -1.30 ± 0.73). The mean treatable percentage of BSA, an estimate of the percentage of skin with atopic dermatitis lesions, decreased from 17.6 ± 5.7 to 8.2 ± 8.9, with a mean change of -9.4 ± 8.1 (a 53% decrease).

In February 2016, Draelos and colleagues reported the results of their post hoc analyses of the effect of crisaborole 2% ointment on pruritus, using data from 58 patients enrolled in one of four phase 1 and 2 clinical trials. Pruritus severity was classified on a 4-point rating scale, with 0 being none and 3 being severe. In the pooled analysis of studies 1 and 2, the percent change from baseline pruritus severity score was 63% on day 8 and 65% on day 29 of treatment (each p < 0.001). Significant reductions in pruritus scores were found in the analysis of the 67 patients in studies 3 and 4.

In the phase 1b open-label study by Zane and colleagues described previously, 34 children and adolescents with lesions involving ≥ 25% BSA were assessed for change in ISGA scores and signs and symptoms after being treated with crisaborole 2% ointment twice daily for 29 days. Mean ISGA scores declined from 2.65 ± 0.49 at baseline to 1.15 ± 1.08 on day 29 in the 31 patients who completed the study, with 47% of patients achieving treatment success, defined as an ISGA of ≤ 1 or a decrease of 2 grades or more from baseline, and 64.7% achieving an ISGA score of 0 (clear) or 1 (almost clear). Mean ISGA scores at day 29 were 0.58 ± 0.79 in the 12-17 year-olds, 1.33 ± 1.16 in the 6-11 year-olds, and 1.60 ± 1.08 in the 2-5 year-olds, representing reductions of 76.4%, 48.6%, and 45.0% in the three cohorts, respectively. The overall change in treatable percentage of BSA from baseline was -77.7 ± 22.1. The change was greatest in the adolescents at -86.6 ± 18.6, compared to -72.8 ± 24.4 in the 6-11 year-olds and -73.0 ± 21.7 in the 2-5 year-olds. Mean signs and symptoms scores decreased throughout the study, with a mean change from baseline to day 29 in erythema of -64.9%, excoriation -58.2%, exudation -64.3%, lichenification -61.3%, and pruritus -63.3%.

While a relatively small study, this paper provides a more in-depth look at age-related response to treatment.

Paller and colleagues published the results of two identical multicenter, randomized, double-blind, vehicle-controlled phase 3 clinical trials with crisaborole in the September 2016 issue of the Journal of the American Academy of Dermatology. Patients 2 to 79 years of age with mild to moderate atopic dermatitis, defined as > 5% treatable BSA and a baseline ISGA of 2 or 3, were randomized in a 2:1 ratio to receive crisaborole 2% ointment or the vehicle applied twice daily to all affected areas except the scalp. The primary endpoint was treatment success at day 29, defined as an ISGA ≤ 1 in addition to a 2-grade or more improvement from baseline. Secondary endpoints included time to success, pruritus severity and the change in disease signs and symptoms from baseline. The two studies, AD-301 and AD-302 enrolled 759 and 763 patients, respectively. More patients in the crisaborole groups achieved treatment success than in the groups using the vehicle alone (32.8% compared to 25.4%, p = 0.038 in AD-301 and 31.4% compared to 18.0%, p < 0.001 in AD-302). Kaplan-Meier analysis revealed that the patients receiving crisaborole achieved treatment success earlier than those given the vehicle alone (p < 0.001). The percentage of patients with ISGA scores ≤ 1, but not meeting the > 2 grade improvement from baseline, was also greater in the crisaborole groups (51.7% versus 40.6%, p = 0.005 in AD-301 and 48.5% versus 29.7%, p < 0.001 in AD-302). Pooled data on days 8, 15, 22, and 29 demonstrated a significantly greater percentage of crisaborole-treated patients with improvement in their pruritus scores (p < 0.001 for days 8, 15, and 22 and p = 0.002 for day 29).

Significantly greater improvement was also noted in the crisaborole-treated group for all the remaining signs and symptoms, with pooled data from the two studies showing a 69% reduction in erythema compared to 40% in the controls (p < 0.001), a 40% reduction in exudation compared to 30% (p < 0.001), a 60% reduction in excoriation versus 48% (p < 0.001), a 55% reduction in induration compared to 46% (p = 0.008), and a 52% reduction in lichenification compared to 41% in the group given the vehicle alone (p < 0.001). Adverse effects were common in both groups, but most were mild to moderate in severity and considered to be unrelated or unlikely to be related to the treatment. The most frequently reported adverse effects were application site pain (in 4.4% of patients given crisaborole and 1.2% of those given vehicle).

Warnings and Precautions
Hypersensitivity reactions have occurred after crisaborole use, although these reactions appear to be rare. Symptoms include severe pruritus, swelling and erythema. Crisaborole should be discontinued in any patient experiencing these symptoms.

Adverse Effects
Crisaborole 2% ointment has been well tolerated in clinical trials. In the study by Tom and colleagues, 10 of the 23 patients (43.5%) reported
a total of 19 adverse effects. Eleven were rated as mild in severity and 8 were moderate. Only one adverse effect (pain at the application site) was considered to be definitely related to crisaborole use and led to discontinuation of the study. Tolerability was assessed by the degree of burning or stinging of the skin at the application site. At study completion (day 29), 20 patients (87.7%) reported no burning or stinging, two reported mild symptoms, and one patient reported severe symptoms (the patient who required discontinuation of treatment). The results of this study mirror those reported in a pooled safety analysis of 168 children and adults enrolled in premarketing clinical trials. Thirty-six percent of patients reported one or more adverse effect, but of these, 73% were considered mild, 25% were moderate, and only 2% were severe. None of the severe adverse effects were considered to be serious or related to the drug. Only two of the patients (1%) discontinued treatment, with either application site pain or dermatitis.

Additional safety data comes from a randomized, double-blind, vehicle-controlled study in 32 adults using crisaborole 2% ointment on sensitive or thin skin, including the face, genitals, extensor and intertriginous areas. There were no differences between treatment groups, with 98.8% of tolerability assessments (burning/stinging, erythema, or pruritus) rated as a grade 0 (no symptoms) and 0.1% rated as 1 (mild). Tolerability did not change over time.

**Availability and Dosing**

Crisaborole 2% ointment (Eucrisa™) is available in 60 gram and 100 gram tubes. Each gram contains 20 mg crisaborole in an ointment consisting of white petrolatum, propylene glycol, mono- and di-glycerides, paraffin, butylated hydroxytoluene, and edetate calcium disodium. It should be applied in a thin layer twice daily to affected areas of the skin. Crisaborole ointment should be stored at room temperature in its original container. Patients or parents should wash their hands after applying the ointment.

**Summary**

Crisaborole is the first of the benoxaborole PDE4 inhibitors to be approved by the FDA for treatment of atopic dermatitis in children and adults. The availability of drugs targeting the generation of cytokines associated with the Th1 and Th2-mediated immune response ushers in a new era in the treatment of this disease. While clinical trials have demonstrated the efficacy and safety of crisaborole for up to a month, continued post-marketing surveillance studies will be needed to confirm the long-term effects of the drug in both children and adults.

**References**


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