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Eucrisa® (crisaborole): A New Topical Agent for the Treatment of Atopic Dermatitis

Jennifer Poulos, PharmD Candidate

Atopic dermatitis (AD) is a chronic inflammatory skin condition commonly referred to as eczema. AD often presents as acute flare-ups of pruritic, erythematous, dry or scaly patches on the skin with decreased skin barrier function. When patients scratch lesions to relieve itching, the scratching may further disrupt the skin barrier, increasing the risk of secondary skin infections. Eczema has been associated with a decrease in quality of life, especially because itching tends to increase during the night, leading to loss of sleep. AD affects 15-20% of children and 1-3% of adults across the globe, with increasing prevalence among low-income countries in Latin America and Southeast Asia.[1] There are several proposed mechanisms as to how eczema manifests, but ultimately its pathophysiology remains unclear. Eczema is an IgE-mediated response; therefore, currently available therapies target the immune system. Eczema is a chronic condition with acute flare-ups associated with a biphasic immune response. Patients who develop AD as children are more likely to develop other atopic conditions, such as asthma and allergic rhinitis.

Pharmacology

Pharmacokinetics

Crisaborole is a relatively small molecule at 251 Daltons, making it a favorable option for topical application and absorption.[3,4] Due to its small size, crisaborole can easily penetrate through the epidermis and dermis of the affected site to be systemically absorbed.[3] Once the drug reaches systemic circulation, it is quickly metabolized into two inactive oxidative metabolites (AN7602 and AN8323).[3,4] Crisaborole and its metabolites are eliminated in the urine.[3,4,5,6] Crisaborole remains in the bloodstream with 97% binding to plasma proteins.[4,5,6] Preclinical trials had varying values regarding Cmax and AUC, and ultimately after review were found to increase when affected body surface area (BSA%) increased.[3,5] A summary of the pharmacokinetic properties are listed in Table 1.[5,6,7]

Mechanism of Action

Crisaborole is a topically applied PDE4 inhibitor. PDE4 is an enzyme present in immune cells that degrades the second messenger cyclic adenosine monophosphate (cAMP). When cAMP is degraded within immune cells, it stimulates the release of cytokines and proinflammatory factors. Increased cAMP suppresses the activity of the NF-κB, CREB, NFAT, Rap1 and Csk, which in turn will decrease the production of cytokines.[3,4] Crisaborole can inhibit certain Th1 and Th2 proinflammatory cytokines, including IFN-γ, TNF-α, IL-2, IL-5 and IL-10.[3,4] Thus, when PDE4 is inhibited, the release and production of inflammatory substances is also inhibited.

Clinical Trials

Phase II Trials

Table 2 provides a brief summary of the results from the phase II trials. Wynnis and colleagues conducted a phase IIa, multicentered, open label trial in order to evaluate systemic exposure, safety, efficacy, pharmacokinetics, and tolerability of crisaborole 2% topical ointment in adolescent patients (ages 12 to 17). The study included male and female patients aged 12 to 17 with 10-35% of body surface area of treatable AD lesions.[8] Patients included in the study needed a score of at least 2 (mild) or 3 (moderate) on the Investigator Static Global Assessment (ISGA).[8] Patients were excluded if they had a disease state (other than AD

Table 1 | Pharmacokinetic properties of crisaborole ointment.[5,6,7]

Cmax	127 ± 196 ng/mL by day 8
$AUC_{(0-12)}$	949 ± 1240 ng*h/mL by day 8
Steady State	~8 days
Elimination	Kidneys (>75% AN7602 inactive metabolite)
Metabolism	Major: oxidative deboronation/hydrolysis (AN7602, inactive) Minor: Phase I oxidation (AN8323, inactive)

AUC_{0-12}= area under the curve from 0 to 12 hours; **Cmax** = maximum concentration; **h** = hour; **mL** = milliliter; **ng** = nanogram

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Table 2 | Summary of Phase II and III trials of crisaborole 2% ointment.

Study	Patient Population	Design	Treatment Arms	Primary Endpoint	Results
Wynnis, et al[8] (2016)	Ages 12-17 Mild to moderate AD	Phase II multicenter, open-label, no control, no blinding	Crisaborole twice daily N = 22	Change from baseline ISGA to an ISGA of 1 or less	Mean ISGA score decreased from 2.43 ± 0.51 at baseline to 1.35 ± 1.03 at day 29 Average 53% decrease in lesion area
Murrell, et. al[9] (2015)	Ages 18-75 Mild to moderate AD	Phase II randomized, double-blind, bilateral, vehicle control	Crisaborole twice daily (N = 28) vs. white petrolatum control twice daily (N= 25)	Change in ADSI from baseline to day 28	68% of patients in crisaborole treatment improved ADSI score (vs 20% vehicle, P = 0.017)
AN2728-AD-301[10]	Ages ≥2 years Mild to moderate AD	Phase III randomized double-blind, vehicle control	Crisaborole twice daily (N = 503) vs. white petrolatum control twice daily (N = 256)	ISGA score at day 29 of clear (0) or almost clear (1)	Greater resolution in ISGA score with crisaborole vs control (32.8% vs 25.4%, P = 0.038)
AN2728-AD-302[10]	Ages ≥2 years Mild to moderate AD	Phase III randomized double-blind, vehicle control	Crisaborole twice daily (N = 513) vs. white petrolatum control twice daily (N = 250)	ISGA score at day 29 of clear (0) or almost clear (1)	Greater resolution in ISGA score with crisaborole vs control (31.4% vs 18.0%, P < 0.001)

or controlled asthma) that would confound the evaluation of the treatment response or adverse events, put them at risk during therapy, or interfered with the patient's ability to take part in the study.[8] Patients were also excluded if their affected lesions were on their scalp or at venous access areas. Other exclusion criteria included severe AD, history of high concentrated topical or systemic corticosteroid therapy, treatment for cancer in the past 5 years, or recent (defined as 2 weeks before baseline visit) exposure to prolonged UV light.[8] Patients were counseled to avoid excessive sun exposure. For patients receiving steroid or UV light therapy, a 35 day washout period was given to wean patients who required step-down therapy.[8] Patients were not allowed to use any other forms of treatment, including UV light therapy, to the lesions being studied. However, patients were allowed to treat lesions that were not being treated with the study drug.

Crisaborole ointment was applied twice daily at least 8 hours apart for 28 days except on days 1 and 8 (only one morning application was done on these days).[8] The dose of 3mg/cm^2 was measured out using cards given to the patients. Treatment was considered successful if patients had a decline in their baseline ISGA to 1 or less and/or had at least a 2-grade improvement from baseline.[8] Mean ISGA score went from 2.43 at baseline to 1.35 at day 29, indicating that AD severity decreased with crisaborole.[8] The efficacy of treatment was also measured in patient's perception of symptoms associated with AD, including pruritus, excoriation, exudation, lichenification, and erythema.[8] Each of these symptoms were assessed using a 4-point score, 0 meaning none present and 3 meaning severe. Mean pruritus score declined from 1.87 at baseline to 0.57 at day 29.[8] Mean treatable BSA% decreased from 17.6% at baseline to 8.2% on day 29, representing an average 53% decrease in lesion area.[8]

Murrell and colleagues conducted a phase II trial to assess the safety, efficacy, and tolerability in adult patients with mild to moderate AD. This study was a 6-week open-label, vehicle-controlled, multicenter, double-blinded, randomized clinical trial. The inclusion criteria were patients aged 18 to 75 years with a clinical diagnosis of AD using the Hanifin and Rajka criteria and at least 2 comparable lesions with a surface area of approximately 10 to 500 cm^2.[9] These lesions were required to be located either on the trunk, upper extremities, or lower extremities, separated by at least 10 cm with an Atopic Dermatitis Severity Index (ADSI) score of at least 6 but no greater than 12.[9] The difference in ADSI score between studied lesions could be no greater than an ADSI of 1. Patients were excluded from the study if they had a history of physical or mental disorder, laboratory findings, or physical exam.[9] Patients were also excluded if they had clinically significant or severe allergies, had active impetigo at one or more study lesions, had unstable AD requiring consistent use of high potency corticosteroids or had received UV light therapy within the past 2 weeks, systemic corticosteroids in the past 4 weeks, or active topical therapy on study lesions in the past 7 days.[9] The primary endpoint of this study was less particular in that the study aimed only for a change in ADSI from baseline to day 28. Patients followed up with clinicians at baseline (day 0) and on days 14, 28, and 42 of treatment.[9] The ADSI is a point-based system with a total maximum of 15 points. There are 5 symptoms (pruritus, erythema, excoriation, exudation, and lichenification) that are scored on a scale of 0 (absent) to 3 (severe). The ADSI is a composite score of all 5 symptom scores. By the end of the study and between follow-up assessments, 68% of patients in the crisaborole treatment arm experienced a statistically significant (vs 20% vehicle, P = 0.017) improvement in AD based on ADSI score.[9]

Phase III Trials

Two phase III trials have been completed for crisaborole thus far, AD-301 and AD-302. Both of these studies were funded by the manufacturer and are identical in design. The objectives of both studies were to assess the efficacy and safety of crisaborole ointment compared to placebo in patients with mild to moderate

AD. A review of the findings from the Phase III trials can be found in Table 2.

Both studies were multicenter, double-blind, vehicle controlled clinical trials performed within the United States. Patients were randomized in a 2:1 ratio of crisaborole ointment to vehicle-controlled treatment.[10] In order to be included in either study, patients were required to be at least 2 years old, have a diagnosis of AD according to Hanifin and Rajka criteria, have 5% or more treatable body surface area involvement, and have a baseline ISGA score of 2 or 3.[10] Patients were excluded if they had active skin infections, previous TCS or TCI use within 14 days prior, any previous biologic use, or systemic corticosteroid use 28 days prior.[10] Patients were allowed to use approved emollients on dry skin around but not occluding the lesions being treated with the investigative drug. Patients in both treatment arms were directed to apply ointment on the affected study area twice a day for 28 days. The primary endpoint was a resolution in AD defined by an ISGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.[10] Secondary endpoints included resolution in the signs and symptoms of AD, measured at baseline by a 4-point system (a score of 0 meaning none, 1 meaning mild, 2 meaning moderate, and 3 meaning severe).[10] Successful improvement in these signs and symptoms was defined as a score of 0 or 1 with at least a 1-grade improvement in that particular sign's baseline score. Pruritus, a common and bothersome symptom, was scored twice daily using an electronic diary. Safety was monitored using adverse events, clinical parameters, and vital signs.

For study AD-301, patients receiving crisaborole were found to be significantly more likely to achieve successful resolution of ISGA score than patients receiving vehicle ointment (32.8% vs 25.4%, $P = 0.038$).[10] Similar results were also observed in the AD-302 study, with crisaborole success rate of 31.4% vs 18.0% with the vehicle control ($P < 0.001$).[10] In both studies, the Kaplan-Meier curves showed that patients receiving crisaborole ointment achieved improvements in ISGA scores sooner than patients being treated with vehicle control ($P < 0.001$).[10] Additionally, more patients in the crisaborole group achieved an ISGA score of 0 or 1 by the end of both studies than patients in the vehicle treatment group (AD-301: 51.7% vs 40.6%, $P = 0.005$; AD-302: 48.5% vs 29.7%, $P < 0.001$).[10]

Patients using crisaborole also reported decreased severity of pruritus sooner than patients in the vehicle-control arm (58% vs 42%, $P < 0.001$ on day 8).[10] Furthermore, 58% of patients in the crisaborole treatment arm achieved improvement on the first follow-up within a week of starting crisaborole, using compared to 42% of patients vehicle control ($P < 0.001$).[10]

Adverse Effects

The adverse effects associated with the application of crisaborole 2% topical ointment were minimal. Many of the adverse events reported in the trials could not be considered as associated with treatment. Most notable and significant of reported events that were associated with treatment was a burning or stinging sensation upon application. In the phase III trials, a pooled 4.4% of the 1012 patients in the crisaborole treatment arm reported site application pain.[10] It should be noted that a large portion of patients reported a decrease in severity of burning or stinging within a week of repeated application. Other treatment associated adverse events that were noted in the phase III trials were atopic dermatitis, pruritus, and treatment site skin infections.[10] Phase IV post-marketing trials should help provide a more comprehensive understanding of the full impact that chronic treatment with crisaborole, including adverse event reporting and benefits or risks of long term use.

Table 3 | Summary of adverse events for crisaborole ointment, 2%.[8,9,10]

Adverse Event	Crisaborole (%)	Vehicle (%)
Treatment-related Application site pain	4.4—13	1.2
Application site pruritis	0.5	1.2
Pyrexia	1.9	1.4
Gastrointestinal	2.7	2.4
Infection	11.7	11.8
Nasopharyngitis	1.8—13	1.2

Dosing and Administration

Eucrisa® (crisaborole 2% topical ointment) received FDA approval for treatment of flare-ups of mild to moderate AD. Crisaborole ointment should be applied to the affected lesions twice daily, which was the application schedule studied in the phase II and III trials. There is currently no recommended timeframe as to when to stop daily application, but generally, application may cease when signs and symptoms of lesions become manageable or clear up completely. Patients should apply the ointment on a scheduled basis. There is also currently no recommended amount of ointment that must be applied to the lesion, rather the package insert recommends to apply a "thin layer to affected areas".[6] Preclinical trial data in rats and rabbits suggests that crisaborole has no detrimental effects on fetal development before, during or after pregnancy and lactation.[5,7] The FDA has not assigned a pregnancy risk category due to lack of data.[5,7] There is not enough data to suggest whether or not crisaborole is passed through breast milk.[5,7]

Conclusion

Eucrisa® (crisaborole 2% topical ointment) provides an additional option for the treatment of mild to moderate AD. In clinical trials, crisaborole 2% ointment was found to be both statistically and clinically significant in decreasing the signs, symptoms, and severity of AD compared to vehicle control. The most commonly reported adverse effect of crisaborole is a burning or stinging sensation upon application. Further studies, particularly head-to-head trials comparing the efficacy of crisaborole with previous therapies, should help to determine which therapy would be most beneficial to patients. Additionally, cost-benefit analysis comparing crisaborole with other therapies may provide insight into its place in therapy for AD. Given the current evidence available, Eucrisa®

(crisaborole 2% topical ointment) presents an effective option with minimal adverse effects for pediatric and adult patients with mild to moderate AD.

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Editor's Corner

The VAST-D Randomized Clinical Trial

A recent study published in the Journal of the American Medical Association investigated the relative effectiveness and safety of 3 common alternate treatments for major depressive disorder (MDD). Previous trials were not powered to the compare efficacy of these alternate therapies.

The study included adult patients of the US Veterans Health Administration (VHA) with MDD unresponsive to at least 1 course of antidepressant treatment meeting the minimal standards for dose and duration of therapy. Previous antidepressant therapies included selective-serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), or mirtazapine and were severely depressed (QIDS-C_{16} >16) for ≥ 6-weeks at moderate to high dose of the mentioned drug, or moderately depressed (QIDS-C_{16} >11) after ≥8 weeks of treatment.

A total of 1522 patients (85% male) were randomized 1:1:1 to the "switch group" of bupropion sustained release (SR) (≤400 mg daily) or augmentation to current treatment with bupropion SR (≤400 mg daily) or the antipsychotic aripiprazole (≤15 mg daily).

The primary outcome was remission of MDD defined as a QIDS-C_{16} score (range of 0-27 with higher scores indicating more severe symptoms) of ≤ 5 at 2 consecutive scheduled follow-up visits during a 12-week acute treatment phase. No difference was found between the augment-aripiprazole group (28.9%) and the augment-bupropion group (26.9%; RR, 1.08 [95% CI, 0.88-1.31]; $P = 0.47$), but a modestly higher remission rate was seen between the augment-aripiprazole group and the switch group (22.3%; RR, 1.30 [95% CI, 1.05-1.60]; P = .02). The remission rates between the augment-bupropion group and the switch group were not significantly different (RR, 1.20 [95% CI, 0.97-1.50]; $P = 0.09$).

Serious adverse events occurred among 165 patients but were not significantly different between the treatment arms. Overall, the incidence of adverse events was greatest in the switch group (1496 events) compared to the augment-bupropion (1458 events) and augment-aripiprazole group (1405 events), but the difference was not statistically significant. Compared to the augment-aripiprazole group, the most common nonserious adverse events in the switch and augment-bupropion group were increased anxiety (P <0.001) and dry mouth (P <0.001). Notable nonserious adverse events in the augment-aripiprazole group compared with both bupropion groups were increased weight gain (P <0.001) and extrapyramidal symptoms (P <0.001).

Although this trial demonstrates the effectiveness of augment therapy with aripiprazole, the benefits were associated with increased risks. Specifically for the aripiprazole arm, weight gain and its relation to metabolic syndrome could lead to increased long-term health risks. The modest benefits seen with bupropion or aripiprazole augment therapy for unresponsive MDD should be weighed to the increased risks associated with each treatment.

For additional information:

Mohamed S, Johnson GR, Chen P, et al. Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. *JAMA.* 2017 Jul 11;318(2):132-45.

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