

Pharmacokinetic Profile, Safety, and Tolerability of Crisaborole Topical Ointment, 2% in Adolescents with Atopic Dermatitis: An Open-Label Phase 2a Study

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Abstract

Background: Phosphodiesterase-4 (PDE4) is an emerging target in treating inflammatory skin diseases. Crisaborole topical ointment, 2% is a novel, boron-based, topical PDE4 inhibitor under investigation for treatment of mild to moderate atopic dermatitis (AD).

Methods: Adolescent patients aged 12 to 17 years with treatable AD lesions involving $\geq 10\%$ to $\leq 35\%$ body surface area (BSA) were enrolled into a phase 2a, open-label study comprising pharmacokinetic (PK), safety, tolerability, and efficacy assessments. Crisaborole topical ointment, 2% was applied twice daily to affected areas for 28 days, with dosage based on baseline treatable BSA. PK blood samples were collected on days 1, 2, 4, 6, 8, and 9. Safety assessments included adverse events (AEs), laboratory parameters, and vital signs. Efficacy assessments included the Investigator's Static Global Assessment (ISGA) score and severity of AD signs and symptoms.

Results: Twenty-three patients were enrolled; 22 completed the study (1 patient discontinued due to an AE [application site dermatitis]). PK analysis demonstrated limited exposure to crisaborole topical ointment, 2% after 8 days of dosing. Ten patients reported a total of 19 AEs, most commonly application site pain and nasopharyngitis (3 patients each). There were no clinically meaningful changes in laboratory or vital sign parameters. Efficacy was demonstrated by reductions in mean ISGA and AD sign and symptom severity scores. At day 29, eight patients (35%) had achieved an ISGA score ≤ 1 with ≥ 2 -grade improvement. Mean treatable BSA declined from 17.6% to 8.2%.

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Conclusion: These results provide preliminary evidence for the limited systemic exposure, safety, and effectiveness of crisaborole topical ointment, 2% in adolescents with mild to moderate AD.

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin disorders, especially in children and adolescents, with estimated prevalences reaching 30% in industrialized countries (1,2). An estimated 85% of children who develop AD experience symptoms by 5 years of age (3). Parental or caregiver concerns regarding efficacy and safety may affect pharmacologic management of AD in young children and adolescents (4).

Current AD treatment guidelines recommend topical therapy with nonpharmacologic moisturizers (emollients), as well as topical glucocorticoids or calcineurin inhibitors for some inflammatory lesions in patients with mild to moderate disease (1). Long-term glucocorticoid use, particularly if uninterrupted or used inappropriately, can induce cutaneous adverse events (AEs; especially skin thinning), increase the risk of adrenal suppression, and slow linear growth (5,6). Topical calcineurin inhibitors (TCIs) carry a boxed warning regarding potential association with rare cases of malignancy (skin cancer, lymphoma), which often causes concerns or fears in patients and caregivers, despite the fact that a direct causal relationship has not been established (1,7–10). Given sensitivities regarding current therapies, an unmet need exists for an AD treatment option that offers significant efficacy and that patients, caregivers, and health care providers perceive as safe.

An emerging target of interest in the treatment of AD is the intracellular enzyme phosphodiesterase-4 (PDE4) (11,12). PDE4 isoenzymes are responsible for converting the intracellular secondary messenger cyclic adenosine monophosphate (AMP) into 5'-AMP, which promotes proinflammatory responses. Conversely, inhibition of PDE4 prevents degradation of cyclic AMP and helps suppress these inflammatory responses (13). Although systemic therapy with PDE4 inhibitors is associated with a high incidence of gastrointestinal side effects, especially nausea and emesis (12,14), a topical PDE4 inhibitor with limited systemic exposure may minimize the occurrence of these side effects.

Crisaborole topical ointment, 2% (formerly AN2728; Anacor Pharmaceuticals, Palo Alto, CA) is a novel, boron-based small molecule that inhibits PDE4 (13). Its low molecular weight (251 Da) facilitates effective skin penetration. The presence of

boron in the chemical structure allows targeting of cells in which PDE4 is inhibited and rapid metabolism to inactive metabolites (13).

In preclinical biochemical and cell-based studies, crisaborole demonstrated considerable antiinflammatory activity; it also inhibited ear edema in a mouse model of phorbol-induced inflammation, demonstrating effective skin penetration (13,15,16). The purpose of this open-label, phase 2a study was to evaluate the systemic exposure, safety, tolerability, and efficacy of crisaborole topical ointment, 2% in adolescents with AD.

METHODS

Study Design and Objectives

This was a phase 2a, multicenter, open-label study designed to evaluate the pharmacokinetics and systemic exposure (days 1–9), safety, tolerability, and efficacy of crisaborole topical ointment, 2% in adolescents with AD.

The study was conducted in accordance with Title 21 of the U.S. Code of Federal Regulations, the International Conference on Harmonisation guidelines, current Good Clinical Practice principles, the Declaration of Helsinki, and local regulatory requirements. All patients and their parents or guardians provided written informed consent before enrollment.

Study Population

Male and female adolescents ages 12 to 17 years (inclusive) with a diagnosis of AD according to the criteria of Hanifin and Rajka (17) were eligible for inclusion. Patients were required to have treatable AD lesions extending over 10% to 35% of the total body surface area (BSA), excluding the scalp and venous access areas (defined as treatable %BSA), and an Investigator Static Global Assessment (ISGA) score of 2 (mild) or 3 (moderate). With the exception of AD or stable, controlled asthma, any clinically significant medical disorder, condition, or disease (including active or recurrent dermatologic conditions other than AD) met the criteria for exclusion if the condition exposed the patient to an unacceptable risk by participating in the study, confounded the evaluation

of treatment response or AEs, or interfered with the patient's ability to complete the study. Patients were also excluded if they had unstable AD or a consistent requirement for high-potency topical corticosteroids or a history of recent or concomitant use of topical or systemic therapies, had undergone treatment for any type of cancer in the last 5 years, or had had recent (within 2 wks of baseline visit) or concomitant exposure to ultraviolet (UV) light, including prolonged exposure to natural sunlight (sunbathing), commercial tanning beds, or UV light therapy. At screening and throughout the study, it was the responsibility of the study investigator to remind patients and caregivers of restrictions regarding exposure to natural sunlight, although normal daily sun exposure and use of sunscreen was permitted.

A screening period of ≤ 35 days served as a washout period from certain exclusionary therapies that might affect the course of AD. During the washout period, twice-daily application of hydrocortisone 1% was allowed in patients with disease who required step-down therapy, until 3 days before baseline, after which time its use was prohibited. Concomitant treatment with other topical therapy was not permitted on treatable lesions. In addition, concomitant phototherapy or sunbathing was prohibited during the study, although patients were allowed to apply topical therapies or approved emollients to nontreatable lesions (lesions not being treated with the study drug).

Study Treatments

Crisaborole topical ointment, 2% was applied twice daily for 28 days to treatable %BSA at a dose of 3 mg/cm^2 , with the exception of days 1 and 8, on which a single morning dose was applied. Morning doses on days 1, 2, 4, 6, 8, and 9 were applied in the clinic—all other doses were applied at home. Twice-daily doses were applied at least 8 hours apart.

During the pharmacokinetic phase, the per-application dosage was calculated based on the patient's baseline treatable %BSA. Patients were instructed to use supplied dosing cards to dispense the correct dosage per application of crisaborole topical ointment, 2%, with the exception of days 1 and 8, when study personnel weighed the application dosage. During the safety and tolerability phase of the study, patients were to apply crisaborole topical ointment, 2% to all treatable areas identified at baseline, regardless of whether the areas cleared clinically during the treatment period, using dosing cards marked with their correct dose and a body map of areas to be treated.

During the safety and tolerability phase, patients were allowed to modify the per-application dosage sufficient to cover any previous lesions present at baseline as well as new lesions. Patients were instructed not to bathe or wash the treated lesions for 4 hours after application of crisaborole topical ointment, 2%.

Study Assessments

The study included visits at screening; at baseline (day 1); and on days 2, 4, 6, 8, 9, 15 (± 1), and 22 (± 1); and at an end-of-study visit on day 29 (± 1). Blood samples for pharmacokinetic analysis (primary assessment) of crisaborole topical ointment, 2% and its oxidative metabolites AN7602 and AN8323 were obtained within 1 hour before dosing on days 1 and 8; within 24 ± 1 hours before dosing on days 2 and 9; before dosing on days 4 and 6; and 1, 2, 4, 6, and 8 hours after application on days 1 and 8. Pharmacokinetic assessments included observed maximum plasma concentration of drug after dosing (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration–time curve from 0 to 12 hours after dosing ($\text{AUC}_{[0-12]}$), and apparent half-life ($t_{1/2}$). The duration of the pharmacokinetic period was chosen to ensure that steady state was captured in the setting of repeated dosing.

Secondary assessments of disease severity and efficacy of crisaborole topical ointment, 2% were conducted at baseline and on days 8, 15, 22, and 29 using the ISGA and individual scales for AD signs and symptoms. The ISGA is a 5-point assessment of overall AD severity ranging from 0 (clear) to 4 (severe). Treatment success was defined as achievement of an ISGA score of 1 or less (clear or almost clear) with 2-grade or greater improvement from baseline. Individual AD signs and symptoms (including erythema, excoriation, exudation, lichenification, and pruritus) were scored on a 4-point scale (0 = none, 3 = severe). Treatable %BSA was also calculated for each patient at baseline and day 29.

Safety was assessed at each visit and included the incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs, as well as change from baseline in clinical evaluations, including vital signs, laboratory values (obtained at screening, baseline, and days 8 and 29), and physical examination (obtained at screening, baseline, and days 8, 15, 22, and 29). In addition, the local tolerability of crisaborole topical ointment, 2% was determined according to the presence of patient-rated burning or stinging symptoms at each study visit, graded on a 4-point scale (0 = none, 3 = severe).

Statistical Analyses

The safety population included all enrolled patients who received any amount of study medication. The pharmacokinetic population included the subset of patients in the safety population who completed any portion of the pharmacokinetic assessments. The per-protocol population included all patients who were enrolled, received study medication, did not miss more than one visit, did not miss more than 3 consecutive days of treatment, used 80% to 120% of the expected doses, and had no major protocol violations.

For pharmacokinetic analyses, analyte plasma concentrations of crisaborole topical ointment, 2% AN7602, and AN8323 and pharmacokinetic parameters were determined (MicroConstants, San Diego, CA) and were prepared using Phoenix WinNonlin version 6.1 (Pharsight, St. Louis, MO). Analyses of safety, tolerability, and efficacy data were conducted using SAS version 9.1 (SAS Institute, Cary, NC). Given the design of this open-label safety and pharmacokinetic study, inferential statistics were not determined. Assessments of safety, pharmacokinetic parameters, disease severity, and AD signs and symptoms were summarized descriptively.

RESULTS

Study Population

Twenty-three patients were enrolled in the study at eight investigational sites; 22 patients completed the study and were included in the per-protocol population (Fig. 1). One patient discontinued because of an AE. Patient demographic and baseline characteristics are summarized in Table 1.

TABLE 1. Study Population Demographic and Baseline Characteristics (Safety Population; N = 23)

Characteristic	Value
Sex, n (%)	
Male	4 (17)
Female	19 (83)
Age, yrs, mean $\pm$ SD (range)	15.0 $\pm$ 1.5 (12.1–17.3)
Race, n (%)	
Asian	2 (9)
Black	11 (48)
Pacific Islander	1 (4)
White	9 (39)
Height, cm, mean $\pm$ SD	162.4 $\pm$ 8.3
Weight, kg, mean $\pm$ SD	72.7 $\pm$ 22.9
Treatable body surface area at baseline, %, mean $\pm$ SD	17.6 $\pm$ 5.7

SD, standard deviation.

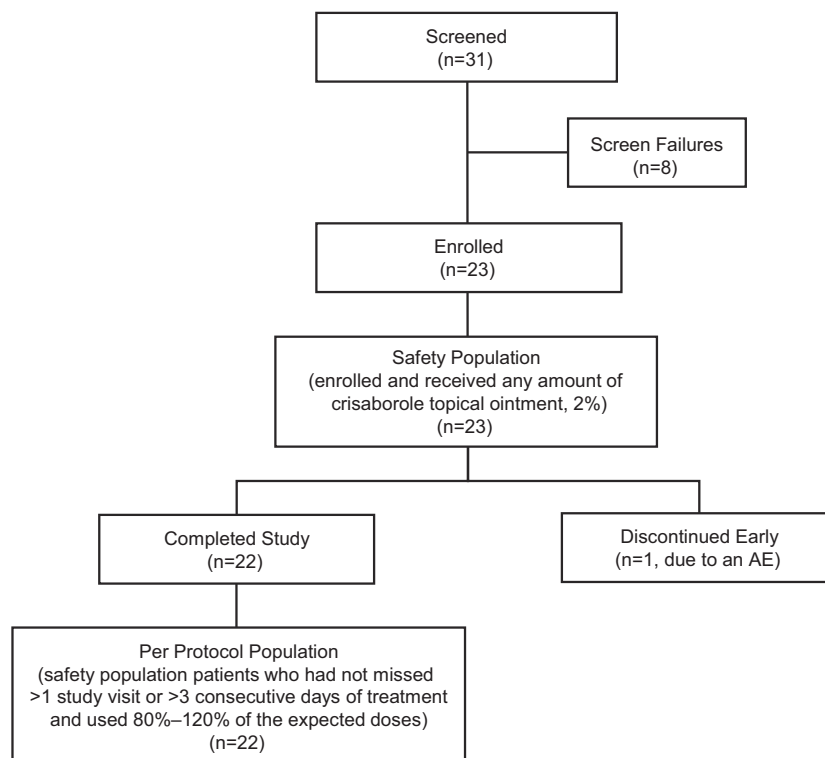


Figure 1. Disposition of study population. AE, adverse event.

TABLE 2. Pharmacokinetic Parameters for Crisaborole and Its Metabolites AN7602 and AN8323 ($N = 23$)

Analyte	Dose day	Observed maximum plasma concentration after dosing, ng/mL, mean $\pm$ SD	Time to reach observed maximum plasma concentration after dosing, hours, median (range)	Area under the plasma concentration–time curve from time 0–12 hours after dosing, ng·h/mL, mean $\pm$ SD	Apparent half-life, hours, mean $\pm$ SD
Crisaborole	1	105 $\pm$ 160	2.37 (1.00–24.0)	448 $\pm$ 527	7.17 $\pm$ 2.30*
	8	94.6 $\pm$ 189†	2.17 (1.00–7.93)†	462 $\pm$ 506†	11.9 $\pm$ 8.28‡
AN7602	1	28.2 $\pm$ 37.0	2.08 (1.00–24.0)	142 $\pm$ 172	8.19 $\pm$ 5.13§
	8	26.3 $\pm$ 43.9†	3.94 (1.00–6.15)†	142 $\pm$ 154†	10.5 $\pm$ 6.38*
AN8323	1	998 $\pm$ 1,220	6.25 (3.95–25.0)	8,900 $\pm$ 11,600	17.7 $\pm$ 1.63¶
	8	1,850 $\pm$ 1,830†	6.00 (0.00–25.1)†	18,200 $\pm$ 18,100†	33.5 $\pm$ 10.1¶

SD, standard deviation. Crisaborole is the parent molecule, AN7602 and AN8323 are inactive metabolites.

$N =$ *16, †22, ‡17, §18, ¶6.

TABLE 3. Day 8:Day 1 Ratios for Observed Maximum Plasma Concentration After Dosing ($C_{\max}$) and Area Under the Plasma Concentration–Time Curve from Time 0–12 Hours After Dosing ($AUC_{(0-12)}$) for Crisaborole, AN7602, and AN8323

Analyte	Day 8:Day 1 ratio* ($N = 22$)			
	$C_{\max}$		$AUC_{(0-12)}$	
	Mean $\pm$ SD	Median (range)	Mean $\pm$ SD	Median (range)
Crisaborole	1.99 $\pm$ 2.09	1.25 (0.087–7.36)	2.28 $\pm$ 2.40	1.12 (0.156–9.16)
AN7602	1.96 $\pm$ 1.80	1.25 (0.088–6.03)	2.40 $\pm$ 2.69	1.43 (0.140–10.4)
AN8323	3.65 $\pm$ 4.04	2.31 (0.139–19.3)	6.64 $\pm$ 11.4	2.64 (0.176–53.6)

SD, standard deviation.

Crisaborole is the parent molecule, AN7602 and AN8323 are inactive metabolites.

*Mean of within-patient ratio of day 1:day 8 parameter values for all patients.

Pharmacokinetic Analysis

Plasma pharmacokinetic profiles of crisaborole topical ointment, 2% and the primary metabolites AN7602 and AN8323 were determined for 23 patients. Mean values for key pharmacokinetic parameters for crisaborole topical ointment, 2%, AN7602, and AN8323 on days 1 and 8 after application of crisaborole topical ointment, 2% are summarized in Table 2. On day 1, the median $T_{\max}$ for crisaborole topical ointment, 2% was 2.37 hours and the mean $C_{\max}$ was 105 ng/mL. Day 1 median $T_{\max}$ values were 2.08 hours for the metabolite AN7602 and 6.25 hours for AN8323. After 8 days of twice-daily dosing, the accumulation of crisaborole topical ointment, 2% and its metabolite AN7602, based on the median $C_{\max}$ and $AUC_{(0-12)}$ day 8:day 1 ratios (Table 3), was limited, ranging from 1.25-fold for $C_{\max}$ to 1.43-fold for $AUC_{(0-12)}$. Values for $C_{\max}$ and $AUC_{(0-12)}$ of crisaborole topical ointment, 2% at day 8 also increased based on individual patients' treatable %BSA (Fig. 2). Levels and accumulation of AN8323 were somewhat higher on day 8 than on day 1, with day 1 $C_{\max}$ approximately 1 μ g/mL and median day 8:day 1 ratios of 2.31 for $C_{\max}$ and 2.64 for $AUC_{(0-12)}$. As shown in Fig. 3, crisaborole topical

ointment, 2% and its metabolites appeared to reach steady state 4 to 6 days after initiation.

Safety and Tolerability

Ten patients (43.5%) reported a total of 19 TEAEs; 11 (58%) were mild and 8 (42%) were moderate in severity. One TEAE (application site dermatitis) was considered definitely related to the study drug and resulted in the patient's discontinuation. Four TEAEs (application site pain) were considered probably related to the study drug and one (application site discomfort) was considered possibly related. There were no serious TEAEs or deaths during the study. The most frequently reported TEAEs were application site pain and nasopharyngitis (each reported by three patients); no more than one patient reported any other TEAE.

No clinically meaningful safety signals were observed with respect to changes from baseline in laboratory values, vital signs, or physical examination.

Mean local tolerability scores (application site burning or stinging) from baseline to study endpoint are shown in Fig. 4. At baseline, the mean burning or stinging score (0.83) was categorized as slightly less

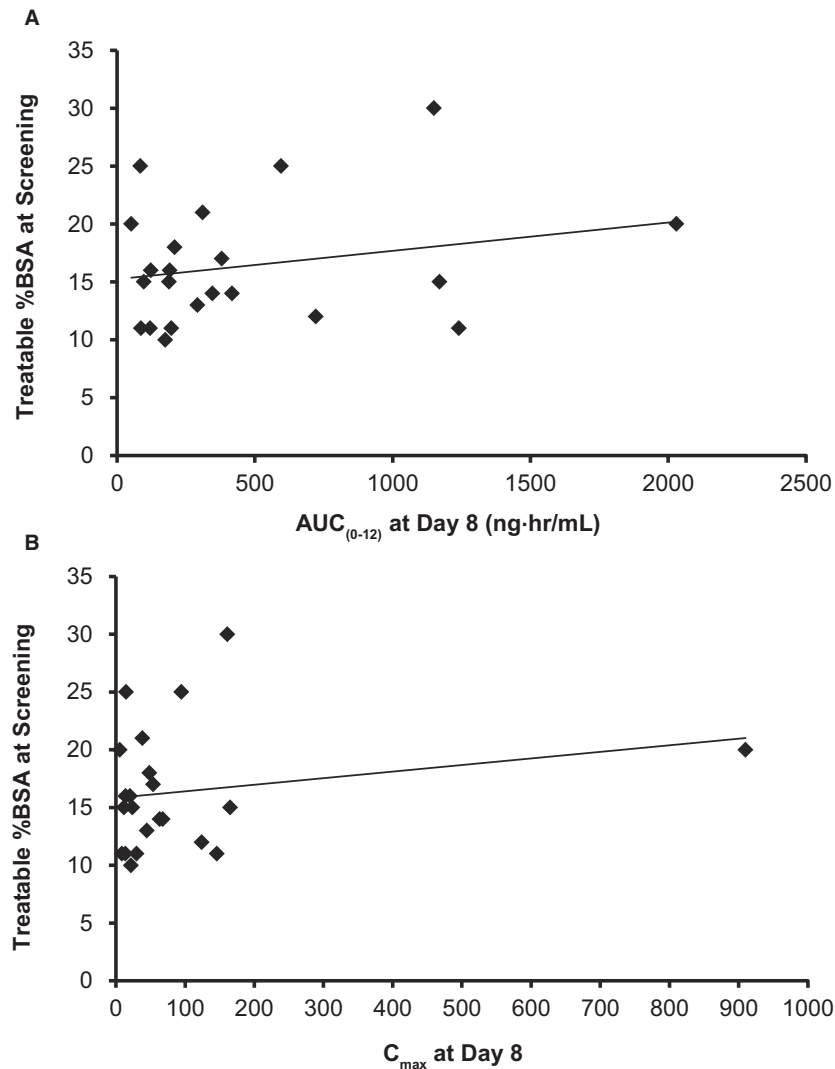


Figure 2. Pharmacokinetic values for crisaborole topical ointment, 2% at day 8 as a function of treatable percent body surface area (%BSA). Each patient's treatable %BSA measured on the day of screening was plotted against (A) their area under the plasma concentration–time curve from 0 to 12 hours after dosing ($AUC_{(0-12)}$) and (B) maximum plasma concentration of drug after dosing (C_{max}) values calculated for crisaborole topical ointment, 2% at day 8. The horizontal line in each panel represents a linear regression trendline.

than mild. At day 29 (endpoint), 87.7% of patients (20/23) had no burning or stinging, 8.7% (2/23) had mild burning or stinging, and 4.3% (1/23) had severe burning or stinging.

Efficacy

The mean ISGA score $\pm$ standard deviation decreased from 2.43 ± 0.51 at baseline to 1.35 ± 1.03 at day 29, a mean change of -1.08 ± 0.85 from baseline. The proportion of patients who achieved various ISGA thresholds (score ≤ 1 , ≥ 2 -grade improvement from baseline, treatment success) throughout the study is summarized in Fig. 5.

At day 29, eight (34.8%) had achieved treatment success (ISGA score ≤ 1 and ≥ 2 -grade improvement from baseline). Throughout the study, nine patients (39%) achieved treatment success at one or more study visits.

Mean scores for all signs and symptoms assessed (pruritus, erythema, exudation, excoriation, lichenification) decreased from baseline to day 29 (Fig. 6). The mean pruritus score declined from 1.87 at baseline to 0.57 at day 29 (mean change -1.30 ± 0.73).

Mean treatable %BSA decreased from 17.6 ± 5.7 at baseline to 8.2 ± 8.9 at day 29, a mean change of -9.4 ± 8.1 (53%).

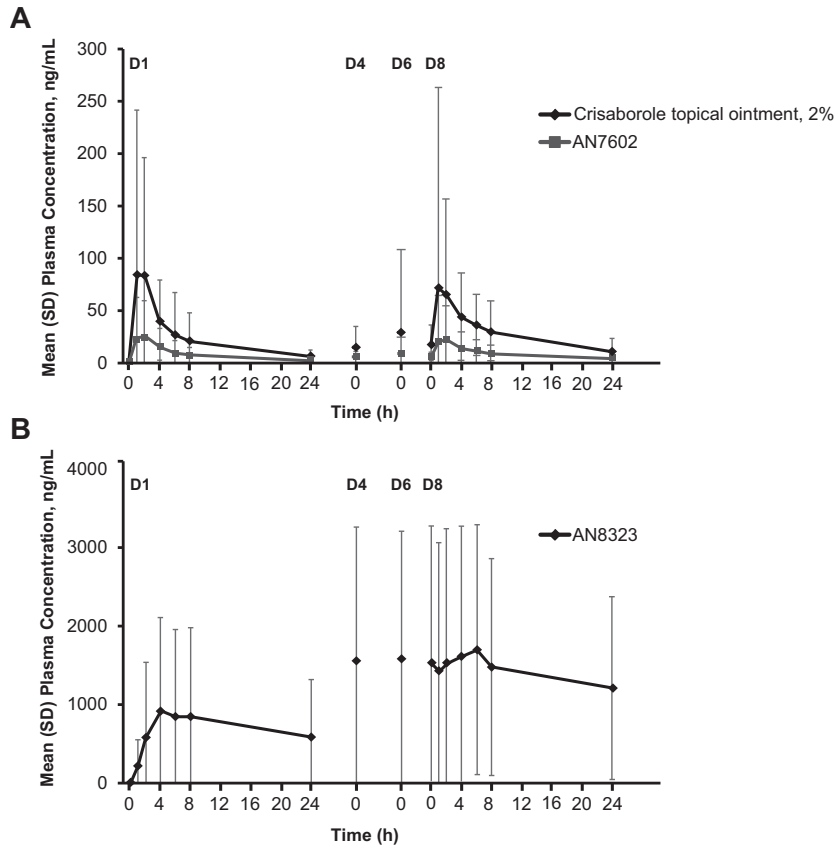


Figure 3. Mean $\pm$ standard deviation plasma concentration–time curves for (A) crisaborole topical ointment, 2% and AN7602 and (B) AN8323 (B). SD, standard deviation.

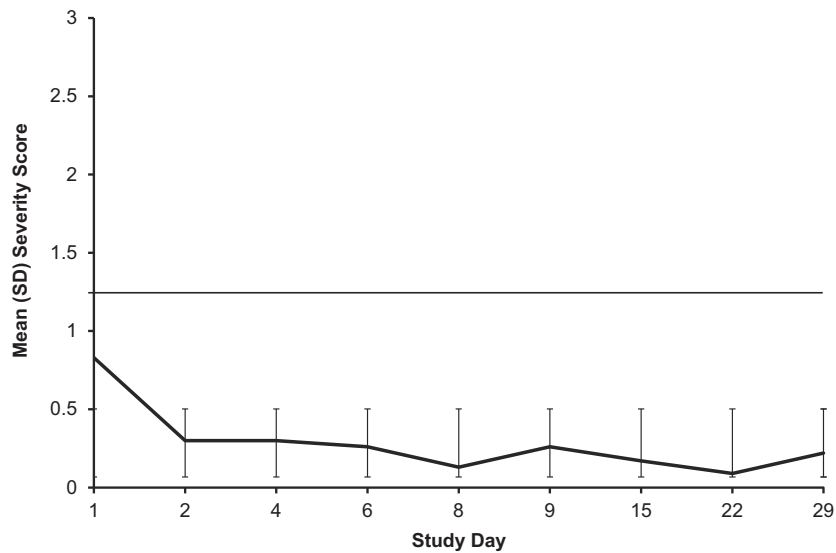


Figure 4. Summary of local tolerability assessments. Mean $\pm$ standard deviation patient-rated severity scores for application site burning or stinging by study day (rated on a 4-point scale; 0 = none, 3 = severe).

DISCUSSION

In this phase 2a, open-label study, twice-daily treatment with crisaborole topical ointment, 2%

for 28 days demonstrated limited systemic exposure to crisaborole and favorable safety and tolerability in adolescents with mild to moderate AD. Cris-

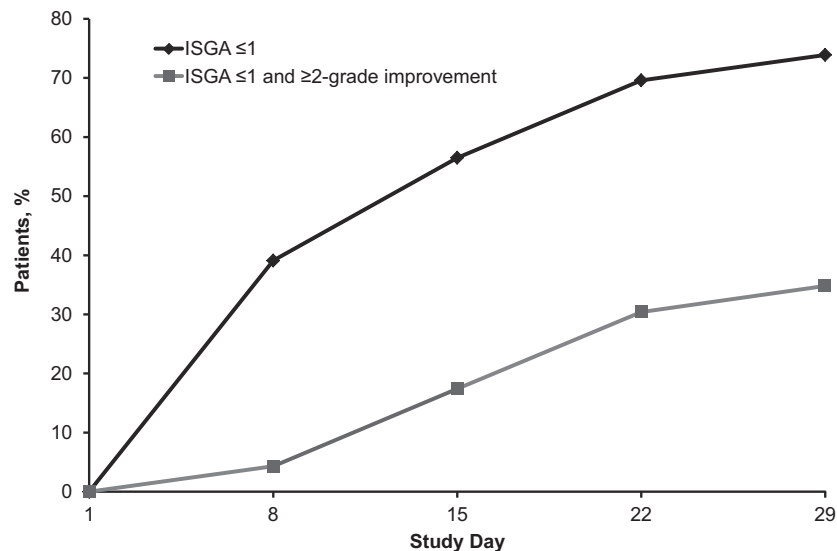


Figure 5. Proportion of patients achieving Investigator Static Global Assessment (ISGA) treatment thresholds. Proportion of patients, according to study day, achieving an ISGA score ≤ 1 or a score ≤ 1 and ≥ 2 -grade improvement in ISGA score (treatment success). ISGA is a 5-grade clinician-rated assessment of overall atopic dermatitis severity (0 = clear, 4 = severe).

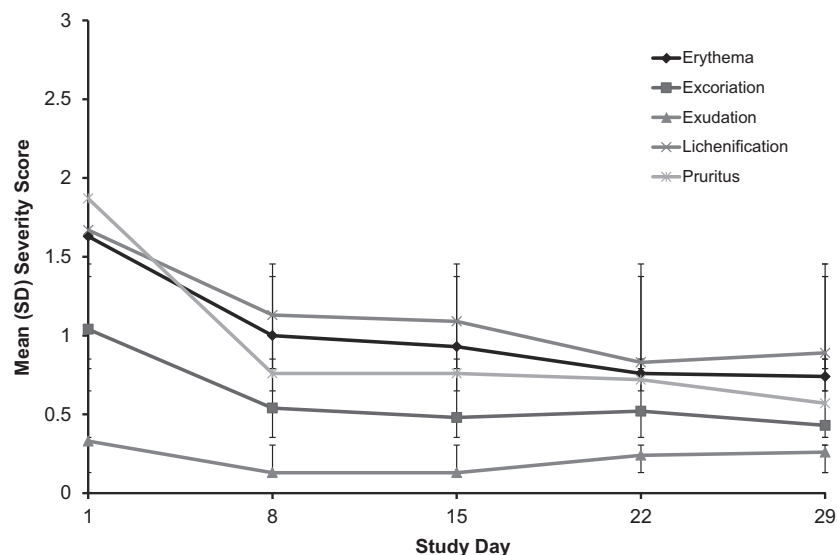


Figure 6. Mean $\pm$ standard deviation severity scores for atopic dermatitis signs and symptoms according to study day. Each of five symptoms (erythema, excoriation, exudation, lichenification, pruritus) was assigned a severity score based on a 4-point scale (0 = none, 3 = severe); for pruritus, patients graded severity based on a self-evaluation card.

aborole is metabolized to AN7602 and AN8323, which are inactive metabolites and are not PDE4 inhibitors (data on file, Anacor Pharmaceuticals). There was minimal accumulation of crisaborole and AN7602 and moderate accumulation of AN8323 through the end of the pharmacokinetic phase. Pharmacokinetic analysis showed that systemic exposure of crisaborole and its metabolites (based on $C_{\max}$ and $AUC_{(0-12)}$) increased as the total dose and area of application of crisaborole topical

ointment, 2% increased. The increased accumulation of AN8323 relative to crisaborole and AN7602 is consistent with its long half-life (mean day 8 $t_{1/2} = 33.5$ hours).

The most commonly reported TEAEs considered to be related to crisaborole topical ointment, 2% treatment were application site reactions. Most were mild to moderate in intensity, transient in nature, and considered to be unrelated to treatment. There were no serious AEs during the study; a single

discontinuation related to an AE (application site dermatitis) that was considered to be related to treatment with crisaborole topical ointment, 2% occurred in a girl with a significant history of AD, and resolved 3 days after discontinuing treatment. The mean local tolerability scores (severity of burning or stinging) were slightly less than mild at baseline, decreased by day 2, and remained low throughout the study.

Crisaborole topical ointment, 2% is being developed for use in the topical treatment of AD, and it has not been (nor is it planned to be) administered systemically (e.g., oral, intravenous) to any individuals, including healthy study volunteers, patients with AD, or patients with any other medical condition. Nevertheless, systemic administration of [14-C]-crisaborole demonstrated large safety margins for the PDE4 target as well as nontarget toxicities in animal pharmacology and toxicology studies (data on file, Anacor Pharmaceuticals). The pharmacokinetic data for crisaborole topical ointment, 2% presented here demonstrate rapid and substantial conversion of the parent molecule to its inactive metabolites in humans. Based on the totality of the data, the pharmacokinetics of topical delivery of crisaborole topical ointment, 2% as well as the safety profile would not be expected to be comparable with those of systemic administration. Fractional saturation of PDE4 ranges from 50% to 75% with oral PDE4 inhibitors. In contrast, fractional saturation of PDE4 with crisaborole topical ointment, 2% is less than 10%. High systemic exposure to agents that inhibit PDE4 can result in gastrointestinal toxicity (14). The U.S. Food and Drug Administration has approved only two orally administered PDE4 inhibitors—apremilast, for the treatment of active psoriatic arthritis and moderate to severe plaque psoriasis (18), and roflumilast, for reducing exacerbations in patients with severe chronic obstructive pulmonary disease (19). Treatment with apremilast and roflumilast is associated with gastrointestinal AEs (20–22). In contrast, in the current study and other phase 2 studies of patients with AD, treatment with crisaborole topical ointment, 2% was not associated with the occurrence of gastrointestinal AEs (23,24), and there has not been any indication of gastrointestinal toxicities or any other systemic PDE4-related toxicities in animal studies with crisaborole (data on file, Anacor Pharmaceuticals). Thus the benefit of topical administration of crisaborole is clear—it facilitates delivery of the active parent molecule to the site of inflammation in the dermis and epidermis, with minimal systemic exposure to crisaborole and a favorable safety profile.

With regard to efficacy, the improvement in AD severity throughout the 28-day study was evidenced by a more than 1-grade reduction in the mean ISGA score, steady improvement in AD signs and symptoms, and a greater than 50% reduction in the mean treatable BSA. In addition, the number of patients achieving predefined ISGA success criteria (score ≤ 1 with a ≥ 2 -grade improvement) steadily increased throughout the study, with more than 30% of patients achieving treatment success by the study's end.

Study limitations include the small study population, the open-label design, and the short treatment duration.

CONCLUSION

This phase 2a study provides preliminary evidence of the safety, tolerability, favorable pharmacokinetic profile, and efficacy of crisaborole topical ointment, 2% in adolescents with mild to moderate AD. Additional phase 2 clinical studies in children and adults have been completed and crisaborole topical ointment, 2% is currently in phase 3 clinical development for the treatment of children, adolescents, and adults with mild to moderate AD.

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CONFLICT OF INTEREST

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