Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults

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Background: Additional topical treatments for atopic dermatitis (AD) are needed that provide relief while minimizing risks.

Objective: We sought to assess the efficacy and safety of crisaborole ointment, a phosphodiesterase 4 inhibitor, in two phase III AD studies (AD-301: NCT02118766; AD-302: NCT02118792).

Methods: Two identically designed, vehicle-controlled, double-blind studies enrolled and randomly assigned (2:1, crisaborole:vehicle) patients aged 2 years or older with an Investigator's Static Global Assessment (ISGA) score of mild or moderate for twice-daily application for 28 days. The primary end point was ISGA score at day 29 of clear (0)/almost clear (1) with 2-grade or greater improvement from baseline. Additional analyses included time to success in ISGA score, percentage of patients achieving clear/almost clear, reduction in severity of AD signs, and time to improvement in pruritus.

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Results: More crisaborole- than vehicle-treated patients achieved ISGA score success (clear/almost clear with ≥2-grade improvement; AD-301: 32.8% vs 25.4%, $P = .038$; AD-302: 31.4% vs 18.0%, $P < .001$), with a greater percentage with clear/almost clear (51.7% vs 40.6%, $P = .005$; 48.5% vs 29.7%, $P < .001$). Crisaborole-treated patients achieved success in ISGA score and improvement in pruritus earlier than those treated with vehicle (both $P \leq .001$). Treatment-related adverse events were infrequent and mild to moderate in severity.

Limitations: Short study duration was a limitation.

Conclusions: Crisaborole demonstrated a favorable safety profile and improvement in all measures of efficacy, including overall disease severity, pruritus, and other signs of AD. (J Am Acad Dermatol 2016;75:494-503.)

Key words: atopic dermatitis; crisaborole ointment; eczema; phosphodiesterase 4; pruritus; topical therapy.

CAPSULE SUMMARY

- Phosphodiesterase 4 regulates inflammation and is overactive in atopic dermatitis.
- In two phase III studies, crisaborole ointment, a novel phosphodiesterase 4 inhibitor, improved disease severity and pruritus with a favorable safety profile in patients with mild to moderate atopic dermatitis.
- Crisaborole represents a promising, nonsteroidal topical treatment to improve management of atopic dermatitis.

Atopic dermatitis (AD), a complex chronic inflammatory skin disease characterized by erythematous, eczematous lesions and often intense pruritus,[1-3] is prevalent worldwide and affects both children and adults, with up to 90% of patients presenting with mild to moderate disease.[4,5] AD-associated pruritus results in frequent scratching and contributes significant psychological, social, and quality-of-life burdens to patients and their families.[6-8] It also generates a substantial financial burden, with cost estimates of up to $3.8 billion annually in the United States alone.[9] More than 80% of children with AD have persistence of symptoms into their adult years, a percentage much higher than previously appreciated.[10] In addition, AD is often associated with significant comorbidities, including asthma and allergic rhinitis.[1,2,8]

Topical treatments are commonly prescribed to alleviate AD symptoms, reduce inflammation, and prevent flares,[11] but no new molecules have been approved for the treatment of AD in the past 15 years, and treatment guidelines recommend the use of topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), or both.[3,8] Despite their efficacy, both TCS and TCI are associated with limitations in their use as a result of application reactions and safety concerns with long-term use. Long-term TCS use is restricted to avoid local cutaneous atrophy (especially in sensitive and thin-skinned areas such as face and groin), striae formation, and systemic side effects,[3,8] TCIs are associated with burning/stinging upon application and require enhanced patient education because of a boxed warning for increased risk of lymphoma.[3,8,12,13] Hence, novel topical therapies that may potentially improve upon the risk-benefit profile of current therapies are needed.

Phosphodiesterase 4 (PDE4) is a key regulator of inflammatory cytokine production in AD through the degradation of cyclic adenosine monophosphate.[14,15] PDE4 activity is increased in circulating inflammatory cells of patients with AD,[16-19] and the inhibition of PDE4 in monocytes in vitro has demonstrated reduction in the release of proinflammatory cytokines.[20] The oral PDE4 inhibitor apremilast was recently approved for treatment of moderate to severe plaque psoriasis and psoriatic arthritis, but requires dose titration to avoid gastrointestinal side effects (nausea and diarrhea) because of PDE4 inhibition in nontarget tissues.[21,22] A topical PDE4 inhibitor formulation could address the need for targeted inhibition of inflammation in skin diseases while avoiding unwanted side effects.

The novel boron chemistry of crisaborole enables synthesis of a low-molecular-weight compound (251 d) that facilitates effective penetration through human skin.[23] Crisaborole enhances cellular control of inflammation by inhibiting PDE4 and its ability to degrade intracellular cyclic adenosine monophosphate,[15,24-27] thereby suppressing the release of cytokines by affecting downstream regulation of the nuclear factor-κB and nuclear factor of activated T-cell signaling pathways.[14,23,28,29]

Abbreviations used:

AD:	atopic dermatitis
AE:	adverse event
ISGA:	Investigator's Static Global Assessment
MedDRA:	Medical Dictionary for Regulatory Activities
PDE4:	phosphodiesterase 4
TCI:	topical calcineurin inhibitor
TCS:	topical corticosteroid
TEAE:	treatment-emergent adverse event

Although systemic exposure to crisaborole may vary with the percentage of body surface area involved, it is rapidly and substantially metabolized to inactive metabolites that have no effect on PDE4 activity or cytokine release, thus limiting systemic exposure and reducing the risk of adverse effects.[30] Preclinical analysis in rats and mice revealed that crisaborole is noncarcinogenic, and early clinical data[31-33] demonstrated a favorable safety profile for crisaborole in children as young as 2 years of age. Two pivotal phase III studies were performed to evaluate the efficacy and safety of crisaborole 2% ointment in patients aged 2 years of age or older with mild to moderate AD.

METHODS

Study design and oversight

Two identically designed multicenter, randomized, double-blind, vehicle-controlled phase III clinical studies conducted in the United States (ClinicalTrials.gov AD-301: NCT02118766; AD-302: NCT02118792) assessed the efficacy and safety of crisaborole in patients with mild to moderate AD. Study protocols were developed and conducted, and data were recorded and reported by the study sponsor (Anacor Pharmaceuticals, Inc) in accordance with the principles of Good Clinical Practice and relevant country-specific regulatory requirements. At each participating investigational center (47 and 42 investigational centers for AD-301 and AD-302, respectively), the institutional review board approved all study protocols, informed consent/assent forms, and relevant supporting data. No participants (principal investigator, study staff, participants, nor parents/guardians) knew the treatment assignment, and blinding was maintained throughout clinical management, data management, and statistical evaluation until a database lock memo was issued.

Patients

Patients were randomized via the interactive World Wide Web response system 2:1 to receive crisaborole:vehicle treatment (Fig 1 and Supplementary Fig 1). Key inclusion criteria required patients to be aged 2 years or older and have a clinical diagnosis of AD according to Hanifin and Rajka[34] criteria, 5% or more treatable body surface area involvement, and a baseline Investigator's Static Global Assessment (ISGA) score of mild (2) or moderate (3) (Supplementary Fig 1). Key exclusion criteria prohibited previous use of biologic therapy or systemic corticosteroids within 28 days or TCS or TCI use within 14 days. Patients with active skin infections were excluded (Supplementary Fig 1). Patients on stable regimens (consistent use ≥14 days before day 1) of inhaled corticosteroids, antihistamines, and topical retinoids for non-AD lesion treatment were allowed to continue their medications. Patients were also allowed to use acceptable bland emollients to manage dry skin areas around, but not overlapping, the treatable AD-involved areas.

Crisaborole ointment treatment

Patients were instructed to apply a layer of study drug to cover each lesion twice daily throughout the 28-day study to all areas affected by AD at baseline. The scalp was excluded from treatment to avoid potential patient dissatisfaction with ointment application to scalp hair. Patients and caregivers were provided with documentation for designated treatment areas at each visit and instructed to apply additional study drug as needed to newly identified AD lesions that appeared after day 1. Application instructions were reviewed at scheduled weekly in-clinic visits (days 8, 15, and 22).

Evaluation

The primary efficacy end point of success in ISGA score at day 29 was defined as clear (0) or almost clear (1) with a 2-grade or more improvement from baseline (Supplementary Table I). Analysis of the secondary efficacy end points included the proportion of patients with an ISGA score of clear (0) or almost clear (1) at day 29, and time to success in ISGA score. Additional predefined end points assessed pruritus severity and signs of AD (erythema, exudation, excoriation, induration/papulation, and lichenification). Pruritus severity was recorded twice daily by the patient or parent/caregiver via electronic diary. Signs of AD were measured throughout the treatment period on investigator visit days 1, 8, 15, 22, and 29. Pruritus and signs of AD were measured on a 4-point scale of none (0), mild (1), moderate (2), and severe (3) (Supplementary Tables II and III). Improvement in these measures was defined as achieving none (0) or mild (1) with a 1-grade or

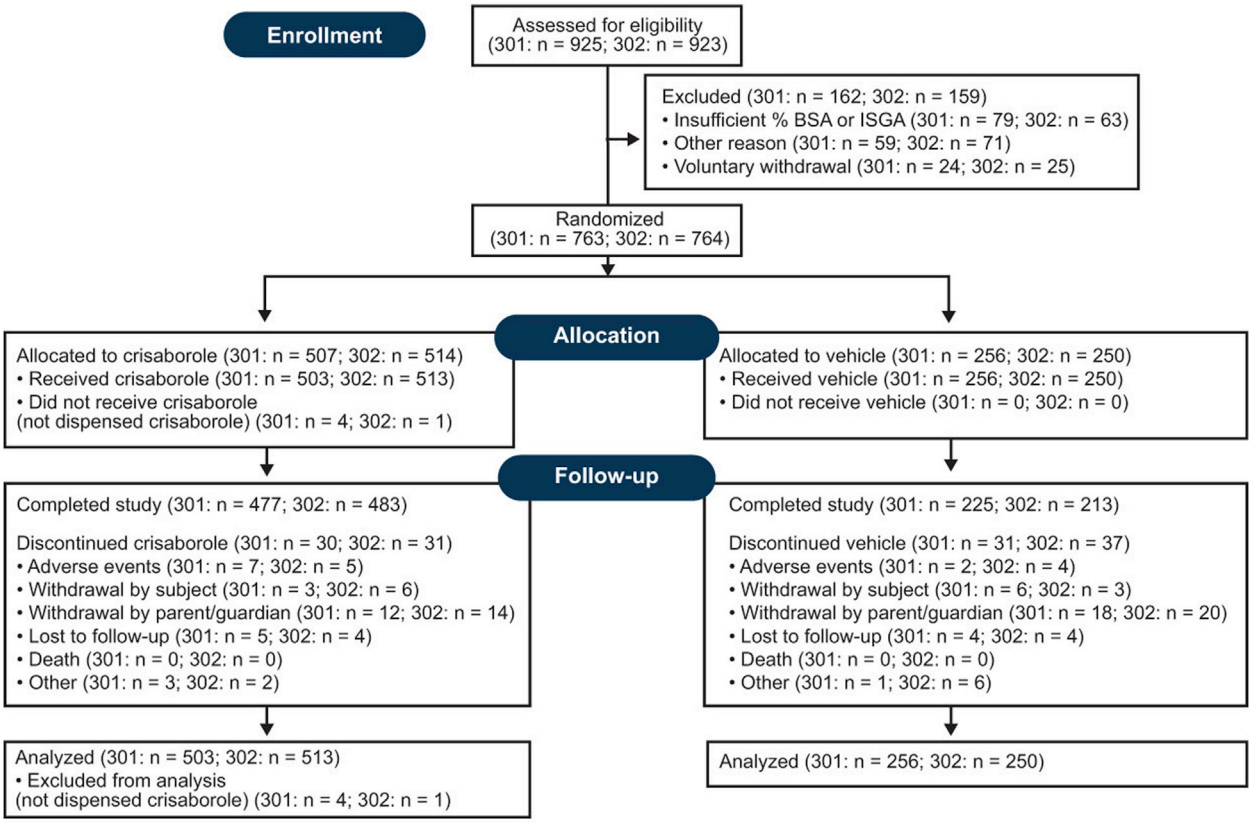

Fig 1. Atopic dermatitis. Enrollment, randomization, treatment, and follow-up. *BSA*, Body surface area; *ISGA*, Investigator's Static Global Assessment.

more improvement from baseline. Change in the severity of each sign of AD was calculated as percentage change from baseline. Primary safety assessments included adverse events (AEs), vital signs, and clinical laboratory parameters. All AEs, including serious AEs, were recorded and classified by the Medical Dictionary for Regulatory Activities (MedDRA) at baseline, investigator visit days, unscheduled doctor visits, and at the end of the study. Cardiac safety was assessed in a subset of participants with electrocardiography as a safety parameter required by the US Food and Drug Administration.

Statistical analysis

The sample size was selected for efficacy to yield at least 90% power to achieve a statistically significant difference (2-sided test at α = .05), assuming success rates of 20% (crisaborole-treated group) and 10% (vehicle-treated group). Efficacy analyses were performed using the intent-to-treat population, which included all patients randomized and dispensed study drug, regardless of discontinuation. The odds ratio of success in ISGA score at day 29 and secondary end points were tested between treatment groups using logistic regression with factors for treatment group and analysis center. Time to success in ISGA score and time to improvement in pruritus were analyzed by Kaplan-Meier methods and the log-rank test. Severity of signs of AD and pruritus were evaluated using descriptive statistics. The analyzed safety population included all patients who were randomized, were confirmed to have received 1 or more doses of the study drug, and who received 1 or more postbaseline assessments. For treatment-emergent AEs (TEAEs), the frequency of patients with 1 or more TEAEs was tabulated and a Fisher exact test was performed on any TEAE that occurred at a frequency of 1% or greater. In addition, a Fisher exact test was performed for any treatment-related event that occurred at a frequency of 1% or greater within any treatment group.

RESULTS

Patients and enrollment

The intent-to-treat population consisted of 503:256 and 513:250 patients randomly assigned to receive crisaborole:vehicle, for AD-301 and AD-302, respectively (Supplementary Fig 1). There were no significant differences across treatment groups or across studies in baseline demographics and disease severity (Table I).

Efficacy end points

More crisaborole-treated patients achieved success in ISGA score at day 29 than vehicle-treated patients (AD-301: 32.8% vs 25.4%, $P = .038$; AD-302: 31.4% vs 18.0%, $P < .001$) (Fig 2, *A*). In addition, Kaplan-Meier analysis demonstrated that patients treated with crisaborole achieved success in ISGA score earlier than those treated with vehicle ointment ($P < .001$) (Fig 2, *B*). More patients achieved ISGA scores of clear (0) or almost clear (1) with crisaborole at day 29 (AD-301: 51.7% vs 40.6%, $P = .005$; AD-302: 48.5% vs 29.7%, $P < .001$) (Fig 2, *C*).

Crisaborole improved disease severity as evidenced by reduction in signs and symptoms of AD (Fig 2, *D* and *E*), including pruritus. Crisaborole-treated patients achieved improvement in pruritus earlier than vehicle-treated patients (pooled data, 1.37 vs 1.70 days, $P = .001$). Across all visits, a greater proportion of crisaborole-treated patients achieved improvement in pruritus (pooled data, days 8, 15, 22: $P < .001$; day 29: $P = .002$) (Fig 3). For all clinical signs of AD, a greater proportion of crisaborole-treated patients than vehicle-treated patients demonstrated improvement at day 29 (Fig 4, *A*), along with a greater reduction in mean severity (pooled data, erythema: $P < .001$; exudation: $P = .001$; excoriation: $P < .001$; induration/papulation: $P = .002$; lichenification: $P < .001$) (Fig 4, *B*).

Safety end points

Crisaborole demonstrated a favorable safety profile in which the majority of TEAEs reported were mild to moderate in severity (pooled data, crisaborole: 94.3% of TEAEs; vehicle: 96.9% of TEAEs), and most were considered unrelated or unlikely to be related to treatment (pooled data, crisaborole: 78.6%; vehicle: 84.2%). Treatment with crisaborole was well tolerated, with similar rates of TEAEs as vehicle (Table II). The majority of treatment-related AEs were application site pain, primarily reported as burning or stinging (Table II). Application site pain was the only treatment-related AE that occurred in 1% or more of patients. Of the patients with application site pain, 76.7% reported it on the first day of treatment, and 77.6% had resolution within 1 day of onset. No reports of treatment-related serious AEs were reported. The rates of study discontinuation because of AEs were the same in the crisaborole (1.2%) and vehicle (1.2%) treatment groups. In addition, no clinically meaningful differences were observed in patients' vital signs, electrocardiograms, and clinical laboratory parameters between treatment groups.

Table I. Baseline patient and disease characteristics

Characteristic	AD-301		AD-302	
	Crisaborole ointment, n = 503	Vehicle, n = 256	Crisaborole ointment, n = 513	Vehicle, n = 250
Age, y				
Mean	12.0	12.4	12.6	11.8
Range	2-65	2-63	2-79	2-79
Age groups, %				
2-6 y	32.2	30.5	33.7	37.2
7-11 y	30.8	28.5	26.7	28.4
12-17 y	24.1	26.2	24.6	22.8
≥18 y	12.9	14.8	15.0	11.6
Sex, %				
Male	43.5	44.1	45.0	44.8
Female	56.5	55.9	55.0	55.2
Ethnicity, %				
Hispanic or Latino	25.0	25.8	14.4	14.0
Not Hispanic or Latino	75.0	74.2	85.6	86.0
Race, %				
American Indian or Alaska Native	1.6	1.2	0.6	0.8
Asian	5.2	6.6	5.1	4.0
Black or African American	27.4	23.8	28.7	31.2
Native Hawaiian or other Pacific Islander	0.0	1.6	1.4	1.6
White	61.2	63.3	60.2	57.6
Other	4.6	3.5	4.1	4.8
Baseline ISGA, %				
Mild (2)	39.0	36.3	38.4	40.0
Moderate (3)	61.0	63.7	61.6	60.0
% BSA				
Mean	18.8	18.6	17.9	17.7
Range	5-95	5-90	5-95	5-90

AD, Atopic dermatitis; *BSA*, body surface area; *ISGA*, Investigator's Static Global Assessment score.

DISCUSSION

Crisaborole ointment, a novel PDE4 inhibitor, significantly reduced the signs and symptoms of AD in children and adults in these two phase III studies. Its positive efficacy profile was based on: (1) improvement in disease severity, as early as day 8 of treatment; (2) reduction in AD signs and symptoms; and (3) early and sustained improvement in pruritus. This novel medication showed relief of pruritus, which is important for AD treatment, as disruption of the itch-scratch cycle can mitigate AD signs, improve quality of life,[35] and reduce the risk for infection and scarring.[6]

The significant efficacy of crisaborole versus vehicle was noted, despite a strong "vehicle effect" observed in these studies, which is a common phenomenon in AD clinical studies that compare

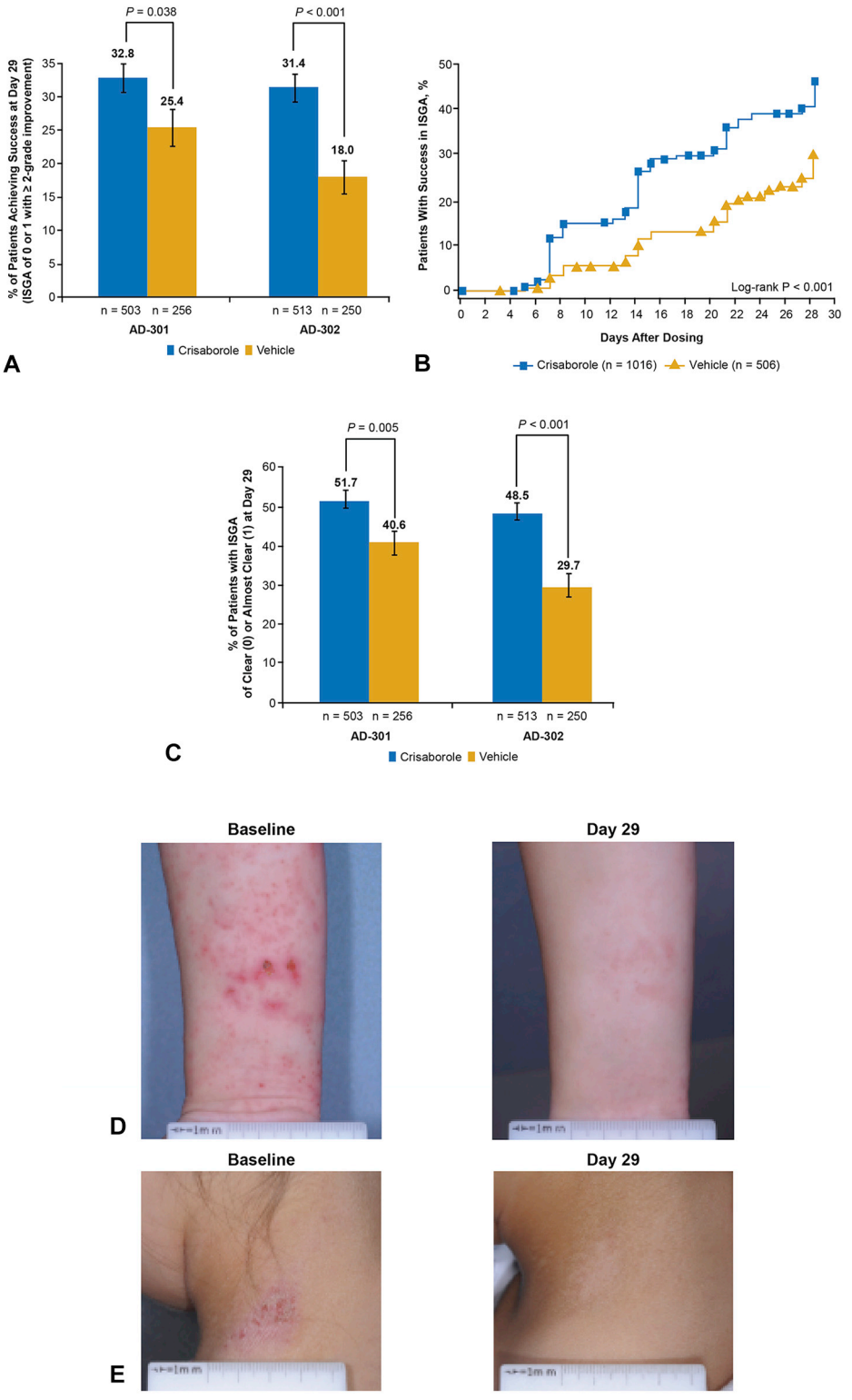

Fig 2. Atopic dermatitis (*AD*). Efficacy analysis. In studies AD-301 and AD-302, a greater proportion of crisaborole-treated patients achieved success in Investigator's Static Global Assessment (*ISGA*) score by day 29 (**A**). In addition, crisaborole-treated patients achieved success in ISGA score earlier than vehicle-treated patients as analyzed by Kaplan-Meier analysis (pooled) (**B**). A greater proportion of crisaborole-treated patients achieved an ISGA score of clear (0) or almost clear (1) by day 29 (**C**). **D** and **E**, Photographs demonstrate success in ISGA score at day 29.

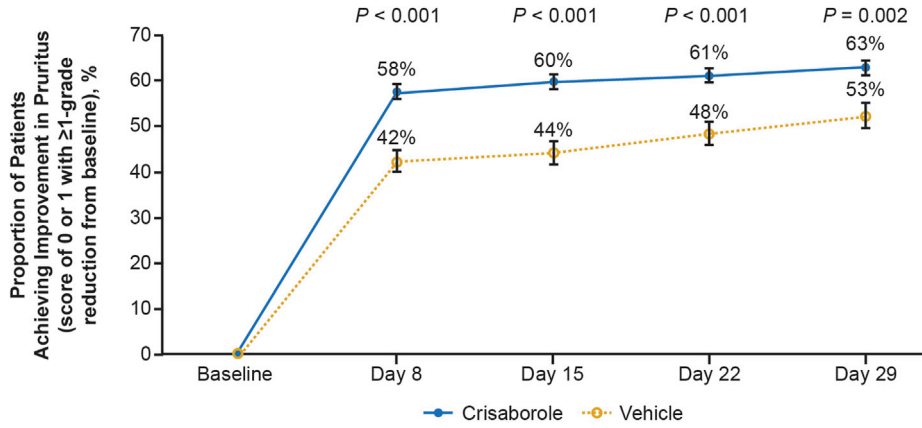

Fig 3. Atopic dermatitis (*AD*). Improvements in pruritus. In a pooled analysis of studies AD-301 and AD-302, a greater percentage of crisaborole-treated patients achieved improvement in pruritus at the earliest evaluation and throughout treatment compared with vehicle-treated patients.

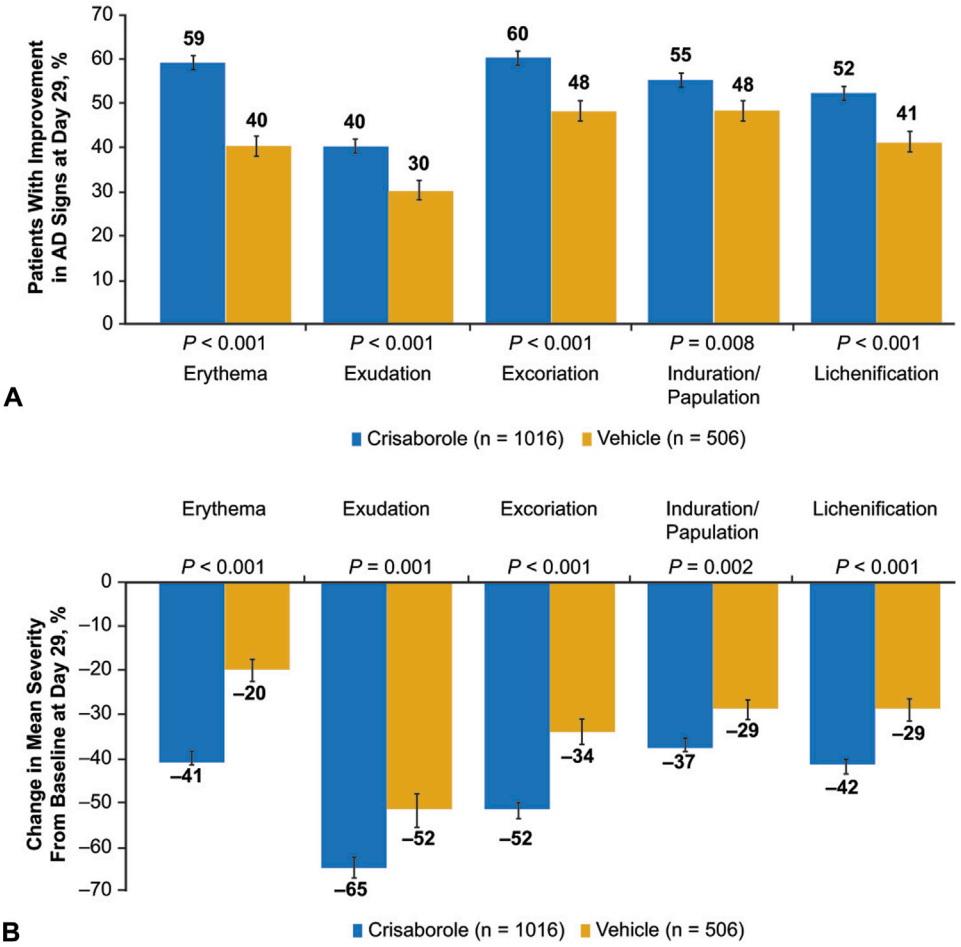

Fig 4. Atopic dermatitis (*AD*). Improvement in signs of AD. In pooled analysis of AD-301 and AD-302, comparison of crisaborole-treated with vehicle-treated patients at day 29 revealed a greater proportion of crisaborole-treated patients achieved improvement in signs of AD (**A**), with greater mean reductions in severity from baseline (**B**).

active therapeutics with their emollient bases.[36] For example, vehicle-treated patients in a tacrolimus study demonstrated therapeutic success in 19.5% of vehicle-treated patients at 4 weeks.[36] In treating patients with AD, a topical medication should ideally disrupt the inflammatory process and provide

Table II. All treatment-related adverse events and treatment-emergent adverse events (≥1% of patients)

	Crisaborole ointment, n = 1012	Vehicle, n = 499
Treatment-related adverse event, n (%)		
Application site pain*	45 (4.4)†	6 (1.2)
Treatment-emergent adverse event, n (%)		
Gastrointestinal disorders	27 (2.7)	12 (2.4)
Vomiting	15 (1.5)	5 (1.0)
General disorders and administration site conditions	75 (7.4)	25 (5.0)
Application site pain*	45 (4.4)†	6 (1.2)
Application site pruritus	5 (0.5)	6 (1.2)
Pyrexia	19 (1.9)	7 (1.4)
Infections and infestations	118 (11.7)	59 (11.8)
Nasopharyngitis	18 (1.8)	6 (1.2)
Staphylococcal skin infection	1 (0.1)‡	5 (1.0)
Upper respiratory tract infection	30 (3.0)	15 (3.0)
Injury, poisoning, and procedural complications	20 (2.0)	9 (1.8)
Investigations§	10 (1.0)	6 (1.2)
Nervous system disorders	14 (1.4)	2 (0.4)
Headache	11 (1.1)	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	47 (4.6)	15 (3.0)
Cough	12 (1.2)	8 (1.6)
Oropharyngeal pain	11 (1.1)	2 (0.4)
Skin and subcutaneous tissue disorders	37 (3.7)	21 (4.2)
Dermatitis atopic	7 (0.7)	8 (1.6)

*Refers to skin burning or stinging.
†*P* value for the difference between treatment groups from Fisher exact test (*P* = .001).
‡*P* value for the difference between treatment groups from Fisher exact test (*P* = .017).
§Included clinical laboratory tests, radiologic tests, physical examination parameters, and physiologic tests.

protective benefits often seen with an emollient, including improving the skin barrier to reduce antigen access and increasing skin hydration by preventing transepidermal water loss.[5] As such, topical drug vehicles have physiologic cutaneous effects, adding to the drug effect in improving outcomes for patients. The incorporation of crisaborole into the vehicle significantly improved the efficacy in treating AD on a global scale and in reducing pruritus and signs of AD.

Because of potential adverse side effects and restricted long-term use of TCS and TCI, a safe and efficacious topical alternative is needed to treat AD. Crisaborole has low systemic absorption and is quickly metabolized to its inactive metabolites, reducing the risk of systemic side effects, making it a promising therapeutic alternative to existing topical therapies.[30,33] Twice-daily application of crisaborole ointment for 28 days demonstrated a favorable safety profile in these two phase III studies based on: (1) low incidence of treatment-related AEs, (2) lack of serious treatment-related AEs, and (3) low discontinuation rates. The low incidence and mild severity of AEs observed indicate that the novel topical formulation of crisaborole allows for targeted therapy at the site of inflammation while reducing the risk of systemic side effects observed with oral PDE4 inhibitors.[22] Gastrointestinal AEs, which have been observed with oral PDE4 inhibitors, were reported by crisaborole-treated patients at a low frequency (2.7%) similar to that in vehicle-treated patients (2.4%) and were not considered treatment related. Application site burning or stinging is a commonly reported side effect with TCS or TCI treatment.[37] Although a direct comparison study with TCS and TCI has yet to be performed, crisaborole ointment demonstrated a low incidence of application site pain (4.4%), defined by updated MedDRA guidelines as stinging and/or burning, compared with rates of application site burning reported by tacrolimus (20%-58%) and pimecrolimus (8%-26%).[38,39] Crisaborole-treated patients did not report cutaneous TCS AEs such as telangiectasia or skin atrophy, but these potential risks only occur with TCS treatment for 4 weeks or longer.[40] The favorable safety profile demonstrated in these 28-day studies will be investigated further with a long-term safety extension study. Overall, twice-daily application of crisaborole ointment to all areas of the body with the exception of the scalp for 28 days demonstrated a favorable safety profile.

Crisaborole represents a first-in-class nonsteroidal topical treatment that inhibits overactive PDE4 in AD to reduce the local inflammation that drives exacerbations of the disease.[15,24-27] The anti-inflammatory effect on AD pathology is clear, and crisaborole also provided early and sustained improvement in pruritus in these two trials. This significant reduction in pruritus provides additional support to the antipruritic effect observed with other PDE4 inhibitors in inflammatory skin diseases such as psoriasis.[41] The mechanism through which PDE4 regulates pruritus is not well understood but is believed to be partially an indirect result of reducing inflammation,[7,42] similar to the antipruritic effects observed with TCS treatment.[42] Preclinical studies have demonstrated that PDE4 directly regulates pruritus through reduction of cutaneous neuron[43] and dorsal root ganglion neuron activity.[7,44] Mounting evidence indicates that PDE4 inhibitors directly regulate pruritus

in inflammatory skin diseases, providing early relief for the most troublesome symptom of AD.[8,45]

Crisaborole represents a promising new option for patients with mild to moderate AD based on the favorable safety profile and improvement in AD seen in these studies. Future studies could apply alternative AD severity grading scales that may provide additional efficacy information by anatomic region to further our understanding and elaborate on the role crisaborole could play in the treatment of AD. In addition, because 45% to 60% of children develop AD in their first 6 months to 1 year of life, respectively,[1] future studies may explore the potential for crisaborole treatment in patients younger than 2 years of age. Future analysis using the Eczema Area and Severity Index will provide valuable insight into site-specific efficacy of crisaborole ointment for comparison with TCS and TCI. In addition, long-term treatment is often required because of the chronic nature of AD, and patients in these two trials were enrolled in an extension study to evaluate the long-term safety of crisaborole ointment. Overall, crisaborole ointment targets the underlying mechanism of the disease and has the potential to effectively treat AD without the limitations of current therapies.

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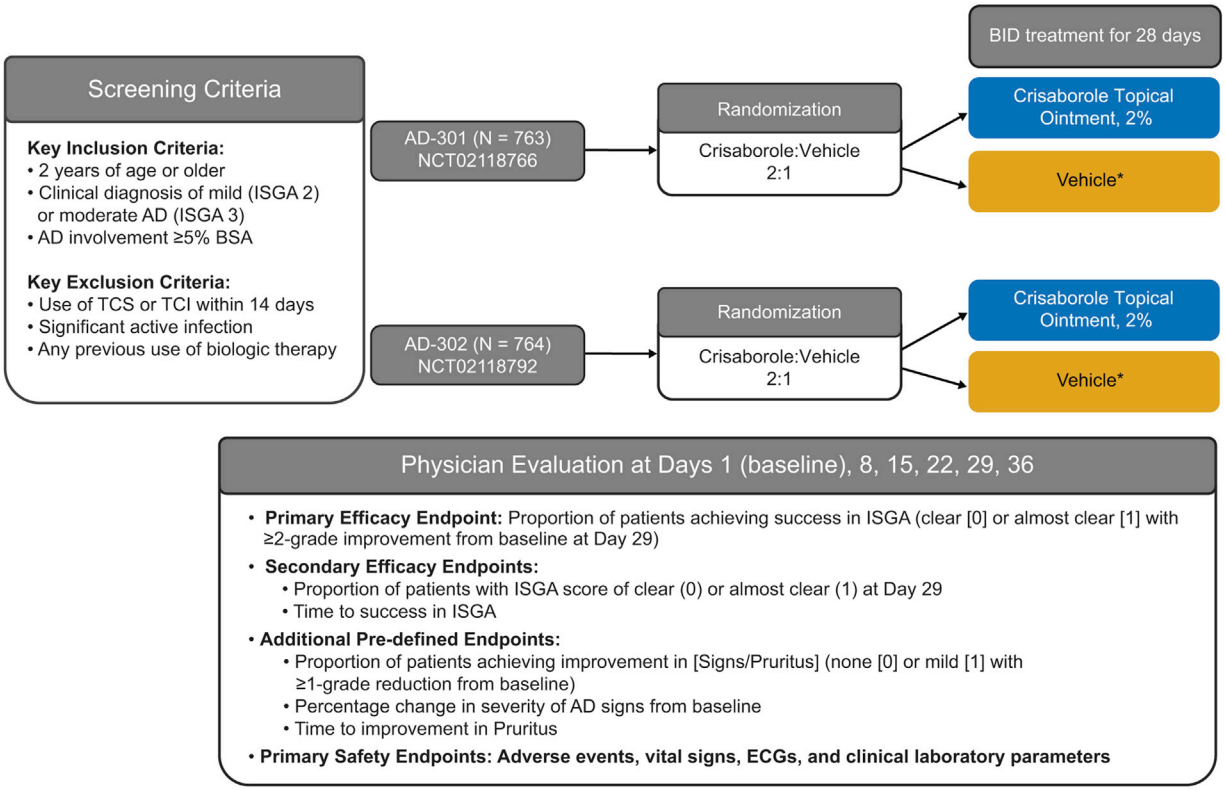

Supplementary Fig 1. Atopic dermatitis (*AD*). Study design and treatment. Key screening criteria, patient enrollment, randomization, and assessments. *AD*, Atopic dermatitis; *BID*, twice daily; *BSA*, body surface area; *ECG*, electrocardiography; *ISGA*, Investigator's Static Global Assessment; *TCI*, topical calcineurin inhibitor; *TCS*, topical corticosteroid. *Proprietary vehicle developed by Anacor Pharmaceuticals, Inc.

Supplementary Table I. Investigator's Static Global Assessment

Scale	Grade	Definition
0	Clear	Minor residual hypopigmentation/hyperpigmentation; no erythema or induration/papulation; no oozing/crusting
1	Almost clear	Trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting
2	Mild	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate	Pink-red erythema with moderate induration/papulation with or without oozing/crusting
4	Severe	Deep or bright red erythema with severe induration/papulation and with oozing/crusting

To assess the patient's overall disease severity across all treatable atopic dermatitis lesions, Investigator's Static Global Assessment (ISGA) was assessed at screening and days 1, 8, 15, 22, and 29. ISGA was assessed on a 5-point scale from clear (0) to severe (4).

Supplementary Table II. Severity of pruritus scale

Scale	Grade	Definition
0	None	No itching
1	Mild	Occasional, slight itching/scratching
2	Moderate	Constant or intermittent itching/scratching that is not disturbing sleep
3	Severe	Bothersome itching/scratching that is disturbing sleep

Severity of pruritus was recorded twice daily via electronic diary by patients or caregivers before study drug was applied from days 1-29. Severity of pruritus was assessed on a 4-point scale from none (0) to severe (3).

Supplementary Table III. Signs of atopic dermatitis scale

Score	Grade	Definition
Erythema (redness)		
0	None	No redness
1	Mild	Mildly detectable erythema; pink
2	Moderate	Dull red; clearly distinguishable
3	Severe	Deep, dark red; marked and extensive
Exudation (oozing and crusting)		
0	None	No oozing or crusting
1	Mild	Minor or faint signs of oozing
2	Moderate	Definite oozing or crusting
3	Severe	Marked and extensive oozing or crusting
Excoriation (evidence of scratching)		
0	None	No evidence of excoriation
1	Mild	Mild excoriation
2	Moderate	Definite excoriation
3	Severe	Marked, deep, or extensive excoriation
Induration/papulation		
0	None	None
1	Mild	Slightly perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
Lichenification (epidermal thickening)		
0	None	No epidermal thickening
1	Mild	Minor epidermal thickening
2	Moderate	Moderate epidermal thickening; accentuated skin lines
3	Severe	Severe epidermal thickening; deeply accentuated skin lines

Signs of atopic dermatitis were assessed at every scheduled in-clinic visit from baseline through day 29. Signs of atopic dermatitis were assessed on a 4-point scale from none (0) to severe (3).