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Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies

Atopic dermatitis (AD), a chronic, relapsing, inflammatory skin disease that is characterized by intense pruritus and eczematous lesions with up to 90% of patients presenting with mild to moderate disease. Current topical treatments for AD have not changed in over 15 years and are associated with safety concerns. In AD, overactivity of phosphodiesterase 4 (PDE4), leads to inflammation and disease exacerbation. Crisaborole Topical Ointment, 2%, is a novel, nonsteroidal, topical anti-inflammatory PDE4 inhibitor currently being investigated for the treatment of mild to moderate AD. Preliminary studies in children and adults demonstrated favorable efficacy and safety profiles. Crisaborole may represent an anti-inflammatory option that safely minimizes the symptoms and severity of AD and that can be used for both acute and long-term management.

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Atopic dermatitis (AD) or eczema, one of the most common inflammatory skin diseases, is characterized by chronic and relapsing episodes of intense pruritus, an impaired epidermal barrier and eczematous lesions [1–3]. It occurs most frequently in children, but also affects adults [4]. In industrialized countries, the incidence of AD has increased by two- to threefold since 1950 [5,6]. The prevalence of AD is 15 to 30% in children and 2 to 10% in adults [2]. Approximately 85% of patients experience symptoms by the time they are 5 years old [5,7]. 20% of individuals who develop AD before the age of 2 years continue to experience manifestations of the disease, with a waxing/waning pattern [7], and these manifestations often persist into their second decade of life [8].

AD-associated pruritus imposes psychological, social and quality of life (QoL) burdens on patients and their families [5,9–12]. AD also represents a significant financial

burden [5,12]. The estimated annual cost of AD, even without its comorbidities, approaches US \$3.8 billion [11]. Mean total direct medical costs in the USA from 1998 to 2005 were significantly higher for patients with AD than for controls without AD (US \$349 vs US \$261 per patient per month, respectively; $p < 0.001$) [13].

Disease management focuses on alleviating symptoms and preventing flares [14]. AD has been called the ‘itch that rashes’ [15], and chronic, localized or general pruritus is the hallmark of the condition [3,16–18]. Up to 90% of patients present with mild to moderate AD [19,20], and disease severity is correlated with the intensity of pruritus [21]. In a study of 89 pediatric patients, 45% of those with mild AD and 75% of those with moderate AD reported daily itch, 20% and 19% experienced weekly itch and the remaining patients experience itch at an interval greater than 7 days [21].

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Etiology

The root cause of AD involves several processes, but both genetic and environmental factors contribute to its development [5]. The strongest known genetic link with AD is related to mutations of the gene encoding filaggrin [3,18,22], a skin matrix protein that promotes keratin aggregation, a part of the completion of the squamous layer [23]. These mutations are thought to be associated with skin barrier impairment, a key feature of the disease [5,6,18,22,24]. Researchers have also identified several other genes that are involved with the skin barrier response and immune dysregulation associated with AD [24,25]. While genetic mutations are associated with AD, there are many AD patients without genetic alterations, indicating that these mutations explain only part of the disease pathology [26].

AD-related skin barrier disruption results in increased water loss [25], leading to dry skin. These changes cause increased susceptibility to allergic sensitization, infection and microbial colonization [6,24,27,28]. Skin barrier disruption is correlated with disease severity [24,29] and associated with an increased risk of the 'atopic march' [5]. Patients affected by this phenomenon experience a progression of atopic manifestations, beginning with AD and progressing to allergic rhinitis or asthma in later life [5].

Inflammation is associated with elevated phosphodiesterase (PDE) activity [12,30]. Increased levels of PDE4, an intracellular enzyme found in inflammatory cells such as macrophages, T cells, monocytes and neutrophils [31], are seen in patients with active AD and in those with inactive allergic rhinitis [30]. PDE4 is involved in controlling the production of inflammatory cytokines, such as interleukin-4 (IL-4), IL-5, IL-10, IL-13 and prostaglandin E2, through the degradation of cyclic adenosine monophosphate (cAMP) [12,31–36]. Inhibition of PDE4 increases intracellular cAMP, which then activates protein kinase A (PKA) [37,38]. Activation of PKA leads to the phosphorylation of target proteins, some of which are involved in the control of cytokine production, such as cAMP-response-element-binding protein (CREB) [39,40], NF- κ B [41,42], NFAT [43], Rap1 [44] and Csk [45]. These changes in cytokine production result in an imbalance of T-cell activity, characterized by a reduction in regulatory T cells and an increase in T-helper (Th)-2 cells [2,22]. Thus, the involvement of PDE4 in the pathology of AD makes it a potential therapeutic target for disrupting the inflammatory cycle characteristic of this disease.

Burden of atopic dermatitis

Because of the associated pruritus, QoL can be substantially impaired for patients with AD and the parents of children with AD. Although there is no specific

diagnostic test for AD, the intensity of pruritus is a major criterion [46,47] for categorizing disease severity and assessing clinical outcomes [4,21,48,49].

In individuals with AD, pruritus can lead to long-term psychological problems, including anxiety, depression and suicidal ideation [50–54]. The prevalence of mental health issues is higher in patients with AD than in the general population, and pruritus has a detrimental effect on comfort levels and sleep [52,55–57].

Clinical depression is common in individuals with AD. In an observational cross-sectional study of adults recruited from dermatologic outpatient clinics in 13 European countries, 10.1% of patients with AD and 4.3% of controls had depression as assessed by the Hospital Anxiety and Depression Scale ($p < 0.001$ for comparison) [57]. The adjusted odds ratio for depression in participants with AD was 3.27 (95% confidence interval: 1.61–6.62) [57]. In addition, multiple studies in a variety of countries have reported suicidal ideation in >15% of patients with AD [56,58,59]. A strong correlation has been found between patient-rated dermatological disease severity, psychologic burden and suicidal ideation [56,60].

Children with pruritus may exhibit increased daytime behavioral changes that are likely secondary to pruritus-related sleep disorders [9,61]. These changes can lead to impaired school performance and an increased risk of developing emotional and social problems during adolescence [9,61]. Attention deficit hyperactivity disorder is 1.5-times more prevalent in children with AD than in those without AD, and this relationship appears to be causal [55].

Given the many negative consequences of AD-related pruritus, achieving improved disease control is essential for breaking the itch-scratch cycle, preventing chronicity and scarring and improving QoL [9,62]. Moreover, better disease control might mitigate the increased risk of mental health problems [51,52,55,56,58,60], prevent recurrent bacterial and viral skin infections [55] and slow the atopic march [55,63]. Improved control could also make it possible to limit the continuous use of and side effects associated with mid- to high-potency topical corticosteroids (TCS) that are commonly prescribed to treat AD [4].

Current topical treatment paradigms for atopic dermatitis

Nonpharmacologic treatments

Nonpharmacologic treatments for AD include physical and psychosocial interventions. Physical interventions that appear to have the greatest therapeutic potential are wearing silk or silver-impregnated clothing, dilute bleach baths, wet-wrap therapy, aggressive moisturization, vitamin D supplementation and phototherapy.

Other approaches include allergen avoidance, climate and temperature changes, dietary modification and probiotic consumption [4,64,65]. The value of these approaches is limited by a lack of research on their optimal frequency and the consequences of combining them with TCS therapy. Psychosocial interventions, including hypnosis and education, as well as biofeedback and participation in support groups, have shown promise, but further investigation is required to understand their efficacy in treating patients with AD [4,64,65]. Nonpharmacologic treatments must be used consistently if they are to be effective, but optimal regimens for patients with the various types of AD have not yet been established.

Pharmacologic treatments

According to guidelines developed by the American Academy of Dermatology and the American Academy of Allergy, Asthma, and Immunology, major considerations in treating AD include using agents that are safe for younger patients and that are both effective and safe for treating AD signs and symptoms in sensitive skin areas and larger body surface areas (BSAs) over an extended period of time [4]. Pharmacologic topical treatments that are commonly prescribed for AD have changed very little over the past 15 years, consisting primarily of topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) [66]. TCS have been used to treat AD since the early 1950s [4,67], and two TCI were introduced as therapies for AD in 2000 and 2001 [4,68].

Topical corticosteroids

TCS reduce inflammation and pruritus [4,9,16,20,49,62] by acting on various immune cells to disrupt antigen processing and presentation and by suppressing the release of proinflammatory cytokines [4,69,70]. They are frequently prescribed to treat the acute and chronic signs of AD in adults and children [4,49]. The type of lesion, age of the patient and area of skin requiring treatment are important considerations in selecting among the many different TCS preparations and doses that are currently available [64].

The effectiveness of TCS for reducing AD-related inflammation and pruritus is well established [4,7,20], but their use is limited by local and systemic adverse effects [4]. These concerns are particularly relevant in children, who have a greater surface area-to-body weight ratio, and thus the potential for more substantial exposure [4]. Local, potency-dependent side effects of short-term TCS treatment include burning and itching [71], secondary infection and skin atrophy [20]. For acute flares, TCS are often used daily for up to several weeks, and proactive use (once to twice weekly) is recommended for chronic relapsing areas [4]. Potential

adverse effects of long-term treatment include striae, folliculitis, acne-like eruptions, focal hypertrichosis, allergic contact dermatitis, glaucoma, papilloedema and telangiectasia [4,66,69]. Long-term TCS treatment is associated with an increase in the risk of tachyphylaxis to TCS, and hypothalamic-pituitary-adrenal axis suppression, Cushing syndrome, growth retardation, glucose intolerance, peptic ulcer disease, neuropsychiatric manifestations and other adverse effects [4,66,69].

Application of high-potency TCS is restricted in areas such as the thin-skinned eyelids, periocular area, face, axillae and genitals due to an increased risk of adverse events [19,20,64,67]. The structure of skin in these areas, characterized by a thin epidermis, extensive vascularization or many epidermal appendages and nerve endings, causes it to be more absorbent [20,69]. Therefore, TCS should not be used under occlusion in these areas [4,20,49,67], and patients prescribed TCS should be closely monitored [20,72,73] and educated about proper uses [16].

Topical calcineurin inhibitors

TCI are immunosuppressants that act by inhibiting T-cell and mast cell activation, thereby reducing the production of proinflammatory cytokines and mediators of the inflammatory reaction in AD [4,14]. Tacrolimus (0.03 and 0.1%) and pimecrolimus (1%) are the TCI drugs that are currently approved to treat moderate to severe or mild to moderate AD, respectively [4,14,16].

The most commonly observed adverse effects associated with TCI treatment are application site burning and stinging [4,14,16]. Additionally, a boxed warning was added to the pimecrolimus and tacrolimus labels in 2006 due to concerns about a potential link between TCI use and increased lymphoma risk [14]. Recent epidemiologic evidence suggests that the incidence of lymphoma is no greater in TCI-treated patients than in the general population [14]. Thus, no causal relationship between TCI use and malignancies or lymphoma as a result of immune suppression has been confirmed [74–76]. The US FDA has concluded that the possibility of such an association may still exist, and the boxed warning for lymphoma risk remains in place [14]. Patient education about the potential side effects of TCI therapy is important for optimizing adherence to the treatment regimen [19].

Development of Crisaborole Topical Ointment, 2%, for atopic dermatitis

Clinical pharmacology & mechanism of action

Crisaborole is a small-molecule, boron-based, selective PDE4 inhibitor that modulates multiple immune and inflammatory pathways (Figure 1) [77–79]. It has a low molecular weight, of 251 Da [77] that provides

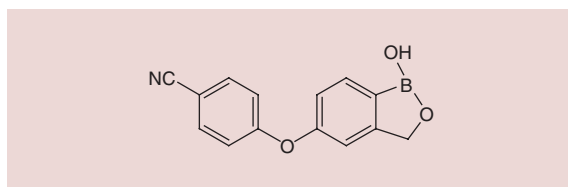


Figure 1. Chemical structure of crisaborole [77].

good skin penetration. The presence of boron in this benzoxaborole structure confers the ability to inhibit PDE4 by acting as a mimic of the phosphate of cAMP [80]. Its unique geometry enables it to target and inhibit PDE4, which degrades cAMP [80]. By inhibiting PDE4, crisaborole increases intracellular cAMP levels [35]. Increased cAMP suppresses the activity of the NF- κ B [42] and other pathways responsible for inflammatory cytokine production [31,36] including CREB [39,40], NFAT [36], Rap1 [44] and Csk [45] leading to the suppression of cytokine synthesis (Figure 2) [80]. *In vitro* analysis demonstrated crisaborole inhibits the production of a selection of Th1 and Th2 proinflammatory cytokines, including IFN- γ , TNF- α , IL-2,

IL-5 and IL-10 [80]. Thus, crisaborole has the potential to control inflammation [78–80], and future studies may elucidate the ability of crisaborole to inhibit other inflammatory mediators.

Crisaborole is suitable for topical formulation because of its physicochemical properties and low molecular weight, which allow it to penetrate the epidermis and dermis to reach the site of inflammation. Once it reaches the systemic circulation, crisaborole is rapidly metabolized to inactive metabolites, resulting in limited systemic exposure [81].

Phase I and II data: pharmacokinetics, efficacy & safety

One Phase Ib and three Phase II clinical trials were performed to analyze the pharmacokinetics, efficacy and safety of crisaborole in children and adults (Table 1) [82–85]. Global disease severity was analyzed by the Investigator's Static Global Assessment (ISGA). The protocols for these studies excluded use of crisaborole on the scalp, due to the anticipated cosmetic

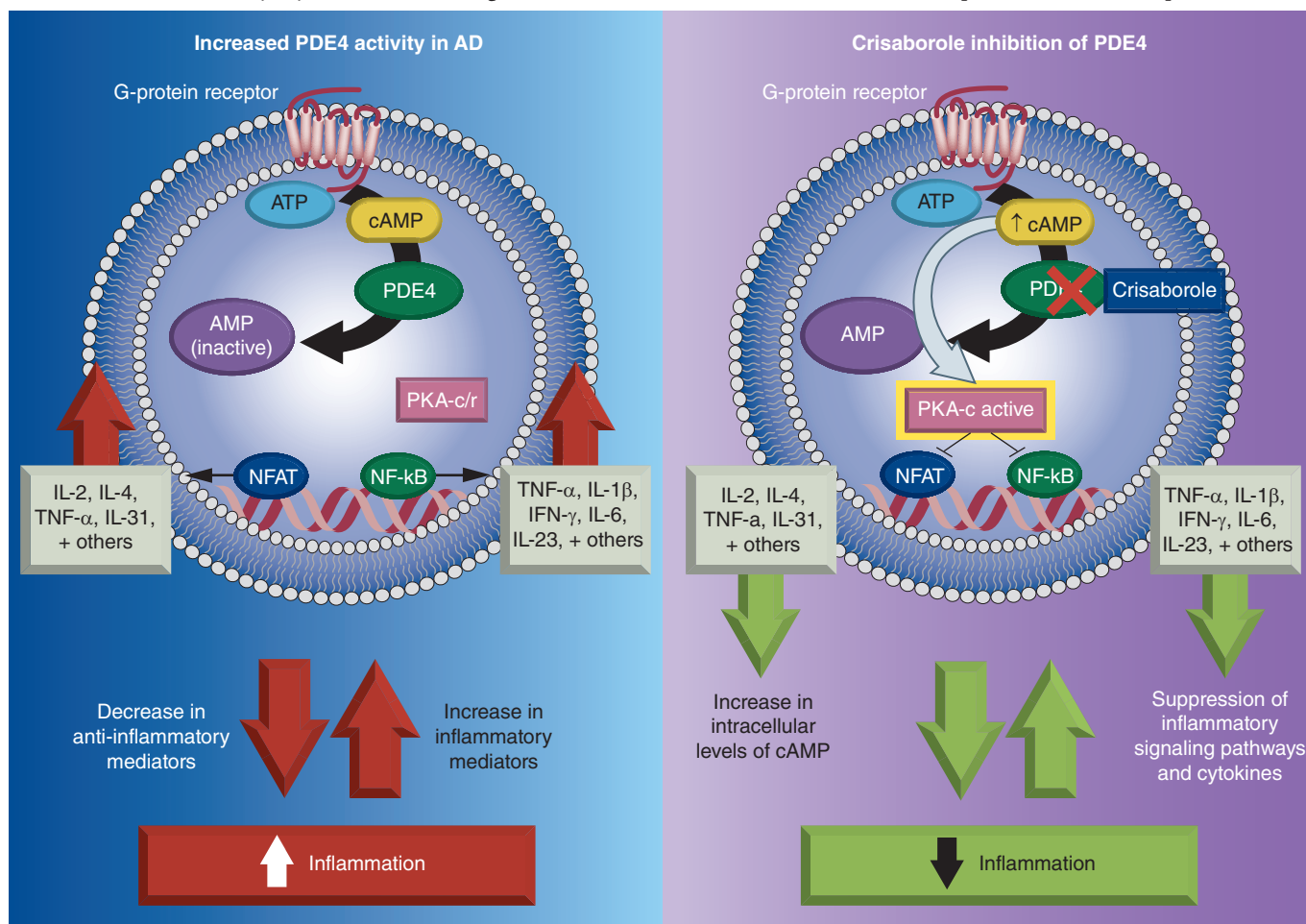


Figure 2. Mechanism of action of crisaborole. AD: Atopic dermatitis; ATP: Adenosine triphosphate; cAMP: cyclic adenosine monophosphate; IFN- γ : Interferon gamma; IL: Interleukin; NFAT: Nuclear factor of activated T cells; NF- κ B: Nuclear factor κ B; PDE4: Phosphodiesterase 4; PKA-c/r: cAMP-dependent protein kinase catalytic subunits c and r; TNF- α : Tumor necrosis factor alpha.

Table 1. Study design and outcomes for Phase I and Phase II clinical trials.						
Study number	Study description	Primary end point	Key secondary end points	Cohort age range, years	AD assessment	
					Efficacy at day 29	Pruritus (pooled analysis)
102	Phase Ib, Open-label, maximal-use study, n = 34, whole body assessment	PK plasma profile and safety	Treatment success at day 29; improvement from baseline in individual AD signs and symptoms at day 29; change from baseline in treatable%BSA at day 29	2–17	47.1% Crisaborole Topical Ointment, 2%-treated patients achieved treatment success	Significant reduction in mean pruritus severity scores by day 8*
203	Phase IIa, open-label, safety, tolerability and PK study, n = 23, whole body assessment	PK plasma profiles of crisaborole and its oxidative metabolites AN7602 and AN8323 on days 1 and 8	Treatment success at days 8, 15, 22 and 29; ISGA score of clear (0) or almost clear (1) and ≥ 2 -grade improvement from baseline at days 8, 15, 22 and 29	12–17	34.8% Crisaborole Topical Ointment, 2%-treated patients achieved treatment success†	
202	Phase IIa, vehicle-controlled, proof-of-concept study, n = 25, target lesion assessment	Change in ADASI score from baseline at day 28	Change from baseline in ADASI score at days 14 and 42	18–75	68.0% vs 20.0% achieved treatment success, (Crisaborole Topical Ointment, 2% vs vehicle)	Significant reduction in mean pruritus severity scores by day 15*
204	Phase II, bi-lateral, dose-finding study, n = 86, target lesion assessment	Change in ADASI score from baseline at days 8, 15, 22 and 29	Proportion of target lesions achieving total or partial clearance (ADSI ≤ 2)	12–17	Crisaborole Topical Ointment, 2% twice daily achieved greatest improvement from baseline ADASI score	

*Day 8 and 15 were the earliest assessment point for pooled analysis between studies 102/203 and 202/204, respectively ($p < 0.001$ for both).
†Proportion of vehicle patients achieving success not analyzed.
AD: Atopic dermatitis; ADASI: Atopic dermatitis severity index; BSA: Body surface area; ISGA: Investigator's Static Global Assessment; PK: Pharmacokinetic; TEAEs: Treatment-emergent adverse events.

incompatibility of ointment and long hair, as well as precluding application near venous access areas. The use of emollients, TCS and TCI was restricted during treatment with crisaborole.

Pharmacokinetics

Studies 102 and 203 analyzed the pharmacokinetic properties of Crisaborole Topical Ointment, 2% (primary end points). In Study 102 (a maximal use systemic exposure study), the mean observed maximum plasma concentration after maximal dosing (C_{\max}) with crisaborole was 111 ng/ml, indicating low systemic exposure; the mean time to reach C_{\max} (T_{\max}) was 3 h on days 1 and 8 [82].

In Study 203 (NCT01652885), the pharmacokinetic profile also reflected rapid absorption of cri-

saborole, with a median T_{\max} of 2.37 h on day 1 and 2.17 h on day 8 (Table 2) [84]. Crisaborole mean C_{\max} and $t_{1/2}$ values in plasma were 105 ng/ml and 7.17 h on day 1, and 94.6 ng/ml and 11.9 h on day 8, respectively. After absorption into the systemic circulation, crisaborole was quickly metabolized to AN7602 and AN8323, the two identified inactive oxidative metabolites in plasma. Both of these metabolites are inactive as PDE4 inhibitors [86]. The extent of systemic exposure to crisaborole increased as the amount of applied crisaborole increased. Steady state of crisaborole and its metabolites was achieved within 4 to 6 days [84].

Safety

Pooled safety analysis across all 4 studies included patients as young as 2 years of age, and patients

Table 2. Mean (SD) plasma pharmacokinetic parameters for crisaborole in Study 102 and 203.

Analyte	Dose day	C _{max} , ng/ml	T _{max} (h), median (range)	AUC _(0–12) ^a , ng•h/ml	t _{1/2} ^a , h
Study 102 (Age range: 2–17)					
Crisaborole	Day 1	111 (113)	3.00 (3–12)	759 (730) [†]	n/a
	Day 8	127 (196) [‡]	3.00 (3–24) [‡]	949 (1240) [†]	n/a
AN7602	Day 1	37.8 (35)	3.00 (3–12)	247 (224) [†]	n/a
[4-(4-hydroxy-3-(hydroxymethyl)pheoxy)benzonitrile]	Day 8	40.8 (48.6) [‡]	3.00 (0–12) [‡]	290 (313) [†]	n/a
AN8323	Day 1	2270 (2640)	12.0 (3–24)	16,800 (16,900) [†]	n/a
[5-(4-cyanophenoxy)-2-hydroxybenzoic acid]	Day 8	6150 (4790) [‡]	3.00 (0–24) [‡]	63,400 (49,000) [†]	n/a
Study 203^a (Age range: 12–17)					
Crisaborole	Day 1	105 (160)	2.37 (1.00–24.0)	448 (527)	7.17 [§] (2.30)
	Day 8	94.6 [¶] (189)	2.17 [¶] (1.00–7.93)	462 [¶] (506)	11.9 [#] (8.28)
AN7602	Day 1	28.2 (37.0)	2.08 (1.00–24.0)	142 (172)	8.19 ^{††} (5.13)
[4-(4-hydroxy-3-(hydroxymethyl)pheoxy)benzonitrile]	Day 8	26.3 [¶] (43.9)	3.94 [¶] (1.00–6.15)	142 [¶] (154)	10.5 [§] (6.38)
AN8323	Day 1	998 (1220)	6.25 (3.95–25.0)	8900 (11,600)	17.7 ^{††} (1.63)
[5-(4-cyanophenoxy)-2-hydroxybenzoic acid]	Day 8	1850 [¶] (1830)	6.00 [¶] (0.00–25.1)	18,200 [¶] (18,100)	33.5 ^f (10.1)

[†]n = 32.
[‡]n = 33.
^aCrisaborole (3 mg/cm²) was applied to a mean% body surface area of 17.6% (n = 23) at baseline (day 1). Patients received 92–334 mg of crisaborole on day 1 and 96–334 mg on day 8.
[§]n = 16.
[¶]n = 22.
[#]n = 17.
^{††}n = 18.
^fn = 6.
AUC_(0–12)^a: Area under the plasma concentration-time curve from time zero to 12 h postdosing; C_{max}: Observed maximum plasma concentration after dosing;
SD: Standard deviation; t_{1/2}: Apparent half-life; T_{max}: Time to reach C_{max}.

exposed to maximal dosing conditions. Across all four studies 61 of 168 participants (36.3%) reported one or more treatment-emergent adverse events (TEAEs) (Table 3). Of the 131 TEAEs reported, 95 (72.5%) were considered mild, 33 (25.2%) were considered moderate and 3 (2.3%) were considered severe. None of the severe TEAEs were considered serious or related to treatment. Only 2 of 168 (1.1%) of patients discontinued treatment due to a treatment-related AE (application site dermatitis, application site pain) [82,84]. The most commonly reported treatment-related AEs were application site pain, dermatitis and pruritus [82–85].

Efficacy

Study 102 was a Phase Ib multicenter, open-label, maximal-use systemic exposure study evaluating Crisaborole Topical Ointment, 2%, applied twice daily for 28 days in patients aged 2–18 years with AD involving ≥25% of treatable BSA [82]. At baseline, the overall patient population had a mean% treatable BSA of 48.7% (range: 27–92%). At day 29, 16 of 34 patients (47.1%) achieved treatment success, defined

as ISGA score of 0 (Clear) or 1 (Almost Clear) with ≥2-grade improvement from baseline (secondary outcome). Mean severity scores for the 5 AD signs and symptoms from baseline to day 29 (secondary outcome) are shown in Figure 3. Throughout the study, crisaborole treatment resulted in a marked reduction in the severity of all signs and symptoms, indicating that crisaborole provides early and sustained relief of the signs and symptoms of AD. The mean % treatable BSA (secondary outcome) decreased throughout the study. The mean (SD) percentage change from baseline in the percentage of affected BSA at day 29 was –77.7% (22.1%) [82].

Study 202 (NCT01301508) was a Phase II, proof-of-concept, multicenter, randomized, double-blind, vehicle-controlled, 6-week study conducted in adults with mild to moderate AD [83]. 25 adults were randomized to apply Crisaborole Topical Ointment, 2%, to one target lesion and ointment vehicle to a second target lesion. At day 28, 17 patients (68.0%) experienced a greater improvement in the Atopic Dermatitis Severity Index (ADSI) score for the crisaborole-treated lesion compared with

Table 3. Summary of treatment-emergent adverse events reported in Phase I/II studies of crisaborole to date.

Variable	Study 202 (n = 25)	Study 203 (n = 23)	Study 204 QD (n = 44)	Study 204 BID (n = 42)	Study 102 (n = 34)	Total (n = 168)
Patients with TEAEs, n (%)	11 (44.0)	10 (43.5)	6 (13.6)	11 (26.2)	23 (67.6)	61 (36.3)
Total number of TEAEs	29	19	8	12	63	131
Total number of TEAEs by severity						
Mild	26	11	8	10	40	95
Moderate	3	8	0	2	20	33
Severe	0	0	0	0	3 [†]	3 [†]
Total number of discontinuations due to treatment-related AEs	0	1	0	0	1	2

[†]None were considered serious or related to treatment.
 AEs: Adverse events; BID: Twice-daily; QD: Once-daily; TEAE: Treatment-emergent adverse event.

the vehicle-treated lesion (primary outcome). Five patients (20.0%) had a greater decrease in the ADASI score for the vehicle-treated lesion compared with the crisaborole-treated lesion. Statistically significant differences favoring crisaborole treatment were observed at day 14 (secondary outcome), day 28 (primary outcome) and day 42 (secondary outcome) (Figure 4) [83]. Overall, more crisaborole-treated patients experienced early and sustained improvement in lesion-specific disease severity, indicating a promising efficacy profile for crisaborole.

Study 203 was a Phase II multicenter, open-label, 29-day safety study that enrolled patients aged 12–17 years who had AD involving 10 to 35% of the treatable BSA [84]. The proportion of patients who achieved various ISGA thresholds throughout the study is summarized in Figure 5 (secondary outcome). At day 29, 8 of 23 patients (34.8%) achieved

treatment success (secondary outcome; ISGA score ≤ 1 and ≥ 2 -grade improvement from baseline).

Study 204 (NCT01602341) was a Phase II multicenter, randomized, double-blind, bilateral, dose-ranging study that included patients aged 12–17 years who had AD involving up to 35% of total BSA [85]. The study assessed the effects of Crisaborole Topical Ointment, 2% and 0.5%, administered once daily or twice daily. Mean ADASI scores improved over time during treatment with Crisaborole Topical Ointment, 2% (primary outcome), with a dose-related effect observed across the four treatment regimens. The greatest improvement from baseline was observed in lesions treated with Crisaborole Topical Ointment, 2%, applied twice daily (Figure 6). Similarly, the proportion of lesions with total or partial clearance (ADASI ≤ 2 ; secondary outcome) increased over time in a dose-related manner.

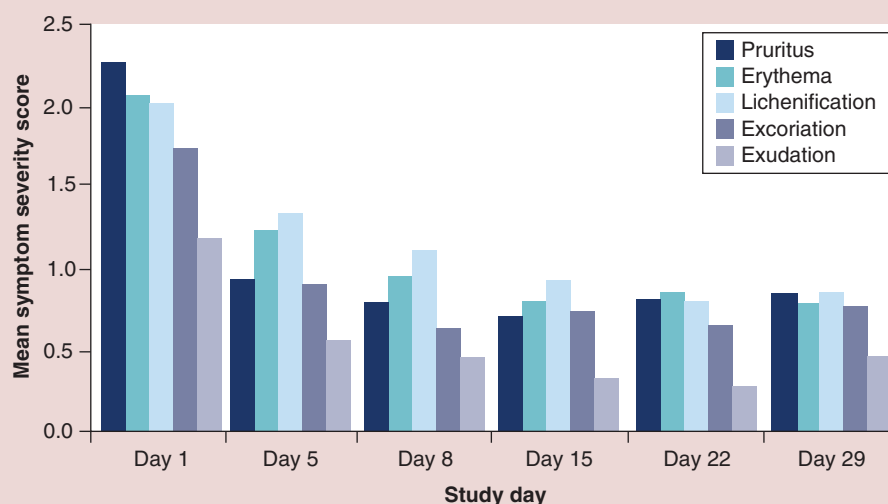


Figure 3. Study 102: Decrease in mean severity scores of signs and symptoms of atopic dermatitis (Atopic Dermatitis Severity Index [ADSI] components) at days 1, 5, 8, 15, 22 and 29.

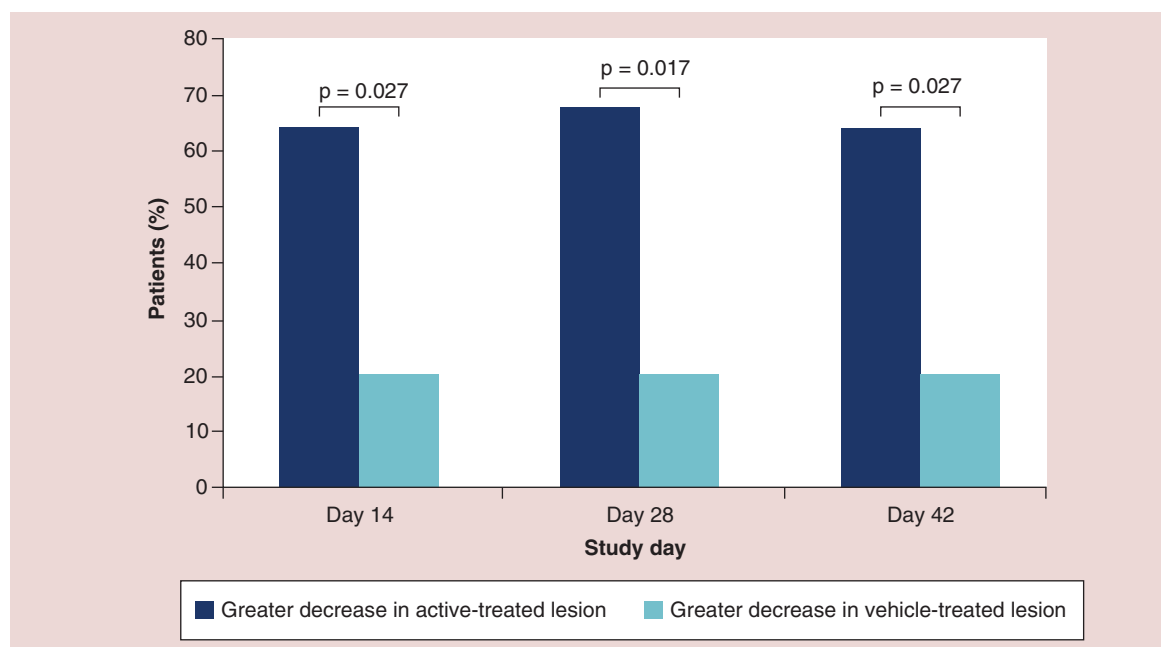


Figure 4. Study 202: Proportion of patients with a greater Atopic Dermatitis Severity Index (ADSI) score decrease from baseline for lesions treated with Crisaborole Topical Ointment, 2%, versus vehicle at days 14, 28 and 42.

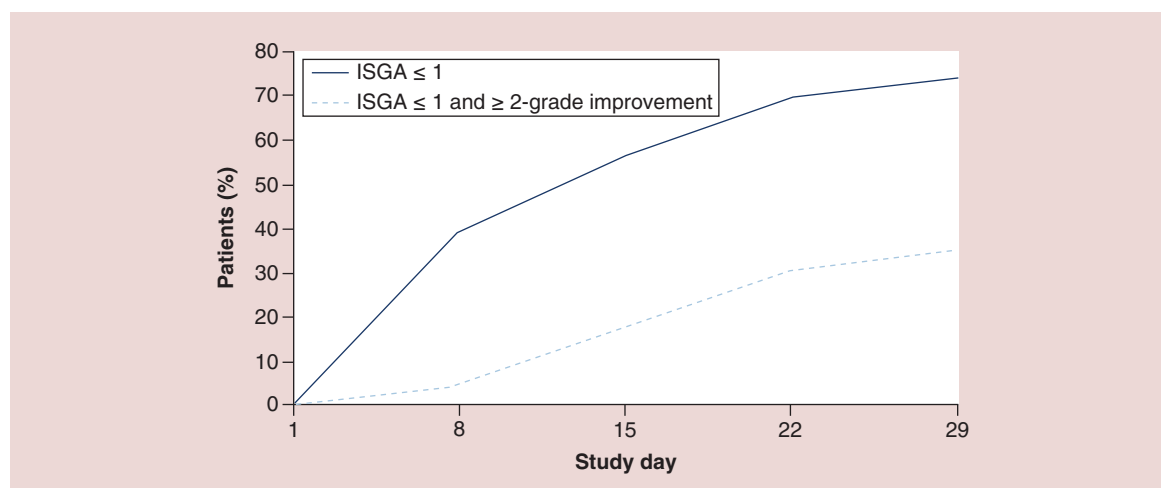


Figure 5. Study 203: Proportion of patients who achieved Investigator's Static Global Assessment (ISGA) thresholds during treatment with Crisaborole Topical Ointment, 2%.

A pooled analysis of Studies 102/203 and 202/204 revealed a significant reduction in the severity of pruritus, which was assessed as a secondary measure using a 4-point scale (0 [none] to 3 [severe]) [87]. The analysis of Studies 102 and 203 (whole-body assessments) revealed that 77.2% of patients had moderate to severe pruritus at baseline. By day 8 (first assessment) of treatment with Crisaborole Topical Ointment, 2%, this number decreased to 8.8% (Figure 7A). Similarly, an analysis of Studies 202 and 204 (bilateral target lesion assessments) demonstrated a reduc-

tion in the proportion of patients with moderate to severe pruritus from 85.1% at baseline to 9.5% by day 8 (Figure 7B). Weekly assessment demonstrated these improvements continued throughout the treatment period.

Future perspective: ongoing development

Potential areas for future research include analysis in patients 3 months to <2 years of age, after a favorable efficacy and safety profile is demonstrated in the older patient population. Two large Phase III clinical trials

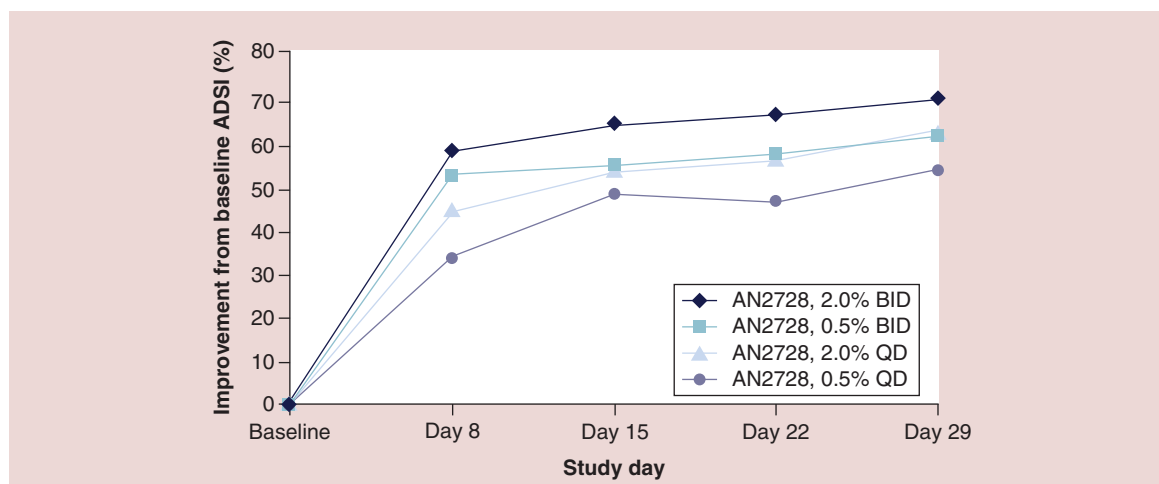


Figure 6. Study 204: Changes from baseline in the ADSI score at days 1, 8, 15, 22 and 29.

ADSI: Atopic Dermatitis Severity Index; BID: twice daily; QD: once daily.

of identical design have been conducted to evaluate the efficacy and safety of Crisaborole Topical Ointment, 2%, in patients as young as 2 years of age with mild to moderate AD (NCT02118766, NCT02118792). Efficacy end points analyzed improvement in global disease severity (primary end point), time to improvement in disease severity, change in severity of signs of AD (secondary end points) and time to improvement in pruritus (additional efficacy end points). Participants in these Phase III studies were eligible to enter an open-label, long-term safety extension trial. Data are being compiled for the two pivotal Phase III trials and the open-label extension trial, all of which have been completed.

Conclusion

AD is a complex chronic inflammatory skin disorder that occurs largely in children and primarily presents as mild to moderate disease [1–4]. The distressing itch and other symptoms of AD impose a significant burden on patients and their parents [5,9–12]. Pruritus-induced scratching can further damage the skin and promote secondary infection, exacerbating symptoms, worsening disease severity and further diminishing patients' QoL [3,16–18].

In patients with AD, skin barrier disruption, combined with immune dysregulation, results in the production of inflammatory cytokines, causing AD exacerbations and pruritus [12,30]. PDE4 is overactive in AD skin, resulting in depressed intracellular cAMP levels, which leads to the production of inflammatory cytokines provoking AD exacerbations [12,31,33–36].

Topical therapies for AD have changed very little over the past 15 years, relying heavily on TCS and TCI [66]. These broadly acting therapeutic categories require healthcare providers to weigh the need

for symptomatic relief against safety concerns [14]. Furthermore, TCS and TCI have restrictions in terms of appropriate treatment areas and duration of use [19,20,64,67]. Given the limitation of these agents, there remains a need for a topical nonsteroidal, anti-inflammatory agent that safely minimizes the symptoms and severity of AD and can be used for acute and maintenance therapy.

Boron chemistry enabled the synthesis of crisaborole, a low-molecular-weight, selective, topical PDE4 inhibitor that effectively penetrates the skin [77–79]. Crisaborole acts by inhibiting PDE4 to reduce inflammation in AD [35,78–80]. Furthermore, the unique topical formulation of crisaborole allows for targeted inhibition at the site of inflammation and rapid metabolism, thus avoiding systemic exposure and potential off-target side effects such as gastrointestinal side effects (nausea and diarrhea) often associated with oral PDE4 inhibitors [88,89].

Results from four Phase I and Phase II studies show that Crisaborole Topical Ointment, 2%, appears to be well tolerated, with limited systemic exposure, including under maximal-use conditions. These findings may support favorable safety and tolerability of crisaborole in adults, adolescents, and children as young as 2 years of age, as analyzed in Study 102. Additionally, treatment with crisaborole improved disease severity, pruritus intensity, and all other assessed AD signs and symptoms. These results suggest that crisaborole may target the underlying pathogenesis of disease in patients with AD. The efficacy and safety demonstrated by Crisaborole Topical Ointment, 2%, an investigational nonsteroidal, topical anti-inflammatory agent, indicates that the drug targets the underlying pathogenesis of AD to reduce the symptoms and severity of mild to moderate AD.

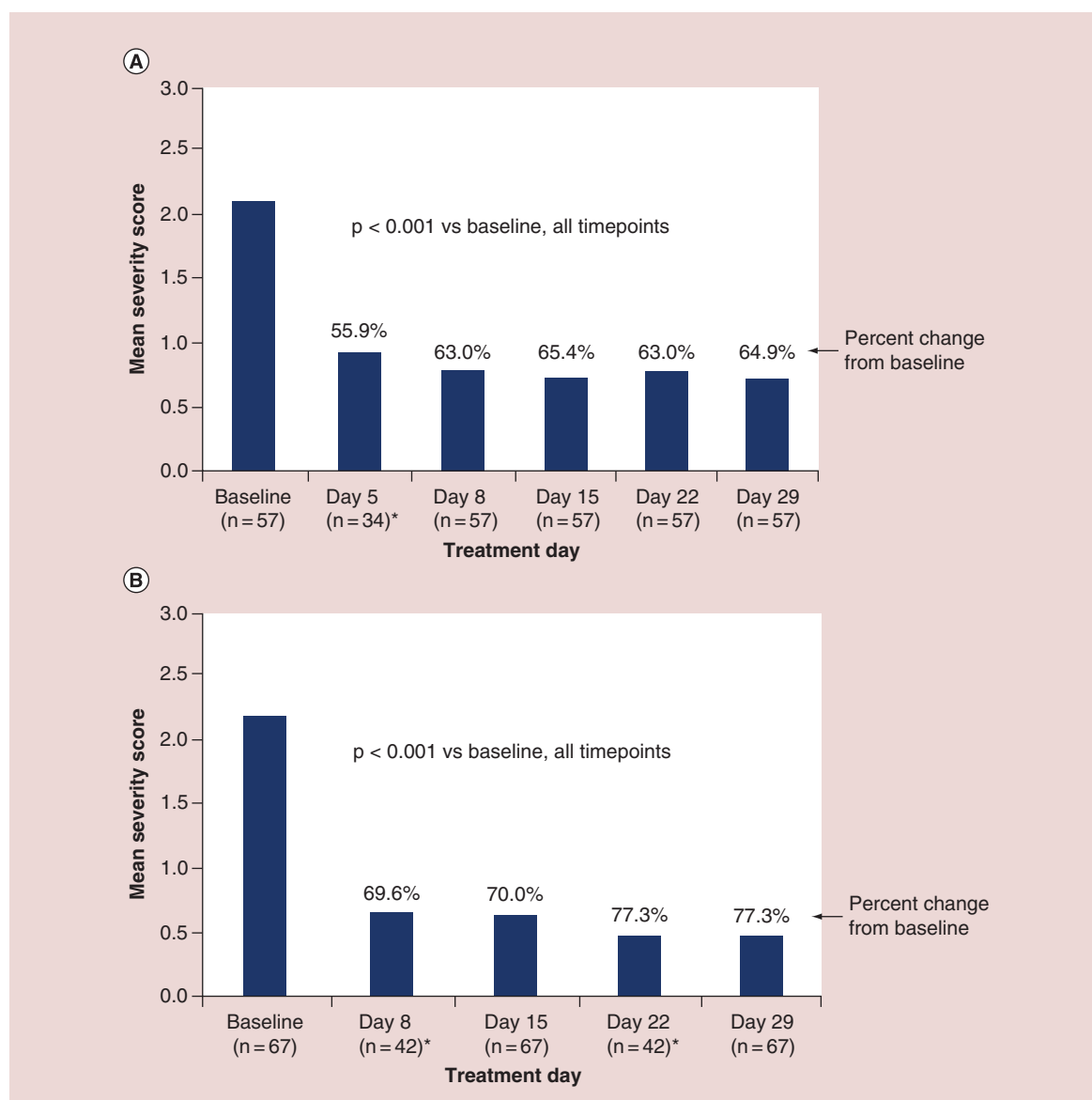


Figure 7. Reduction in pruritus severity scores in children and adolescents treated with Crisaborole Topical Ointment, 2%. These data are from a pooled analysis of whole-body assessments from (A) studies 102 (Phase Ib) and 203 (Phase II) and (B) target lesion assessment from studies 202 and 204 (both Phase II). *Day 5 scores were available from study 202 only.

Pruritus severity scale: 0 = no itching; 1 = occasional, slight itching; 2 = constant or intermittent itching with no sleep disturbance; 3 = bothersome itching that disturbs sleep or normal activity.

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Executive summary

Etiology

- Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting infants, children and adults.
- Increased levels of phosphodiesterase 4 (PDE4) activity and subsequent increases in inflammation are seen in patients with active AD.

Burden of atopic dermatitis

- One of the major criteria for AD diagnosis, pruritus, is a key contributor to the reduced quality of life observed in patients with AD.
- Breaking the itch-scratch cycle is essential to improve disease control, prevent chronicity and scarring and improve patient quality of life.

Current topical treatment paradigms for atopic dermatitis

- Current pharmacologic treatments for atopic dermatitis have not changed over the past 15 years and consist of topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI).
- TCS and TCI are associated with use restrictions and safety concerns, therefore a targeted, safe and effective treatment is much needed.

Development of Crisaborole Topical Ointment, 2%, for atopic dermatitis

- Crisaborole is a small-molecule, boron-based, nonsteroidal anti-inflammatory PDE4 inhibitor.
- The physicochemical properties and low molecular weight of crisaborole make it suitable for topical formulation and allow it to penetrate the epidermis and dermis to reach the site of inflammation.
- Phase I and II clinical trials have been completed for Crisaborole Topical Ointment, 2%, as a monotherapy for the treatment of mild to moderate AD.
- Pharmacokinetic studies have demonstrated that crisaborole is rapidly absorbed and quickly metabolized to two identified inactive metabolites, reducing the risk of systemic exposure and unwanted systemic side effects.
- Across all four Phase I and II studies, the majority of treatment-emergent adverse events were mild to moderate, demonstrating a favorable safety profile for crisaborole.
- Crisaborole-treated patients demonstrated significant improvements in disease severity, as well as a significant reduction in pruritus.

Conclusion

- Crisaborole is a first-in class, nonsteroidal, topical anti-inflammatory, PDE inhibitor for the treatment of mild to moderate AD.
- Studies performed indicate a favorable efficacy and safety profile for crisaborole in children and adults with mild to moderate AD.
- Significant improvement in disease severity, pruritus intensity, and all other assessed signs and symptoms of AD indicate that crisaborole may target the underlying pathogenesis of the disease.

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