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ADIS DRUG EVALUATION

# Crisaborole Ointment 2%: A Review in Mild to Moderate Atopic Dermatitis

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**Abstract** Crisaborole ointment 2% (Eucrisa™) is a novel, anti-inflammatory inhibitor of phosphodiesterase 4 (PDE4) that is available in the USA for the topical treatment of mild to moderate atopic dermatitis in patients aged ≥ 2 years. In two short-term (28 days), identically designed, multicentre, phase III studies in this patient population, topical therapy with crisaborole ointment 2% reduced disease severity and pruritus severity compared with vehicle, with the effect established early and sustained over the course of treatment. Improvements in the other signs of atopic dermatitis (erythema, exudation, excoriation, induration/papulation, and lichenification) were also seen. Crisaborole ointment 2% was generally well tolerated in the short-term studies, with its favorable safety profile maintained over the longer term (up to 52 weeks) in a multicentre, extension study. Most treatment-emergent adverse events (TEAEs) were of mild to moderate severity and considered unrelated to the study medication. Moreover, the incidence of application-site pain following short- and longer-term topical therapy with crisaborole ointment 2% was low. In conclusion, crisaborole ointment 2% is an effective and generally well tolerated new topical option for the management of mild to moderate atopic dermatitis in patients aged ≥ 2 years, with the potential to effectively treat this patient population over the longer term without the safety concerns associated with other current topical anti-inflammatory agents.

**Crisaborole ointment 2%: clinical considerations in mild to moderate atopic dermatitis**

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| Inhibits pro-inflammatory and T-cell cytokine production by inhibiting PDE4 |
| Reduces disease severity and pruritus severity, with the effect established early and sustained over the course of treatment, in patients aged ≥ 2 years |
| Improves the other signs of atopic dermatitis (erythema, exudation, excoriation, induration/papulation, and lichenification) |
| Has a favorable short-term (28 days) and longer-term (up to 52 weeks) safety profile, with most TEAEs being of mild to moderate severity and considered to be unrelated to crisaborole ointment 2% |

## 1 Introduction

Atopic dermatitis is a chronic, pruritic, inflammatory skin disorder that commonly presents in children, but may also affect adults [1]. Most affected individuals achieve disease resolution by adulthood; however, 10 to 30% do not [2]. The estimated prevalence of atopic dermatitis in adults is 1–3% [2]. The presentation of atopic dermatitis varies with

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age and the course of the disease, but typically manifests as pruritus and eczematous lesions (which are associated with oozing, crusted, eroded vesicles or papules on erythematous plaques in the acute form; thick and excoriated plaques in the subacute form; and lichenified, slightly pigmented, excoriated plaques in the chronic form) [1, 3–5].

There are numerous approaches to the therapeutic management of atopic dermatitis (which focus on alleviating symptoms and avoiding triggers [6]) owing to its multifactorial pathogenesis [4]. Topical therapies (e.g. anti-inflammatory agents such as corticosteroids and calcineurin inhibitors) are the mainstay of treatment, although (as with any agent) there are limitations to their use [4, 5, 7], creating a need for other treatment options.

Among several pro-inflammatory molecules that have been identified as potential therapeutic targets for atopic dermatitis is phosphodiesterase 4 (PDE4) [8], which is the most prevalent PDE in keratinocytes and the cells of the immune and nervous systems [9]. PDEs hydrolyse cAMP [9]; in patients with atopic dermatitis, PDE activity is increased, intracellular cAMP levels are decreased and several cytokines, including Th2 [interleukin (IL)-4, IL-13, IL-31] and Th22 (IL-22) cytokines, are commonly overexpressed [8, 10]. Inhibiting PDE increases intracellular cAMP levels, thereby lowering the release of cytokine mediators of inflammation [8].

Crisaborole is a novel, anti-inflammatory PDE4 inhibitor [9, 11]. This narrative review discusses pharmacologic, therapeutic efficacy, and tolerability data relevant to the topical use of crisaborole ointment 2% (Eucrisa$^{TM}$) in patients with mild to moderate atopic dermatitis.

## 2 Pharmacodynamic Properties of Crisaborole Ointment 2%

Crisaborole is a boron-containing, small molecule (251.1 Da) inhibitor of PDE4 [12]. The low molecular weight of crisaborole permits effective skin penetration and target cell access, with the presence of the boron atom thought to contribute to the target-binding capacity and selectivity of crisaborole (as its replacement results in a loss of PDE4 enzyme and cytokine inhibitory activity) [8, 13]. Although the exact mechanism through which crisaborole exerts its therapeutic effect in atopic dermatitis is unclear, the inhibition of PDE4 by crisaborole results in increased intracellular cAMP levels and the subsequent inhibition of pro-inflammatory and T-cell cytokine production [12, 13]. Specifically, in human peripheral blood mononuclear cells, crisaborole inhibited (with a half-maximal inhibitory concentration of $\leq 5.3$ μmol/L) the production of tumor necrosis factor-α, interferon-γ, IL-2, IL-5, and IL-10 [11, 13].

Crisaborole ointment 2% (administered twice daily for 21 days) was well tolerated when applied to thin-skinned and sensitive areas (including the face/hairline, genitals, and extensor and intertriginous areas), with almost all (99%) tolerability assessments showing no signs/symptoms of irritation, according to a randomized, double-blind, vehicle-controlled, phase I study in 32 healthy volunteers [14].

Therapeutic doses of crisaborole ointment 2% are not expected to prolong corrected QT intervals to any clinically relevant extent [12].

## 3 Pharmacokinetic Properties of Crisaborole Ointment 2%

Crisaborole is systemically absorbed, but systemic exposure following topical administration is minimal, albeit rapid, and increases as the area of application [i.e. the affected body surface area (BSA)] increases [15]. In an open-label, multicentre, phase Ib study in patients aged 2–17 years with mild to moderate atopic dermatitis (enrolled $n = 34$; completed $n = 31$) who applied crisaborole ointment 2% (intended dose 3 mg/cm$^2$) twice daily for 28 days, mean maximum plasma concentration ($C_{max}$), median time to $C_{max}$ ($t_{max}$), and mean area under the concentration–time curve (AUC) from time 0 to 12 hours values on day 8 (assessed $n = 33$) were 127 ng/mL, 3 h, and 949 ng · h/mL, respectively. Of note, crisaborole does not demonstrate age-based pharmacokinetics, with $C_{max}$ and AUC from time 0 to 24 h values not significantly differing between patients aged 2–5, 6–11, and 12–17 years [15].

Following systemic uptake, crisaborole is rapidly and substantially metabolized into inactive metabolites, the major ones being AN7602 (which is formed via hydrolysis) and AN8323 (which is formed via oxidation) [median $t_{max}$ on day 8 of 3 and 3 h] [12, 15]. Steady-state plasma concentrations of crisaborole, AN7602, and AN8323 were reached by day 8 (mean accumulation factors of 1.9, 1.7, and 6.3, respectively) [12, 15]. In vitro, crisaborole is highly bound (97%) to human plasma proteins [12]. Systemically absorbed crisaborole is eliminated via renal excretion as metabolites [12].

Under the conditions of clinical use, crisaborole, AN7602 and AN8323 are not expected to induce cytochrome P450 (CYP) isoenzymes and crisaborole and AN7602 are not expected to inhibit CYP isoenzymes, according to in vitro studies [12]. AN8323 did not inhibit the activities of CYP2C19, 2D6, and 3A4, but was a moderate inhibitor of CYP2C8 and 2C9 and a weak inhibitor of CYP1A2 and 2B6. No drug interaction potential was demonstrated between crisaborole and warfarin (a CYP2C9 substrate) in a clinical study [12].

## 4 Therapeutic Efficacy of Crisaborole Ointment 2%

Two identically designed, randomized, double-blind, vehicle-controlled, multicentre, phase III studies evaluated the therapeutic efficacy of crisaborole ointment 2% in patients aged ≥ 2 years with mild to moderate atopic dermatitis (AD-301 and AD-302) [16]. Individual and pooled data (some of which are from abstracts plus oral presentations [17, 18]) from these studies are discussed [12, 16–19].

Patients with clinically diagnosed atopic dermatitis (according to Hanifin and Rajka criteria) of mild or moderate severity [defined as an Investigator's Static Global Assessment (ISGA) score of 2 or 3; scores range from 0 to 4] affecting ≥ 5% of their BSA were eligible for enrollment [16]. Patients were excluded if they had active skin infections or had used topical calcineurin inhibitors or topical corticosteroids within the previous 14 days, or biologic therapies or systemic corticosteroids within the previous 28 days. Stable (i.e. consistent use for ≥ 14 days prior to day 1) regimens of antihistamines, inhaled corticosteroids, and topical retinoids for non-atopic dermatitis lesion treatment were permitted, as were acceptable bland emollients (to manage the dry skin areas around, but not overlapping, the treatable atopic dermatitis-involved areas) [16].

Patients were instructed to apply a layer of crisaborole ointment 2% or vehicle (to cover each lesion) to all areas affected by atopic dermatitis at baseline and to newly identified lesions that appeared after day 1 (excluding the scalp) twice daily for 28 days [16]. Baseline demographics and disease severity did not significantly differ across the treatment groups or the studies [16]. At baseline, 86.3% of the total population of 1522 patients (from AD-301 and AD-302) were aged 2–17 years and 38.5 and 61.5% had an ISGA grade of mild or moderate (score of 2 or 3); the BSA affected ranged from 5 to 95% [12]. The primary efficacy endpoint was the proportion of patients at day 29 who achieved success [defined as an ISGA grade of clear (score of 0) or almost clear (score of 1) with a ≥ 2-grade improvement from baseline] [16]. The secondary efficacy endpoints (the proportion of patients with an ISGA grade of clear or almost clear at day 29 and the time to success) were assessed in a hierarchical manner (i.e. time to success was analysed only if the between-group difference in the proportion of patients with an ISGA grade of clear or almost clear at day 29 was statistically significant) [19]. Efficacy analyses were conducted in the intent-to-treat population [16].

Topical therapy with crisaborole ointment 2% was effective in improving disease severity and the signs and symptoms of mild to moderate atopic dermatitis in patients aged ≥ 2 years [16]. Success rates at day 29 were significantly higher with crisaborole ointment 2% than vehicle in AD-301, AD-302, and a pooled analysis of these studies (Table 1) [16, 17]. A treatment effect was observed as early as day 8 [with crisaborole ointment 2% associated with a significantly ($p < 0.001$) higher success rate at this timepoint (14.7 vs. 5.4%)] and sustained at all subsequent timepoints through to day 29 [day 15: 24.4 vs. 11.0% ($p < 0.001$); day 22: 29.8 vs. 15.9% ($p < 0.001$)], according to the pooled analysis [17].

Improvements in other ISGA-related endpoints were also seen. Compared with vehicle, crisaborole ointment 2% significantly increased the proportion of patients with an ISGA grade of clear or almost clear at day 29 in AD-301, AD-302 and the pooled analysis (Table 1) [16, 17]. Significant ($p < 0.001$) between-group differences in this endpoint were seen as early as day 8 and sustained at all subsequent timepoints through to day 29 (pooled analysis) [17]. Success occurred significantly ($p < 0.001$) earlier with crisaborole ointment 2% than vehicle in both studies (according to Kaplan-Meier curves) [19]. In addition, crisaborole ointment 2% was associated with a significantly ($p < 0.001$) higher mean change from baseline in ISGA score at day 8 (− 0.7 vs. − 0.4), day 15 (− 0.9 vs. − 0.5), day 22 (− 1.0 vs. − 0.6), and day 29 (− 1.1 vs. − 0.7) compared with vehicle (pooled analysis) [17].

Crisaborole ointment 2% reduced the signs and symptoms of atopic dermatitis, including pruritus, according to the pooled analysis of data from AD-301 and AD-302 (with all *p*-values considered descriptive) [16]. A significantly ($p < 0.01$) higher proportion of patients receiving crisaborole ointment 2% than vehicle demonstrated improvements from baseline to day 29 in erythema (59 vs. 40%), exudation (40 vs. 30%), excoriation (60 vs. 48%), induration/papulation (55 vs. 48%), and lichenification (52 vs. 41%). Improvement was defined as an atopic dermatitis grade of none (score of 0) or mild (score of 1) [scores range from 0 to 3] with a ≥ 1-grade improvement from baseline. Moreover, significant ($p < 0.005$) between-group differences favoring crisaborole ointment 2% over vehicle were seen in the changes from baseline to day 29 in the mean severity of erythema (− 41 vs. − 20%), exudation (− 65 vs. − 52%), excoriation (− 52 vs. − 34%), induration/papulation (− 37 vs. − 29%), and lichenification (− 42 vs. − 29%) [16].

An early and sustained improvement in pruritus was seen with crisaborole ointment 2% therapy (pooled analysis) [16]. Specifically, a significantly ($p < 0.005$) higher proportion of crisaborole ointment 2% recipients than vehicle recipients achieved improvements from baseline to day 8 (58 vs. 42%), day 15 (60 vs. 44%), day 22 (61 vs. 48%), and day 29 (63 vs. 53%) in pruritus. Improvement

**Table 1** Efficacy of crisaborole ointment 2% in patients aged ≥ 2 years with mild to moderate atopic dermatitis

| Study | Treatment | No. of pts | Success[a] (% of pts) | ISGA score of 0 or 1 (% of pts) |
|---|---|---|---|---|
| AD-301 | Crisaborole ointment 2% | 503 | 32.8* | 51.7** |
| | Vehicle | 256 | 25.4 | 40.6 |
| AD-302 | Crisaborole ointment 2% | 513 | 31.4*** | 48.5*** |
| | Vehicle | 250 | 18.0 | 29.7 |
| Pooled analysis[b] | Crisaborole ointment 2% | 1016 | 32.1*** | 50.0*** |
| | Vehicle | 506 | 21.8 | 35.2 |

Results at day 29 from two identically-designed, multicentre, phase III studies [16] and a pooled analysis of the studies [17]

*ISGA* Investigator's Static Global Assessment, *pts* patients

*$p = 0.038$, **$p = 0.005$, ***$p < 0.001$ vs. vehicle

[a] Defined as an ISGA grade of clear (score of 0) or almost clear (score of 1) with a ≥ 2-grade improvement from baseline; primary endpoint

[b] Abstract plus oral presentation data

was defined as a pruritus grade of none (score of 0) or mild (score of 1) [scores range from 0 to 3] with a ≥ 1-grade improvement from baseline. A treatment effect was observed earlier with crisaborole ointment 2% than vehicle (1.4 vs. 1.7 days; $p = 0.001$) [16]. Moreover, according to a post hoc subgroup analysis, beneficial effects with crisaborole ointment 2% versus vehicle on the proportion of patients achieving an early improvement in pruritus were demonstrated regardless of baseline disease severity [18]. Specifically, the proportion of patients achieving an improvement from baseline to day 6 in pruritus was significantly ($p < 0.001$) higher with crisaborole ointment 2% than vehicle regardless of whether the patients had mild (59.5% of 393 patients vs. 41.3% of 193 patients) or moderate (54.7% of 623 patients vs. 38.3% of 313 patients) atopic dermatitis. A significant between-group difference in this endpoint favoring crisaborole ointment 2% over vehicle was observed at day 2 in patients with mild (37.6 vs. 26.9%; $p = 0.02$), but not in those with moderate (32.3 vs. 27.6%), atopic dermatitis. Crisaborole ointment 2% was associated with a significantly ($p < 0.01$) higher mean percentage change from baseline to day 6 in pruritus severity both in patients with mild atopic dermatitis (−42.9 vs. −29.2%) and in those with moderate atopic dermatitis (−40.9 vs. −26.1%) [18].

## 5 Tolerability and Safety of Crisaborole Ointment 2%

### 5.1 Short-Term Tolerability and Safety

Twice-daily topical therapy with crisaborole ointment 2% demonstrated a favorable short-term safety profile in patients aged ≥ 2 years with mild to moderate atopic dermatitis participating in the two phase III studies (AD-301 and AD-302) discussed in Sect. 4. In a pooled analysis of these studies, therapy with crisaborole ointment 2% was well tolerated over 28 days, with ≥ 1 treatment-emergent adverse event (TEAE) reported in 29.3% of 1012 crisaborole ointment 2% recipients and 25.9% of 499 vehicle recipients [17]. Most TEAEs were of mild to moderate severity (94.3% of crisaborole ointment 2% recipients and 96.9% of vehicle recipients) and considered unrelated or unlikely to be related to treatment (78.6 and 84.2%) [16, 17].

The incidence of individual TEAEs was generally similar between the treatment groups [16]. Application-site pain (reported as burning or stinging) was the most frequently reported TEAE (incidence ≥ 2% of patients in either treatment group), occurring in a significantly higher proportion of crisaborole ointment 2% recipients than vehicle recipients (4.4 vs. 1.2%; $p = 0.001$) [16, 17]. Among patients with application-site pain, 76.7% reported it on the first day of treatment and 77.6% had a resolution within 1 day of onset [16]. No cutaneous adverse events (e.g. skin atrophy or telangiectasia) were seen in the crisaborole ointment 2% group. Of note, gastrointestinal adverse events (which have been seen with oral PDE4 inhibitor therapy) occurred in few (2.7%) crisaborole 2% ointment recipients (vs. 2.4% of vehicle recipients) and were not considered to be related to the study medication. Significantly fewer crisaborole ointment 2% recipients than vehicle recipients developed a staphylococcal skin infection (0.1 vs. 1.0%; $p = 0.017$) [16].

Treatment-related adverse events (TRAEs) were reported in 7.3 and 5.0% of patients receiving crisaborole ointment 2% or vehicle, with serious TRAEs occurring in 0 and < 1% of patients [17]. Application-site pain was the only TRAE reported in ≥ 1% of patients in either treatment group [16, 17] and made up the majority of TRAEs reported [16]. Serious TEAEs occurred in ≤ 1% of patients [17]. Overall, 1.2% of patients in each treatment group discontinued therapy because of adverse events [16].

### 5.2 Longer-Term Tolerability and Safety

Patients who completed AD-301 or AD-302 without experiencing a serious or crisaborole-related adverse event that precluded further treatment with crisaborole ointment 2% were eligible to enter a 48-week, open-label, multicentre, extension study (AD-303) [20]. In this study, patients ($n = 517$) were assessed for atopic dermatitis severity every 28 days and treated as needed (i.e. if the patient had an ISGA score of $\geq 2$) with crisaborole ointment 2% twice daily for 28 days. On average, patients underwent 6.2 on-treatment periods during the initial and extension studies. During the extension study, 68.5% of patients experienced $\geq 2$ consecutive on-treatment periods during weeks 1–12, and 74.3, 67.3 and 68.2% experienced $\geq 1$ on-treatment period during weeks 13–24, 25–36 and 37–48, respectively. A mean of approximately 133 g of crisaborole ointment 2% was applied per patient per month. At baseline of AD-303, 69.1 and 30.9% of patients had originally been treated (in AD-301 or AD-302) with crisaborole and vehicle [20].

The favorable safety profile of twice-daily crisaborole ointment 2% was maintained over the longer term (up to 52 weeks) [20]. Across the initial and extension studies, $\geq 1$ TEAE occurred in 65% of patients. Most TEAEs were mild (51.2%) or moderate (44.6%) in severity, did not differ among the treatment periods and were considered unrelated to treatment (93.1%). The most frequently reported TEAEs (occurring in $\geq 5\%$ of patients) were atopic dermatitis (11.2% of patients), upper respiratory tract infection (URTI) [10.3%], nasopharyngitis (7.7%), cough (6.8%), and pyrexia (5.6%). In patients aged 2–11 years ($n = 308$), 12–17 years ($n = 146$), and $\geq 18$ years ($n = 63$), respectively, atopic dermatitis occurred in 12.0, 11.0, and 7.9% of patients, URTI in 12.3, 8.2, and 4.8%, nasopharyngitis in 6.8, 10.3, and 6.3%, cough in 8.8, 4.1, and 3.2% and pyrexia in 8.8, 1.4, and 0% [20].

Across the initial and extension studies, TRAEs occurred in 10.3% of patients; most (85.9%) TRAEs were mild or moderate in severity [20]. Of note, the frequency of TRAEs during AD-303 did not increase over time. Atopic dermatitis (3.1%), application-site pain (2.3%), and application-site infection (1.2%) were the most frequently reported TRAEs during the initial and extension studies, with only half of the 12 application-site pain events occurring during the extension study. The median duration of atopic dermatitis, application-site pain, and application-site infection was 17.5, 5.0, and 12.0 days, respectively. Application-site pain TRAEs in 4 of 12 patients resolved within a day of onset, while most atopic dermatitis occurrences (90.0% of patients) and application-site infections (75.0%) resolved within one treatment period. Seven serious TEAEs occurred in the extension study, with none considered to be related to treatment. Overall, 1.7% of patients discontinued the extension study because of TEAEs [20].

No application-site cutaneous adverse reactions (e.g. atrophy or telangiectasia) [which have been seen with longer-term topical corticosteroid therapy] were seen in AD-303 [20]. Moreover, the incidence of gastrointestinal adverse events was low (with diarrhea and vomiting each occurring in $<2\%$ of patients in each of the four 12-week treatment periods). No safety signals were identified from vital signs or laboratory assessments, with the incidence of infection or neoplasm not increasing with longer-term therapy [20].

Rescue therapy (defined as a requirement for the concomitant, nonconcurrent use of low- to mid-potency topical corticosteroids or topical calcineurin inhibitors) was not required by most (77.8%) patients during the extension study [20]. Among those who did require rescue therapy (22.4, 26.0, and 12.7% of patients aged 2–11 years, 12–17 years, and $\geq 18$ years, respectively), most had it initiated because of mild or moderate atopic dermatitis (i.e. ISGA scores of 2 or 3), with an average of 150 treatment days preceding initiation. Patients received topical corticosteroid ($n = 155$) or topical calcineurin inhibitor ($n = 6$) rescue therapy for a mean of 21.4 and 24.2 days. Crisaborole ointment 2% therapy was restarted in most (79.1%) of the patients who received rescue therapy, with most (75.7%) remaining in the study until week 48 or study closure. The mean number of days before restarting crisaborole ointment 2% therapy was 14.4 days for patients who received topical corticosteroids and 25.7 days for those who received topical calcineurin inhibitors [20].

## 6 Dosage and Administration of Crisaborole Ointment 2%

Crisaborole ointment 2% (20 mg of crisaborole per gram of ointment) is approved in the USA for the topical treatment of mild to moderate atopic dermatitis in patients aged $\geq 2$ years [12]. A thin layer of crisaborole ointment 2% is to be applied twice daily to the affected areas. The efficacy and safety of crisaborole ointment 2% in patients aged $<2$ years have not been established [12].

The prescribing information should be consulted for detailed information regarding contraindications, use in special patient populations, and warnings and precautions.

## 7 Current Status of Crisaborole Ointment 2% in Mild to Moderate Atopic Dermatitis

Topical therapies form the cornerstone of treatment for atopic dermatitis and are used to restore skin barrier function (e.g. moisturizers) and control the inflammatory aspects of the disease (e.g. corticosteroids and calcineurin inhibitors) [4, 6]. Moisturizers are recommended as a first-

line therapy [5] for mild disease and as an adjuvant therapy for moderate to severe disease [4, 7], with topical corticosteroids indicated when moisturizers have failed [4, 5, 7]. Although effective, topical corticosteroid use is hampered by cutaneous adverse events and safety concerns associated with systemic absorption (the risks of which are affected by the surface area and thickness of the skin, the use of occlusive dressings, and the potency and duration of topical corticosteroid use) [4, 5, 7]. Topical calcineurin inhibitors (e.g. tacrolimus and pimecrolimus) are recommended as second-line anti-inflammatory therapy for the acute and intermittent chronic treatment of atopic dermatitis in patients who have not responded adequately to other topical therapies or when those therapies are not recommended [4, 7]. However, they are associated with transient localized burning and pruritus (particularly when applied to acutely inflamed skin [7]) and a theoretical risk of cutaneous viral infections, and have boxed warnings relating to potential carcinogenicity [4, 5, 7]. Until recently, no new topical therapies have been approved for the treatment of atopic dermatitis for over 15 years [4, 5, 7].

Crisaborole ointment 2% is a novel, topically administered anti-inflammatory agent; it inhibits pro-inflammatory and T-cell cytokine production by inhibiting PDE4 (Sect. 2). Although systemically absorbed, crisaborole is rapidly and substantially metabolized into inactive metabolites; its systemic exposure is minimal, but increases as the area of application increases (Sect. 3). Crisaborole does not demonstrate age-related pharmacokinetics in patients aged 2–17 years (Sect. 3).

In two identically designed, multicentre, phase III studies in patients aged $\geq 2$ years with mild to moderate atopic dermatitis, short-term (28 days) topical therapy with crisaborole ointment 2% was associated with an early and sustained reduction in disease severity and pruritus severity, and improvements in the other signs and symptoms of atopic dermatitis (Sect. 4). Relieving pruritus is crucial for the treatment of atopic dermatitis as disrupting the itch–scratch cycle can alleviate the signs of atopic dermatitis, improve quality of life, and reduce the risk of infections and scarring [16]. It is worth noting that the efficacy of crisaborole ointment 2% was demonstrated despite a considerable 'vehicle effect' (which is commonly observed in atopic dermatitis studies comparing active therapies with their emollient bases) [16].

Crisaborole ointment 2% was generally well tolerated in patients aged $\geq 2$ years with mild to moderate atopic dermatitis participating in the short-term (28 days) studies (Sect. 5.1), with its favorable safety profile maintained over the longer term (up to 52 weeks) [Sect. 5.2]. In both the initial and extension studies, most TEAEs were of mild to moderate severity and considered unrelated to the study medication, with few patients discontinuing treatment because of adverse events (Sect. 5). Moreover, no serious adverse events considered related to the study medication were reported. Application-site pain (i.e. burning and stinging) is a commonly reported adverse event with topical calcineurin inhibitors or topical corticosteroid therapy [21]. However, following short- and longer-term topical therapy with crisaborole ointment 2%, the incidence of application-site pain was low (Sect. 5). Moreover, the incidence of gastrointestinal adverse events (which have been seen with oral PDE4 inhibitor therapy) was low and no cutaneous adverse events were observed (Sect. 5). Rescue therapy was not required by over three-quarters of patients receiving longer-term (up to 52 weeks) therapy (Sect. 5.2). Among those who did require rescue therapy, most had it initiated because of atopic dermatitis (i.e. ISGA scores of 2 or 3) and restarted treatment with crisaborole ointment 2% (Sect. 5.2).

In conclusion, crisaborole ointment 2% is an effective and generally well tolerated new topical option for the management of mild to moderate atopic dermatitis in patients aged $\geq 2$ years, with the potential to effectively treat this patient population over the longer term without the safety concerns associated with other current topical anti-inflammatory agents.

| Data Selection Crisaborole: 96 records identified | |
|---|---|
| Duplicates removed | 27 |
| Excluded at initial screening (e.g. press releases; news reports; not relevant drug/indication) | 3 |
| Excluded during initial selection (e.g. preclinical study; reviews; case reports; not randomized trial) | 6 |
| Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials) | 39 |
| **Cited efficacy/tolerability articles** | 4 |
| **Cited articles not efficacy/tolerability** | 17 |
| Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Crisaborole, Eucrisa, AN-2728, PF-06930164, atopic, eczema. Records were limited to those in English language. Searches last updated 2 October 2017 | |

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**Compliance with Ethical Standards**

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**Conflict of interest** Sheridan Hoy is a salaried employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest.

Additional information about this Adis Drug Review can be found at http://www.medengine.com/Redeem/DA98F0600F347AE8.

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