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ORIGINAL RESEARCH ARTICLE

Once-Daily Crisaborole Ointment, 2%, as a Long-Term Maintenance Treatment in Patients Aged ≥ 3 Months with Mild-to-Moderate Atopic Dermatitis: A 52-Week Clinical Study

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Abstract

Background Topical treatments for atopic dermatitis (AD) used reactively often fail to achieve lasting disease control; many of these therapies are associated with safety concerns that limit long-term use. Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD that has potential as a long-term maintenance therapy.

Objective The aim was to evaluate the long-term efficacy and safety of crisaborole once daily (QD) compared to vehicle QD as a maintenance therapy to reduce the incidence of flares in patients with AD who previously responded to crisaborole twice daily (BID).

Methods CrisADe CONTROL was a randomized, double-blind, vehicle-controlled, 52-week, phase III study of patients aged ≥ 3 months with mild-to-moderate AD involving ≥ 5% treatable body surface area. Eligible patients received crisaborole BID during an open-label run-in period of up to 8 weeks. Responders were randomly assigned in the double-blind maintenance period to receive either crisaborole QD or vehicle QD. Responders were defined as patients who achieved Investigator's Static Global Assessment (ISGA) success (ISGA score of 0 [clear] or 1 [almost clear] with a ≥ 2-grade improvement) and ≥ 50% improvement in Eczema Area and Severity Index total score (EASI-50) from baseline. Patients who experienced a flare (ISGA score ≥ 2) during the double-blind maintenance period switched to crisaborole BID for up to 12 weeks. During this period, patients were assessed every 4 weeks; if the flare resolved (ISGA score ≤ 1), patients resumed their assigned treatment. The primary endpoint was flare-free maintenance until onset of the first flare. Key secondary endpoints were number of flare-free days, number of flares, and maintenance of pruritus response until onset of the first flare. The incidence of treatment-emergent adverse events was also analyzed.

Results Overall, 497 patients entered the open-label run-in period with crisaborole BID, of which 270 patients were randomized into the 52-week double-blind maintenance period of the study. Of the 270 patients, 135 were randomly assigned to the crisaborole QD group and 135 were randomly assigned to the vehicle QD group. Median time of flare-free maintenance was longer for patients who received crisaborole versus vehicle (111 vs 30 days, respectively; $p = 0.0034$). The mean number of flare-free days was higher for patients who received crisaborole versus vehicle (234.0 vs 199.4 days, respectively; $p = 0.0346$). The mean number of flares was lower for patients who received crisaborole versus vehicle (0.95 vs 1.36, respectively; $p = 0.0042$). No clear trend was observed in maintenance of pruritus response between crisaborole- and vehicle-treated patients. Crisaborole was well tolerated, with no new or unexpected safety findings when used as maintenance treatment.

Conclusions Crisaborole QD was effective and well tolerated for long-term maintenance treatment and flare reduction in adult and pediatric patients with mild-to-moderate AD.

Trial Registration ClinicalTrials.gov, NCT04040192, 31 July 2019.

Plain Language Summary

Atopic dermatitis (AD) is an immuno-inflammatory skin disease that can last a long time. It causes skin lesions and intense itching. Topical AD treatments used reactively often fail to control the disease over a long period of time. Many are associated

Extended author information available on the last page of the article

with safety concerns that limit long-term use. Crisaborole ointment is a nonsteroidal treatment for the skin and is used to treat mild-to-moderate AD. Previous studies showed that using crisaborole twice daily was effective and had few side effects in patients with mild-to-moderate AD. This study evaluated how effective and safe long-term treatment with once-daily crisaborole was compared with an ointment with no drug (vehicle). The study included patients aged ≥ 3 months with mild-to-moderate AD whose AD improved after previous treatment with twice-daily crisaborole. This study was designed to investigate how much crisaborole reduced the incidence of AD flares over 52 weeks in these patients.
The study included 270 patients whose AD had improved after treatment with twice-daily crisaborole. Of these patients, 135 were randomly assigned to receive crisaborole once a day and 135 to receive vehicle once a day. Patients who received crisaborole had a significantly longer time before experiencing AD flares than those who received vehicle. Crisaborole was well tolerated, and no new or unexpected side effects were found when used as a once-daily maintenance treatment for 52 weeks. These results indicate that once-daily treatment with crisaborole could be a potential long-term maintenance treatment option in children and adults with mild-to-moderate AD.

Key Points

Long-term maintenance treatment with once-daily crisaborole resulted in delayed onset of first flare, greater number of flare-free days, and decreased number of flares compared to vehicle in patients with mild-to-moderate atopic dermatitis who responded to crisaborole twice daily.

Crisaborole once daily was well tolerated when used as a long-term maintenance treatment.

1 Introduction

Atopic dermatitis (AD) is a chronic, relapsing, immunoinflammatory skin disorder characterized by eczematous, scaly skin lesions, intense pruritus, and a general deterioration in quality of life (QoL) [1–3]. Moreover, studies have suggested that AD has a negative effect on linear growth depending on the age at onset, extent, and duration of AD [4, 5]. AD has an estimated global prevalence of 230 million, affecting 15–30% and 2–10% of the pediatric and adult populations, respectively [3, 6]. The etiology of AD is complex and influenced by several factors, including genetics, environmental issues, skin barrier defects, altered skin microbiome, and the immune system. These factors affect the severity, frequency, timing, and intensity of flares [7, 8].

Topical treatments used for AD often fail to achieve lasting disease control. AD flares occur at variable and unpredictable intervals [9]. A web-based survey completed by adults diagnosed with AD indicated that 84% of the patients were either currently experiencing a flare or had experienced one in the last month [10]. Patients with moderate AD may experience approximately eight flares per year, each lasting approximately 14 days [9].

In addition to the basic management of AD, which includes skin care (the use of moisturizers, emollients, warm baths, and nonsoap cleansers) and the avoidance of triggers, proactive therapy to control residual disease and reduce AD relapses is proposed in treatment guidance documents and data rather than taking only a reactive approach when the condition flares [2, 11–13]. A proactive approach starts with an intensive topical anti-inflammatory therapy until all lesions have mostly cleared, followed by long-term, low-dose intermittent application of anti-inflammatory therapy [12–15]. Topical corticosteroids (TCSs) have limitations for long-term continuous use because of safety concerns, while topical calcineurin inhibitors (TCIs) have a boxed warning based on reporting of rare cases of lymphoma, although a causal relationship has not been established [15–18].

Long-term TCS use is restricted to avoid local cutaneous atrophy, striae rubrae, telangiectasia, skin burning, tachyphylaxis, erythema, and acneiform/rosacea-like eruptions. In addition, high- and very-high-potency TCS agents can potentially result in further systemic side effects [15, 19].

TCIs are approved for short-term and noncontinuous chronic treatment in recalcitrant AD and use in sensitive skin areas [15, 16]. According to the European Medicines Agency and the most recent position paper on the treatment of AD by the European Task Force on Atopic Dermatitis of the European Academy of Dermatology and Venereology, tacrolimus is approved for the maintenance treatment of moderate-to-severe AD for the prevention of flares and the prolongation of flare-free intervals in patients experiencing frequent disease exacerbations [12, 20]. Moreover, in some countries, the use of TCIs has been approved for use in patients aged ≥ 2 years, while in other countries, their use has been approved for patients aged > 3 months [21]. TCIs are associated with burning/stinging upon application, and patient education is required due to a boxed warning for an increased risk of lymphoma [15].

Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 (PDE4) inhibitor that has been approved for the treatment of mild-to-moderate AD in adult and pediatric

patients aged ≥ 2 years in 2016 and pediatric patients aged ≥ 3 months since 2020 in multiple countries [22–24]. It has a favorable safety profile, with no limitations on duration of use and can be used on sensitive skin areas [2].

In a 48-week, phase III, long-term safety extension study of patients aged ≥ 2 years with mild-to-moderate AD, treatment with crisaborole twice daily (BID) showed a low frequency of treatment-related adverse events (TRAEs) [25]. Crisaborole therefore also represents a potential long-term maintenance treatment option for AD. Here, we report results of CrisADe CONTROL (NCT04040192), a phase III clinical study conducted to investigate the use of crisaborole once-daily (QD) regimen as a long-term maintenance therapy in patients aged ≥ 3 months with mild-to-moderate AD who were previously responsive to crisaborole BID.

2 Methods

2.1 Study Design

CrisADe CONTROL was a randomized, double-blind, vehicle-controlled, 52-week, phase III clinical study that included patients aged ≥ 3 months with mild-to-moderate AD involving a percentage of treatable body surface area (%BSA) of ≥ 5. An initial screening period (up to 4 weeks) was used to screen potential patients, ensuring compliance with the predetermined inclusion criteria and the absence of any exclusion criteria. Eligible patients were enrolled to receive crisaborole BID in the open-label run-in period up to a maximum of 8 weeks in duration (with follow-up visits every 2 weeks) for responder qualification. A responder was defined as a patient who achieved both Investigator's Static Global Assessment (ISGA) success (ISGA score of 0 [clear] or 1 [almost clear] with a ≥ 2-grade improvement from the run-in baseline) and ≥ 50% improvement in the Eczema Area and Severity Index score (EASI-50).

Patients who responded to treatment (crisaborole BID) at any time point during the run-in period were randomly assigned to the double-blind maintenance period in a 1:1 ratio to receive crisaborole QD or vehicle QD for 52 weeks. Nonresponders at the end of the run-in period were discontinued from the study. After randomization, the follow-up visits were conducted every 4 weeks during the 52-week double-blind maintenance period for efficacy and safety assessments. If a flare (defined per protocol) or an adverse event (AE) was suspected at times outside of the planned follow-up visits, an unscheduled study visit was conducted. Any incidence of flare outside of the study visits was reported by patients or caregivers by means of an electronic diary or direct reporting by the patients. If the patient met the criteria for experiencing a flare (ISGA ≥ 2), the patient was switched to enter a flare treatment period (a nested period within the 52-week double-blind maintenance period), during which time the patient received open-label crisaborole BID for up to 12 weeks per flare (a maximum of three consecutive 4-week treatment courses). During the flare treatment periods, patients were assessed every 4 weeks; this replaced maintenance visits. Resolution of flare was defined as ISGA ≤ 1. If the flare resolved after 4, 8, or 12 weeks of flare treatment, the patient was switched back to their original assigned blinded maintenance QD treatment and returned to the maintenance visit schedule. Flare treatment had a fixed duration of either 4, 8, or 12 weeks. If the flare did not resolve after 12 weeks of crisaborole BID treatment, the patient was withdrawn from the study. A post-treatment follow-up assessment by phone call 4 weeks after the last study dose (end of treatment [EOT]) was conducted for all patients. Once this assessment had concluded, it marked the end of study (EOS). The total duration of the study was up to 68 weeks, including up to 4 weeks for screening, an open-label run-in period of up to 8 weeks, a 52-week double-blind maintenance period, and a 4-week post-treatment follow-up period (Fig. 1).

2.2 Patients and Treatment

All patients were aged ≥ 3 months at the time of informed consent/assent and had a confirmed clinical diagnosis of AD per Hanifin and Rajka criteria [26]. Patients had mild-to-moderate AD defined as ISGA grade 2 (mild) or 3 (moderate), with a treatable %BSA of ≥ 5 (excluding the scalp) at entry into the run-in period. All patients had a history of prior treatments such as emollients, antihistamines, TCSs, or TCIs.

Patients with clinically significant medical conditions, patients using any prohibited medications as per the study protocol without the minimum washout periods, and patients with unstable AD, a known lack of efficacy to crisaborole, or a prior history of use of biologic therapy were excluded from this study.

During the open-label run-in period, patients or their caregivers were instructed to apply an even layer of crisaborole ointment covering all treatable AD lesions (excluding the scalp) BID, even when the skin became clinically clear. This included any newly identified AD lesions. Patients were permitted to use nonmedicated emollients during the study to manage dry skin if it was not used on the treatable AD lesion areas within 60 min before and after dosing with the study ointment.

For each patient, the treatable skin areas were the most commonly affected skin areas identified at randomization and reviewed after 6 months. During the maintenance period, the patients were instructed to continue to apply the study ointment to the most commonly affected skin areas even if they appeared normal. Crisaborole, or vehicle

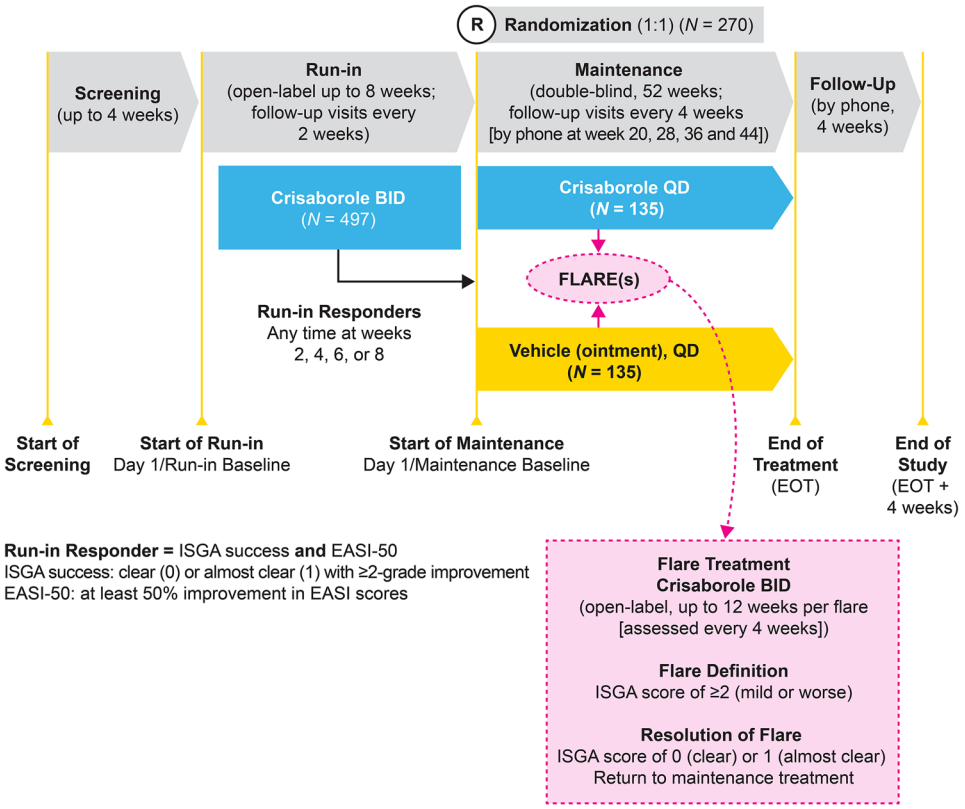

Fig. 1 CrisADe CONTROL study design. *BID* twice daily, *EASI* Eczema Area and Severity Index, *EASI-50* 50% improvement on the Eczema Area and Severity Index, *EOT* end of treatment, *ISGA* Investigator's Static Global Assessment, *QD* once daily

(matching ointment), QD was applied during the 52-week, double-blind maintenance period. Crisaborole was applied BID during all flares occurring within the maintenance period.

2.3 Endpoints and Assessments

2.3.1 Efficacy Endpoints

Efficacy assessments during the 52-week double-blind maintenance treatment period of the study were performed during scheduled in-clinic visits every 4 or 8 weeks (by phone at week 20, 28, 36, and 44) (Fig. 1).

The primary endpoint was flare-free maintenance until onset of first flare during the 52-week double-blind maintenance treatment period. Key secondary endpoints included the number of flare-free days, the number of flares, and the maintenance of pruritus response until the onset of first flare during the 52-week double-blind maintenance treatment period.

Maintenance of pruritus response (defined as the maintenance of a ≥ 50% improvement from baseline obtained at randomization) until the onset of first flare was assessed by three different age-appropriate scales, including the Peak Pruritus Numerical Rating Scale (an 11-point scale in which 0 indicates "no itch" and 10 indicates "worst itch imaginable"; used with permission from Regeneron Pharmaceuticals, Inc., and Sanofi) completed by patients aged ≥ 12 years [27], the Patient-Reported Itch Severity 5-point scale completed by patients aged 6–11 years, and the Observer-Reported Itch Severity 11-point scale completed by the caregivers of patients for patients aged 3 months to 5 years. These were performed electronically on a provisioned device.

2.3.2 Safety Endpoints

Safety was assessed using rates of treatment-emergent adverse events (TEAEs). TEAEs were defined as AEs with an onset on or after the day of the first dose. TEAEs were classified as treatment related if they were determined by the study investigator to be related to the study medication. AEs were defined as any untoward medical occurrence in a study patient regardless of whether these were considered related to the study medication.

Data on AEs were elicited and collected for the entire study period from the time of informed consent/assent until the EOS. Predose AEs, which occurred prior to the initiation of the study medication after informed consent/assent, were assessed as medical history. On-treatment AEs were assessed as TEAEs. Reporting of AEs included the assessments of the severity of AEs for serious adverse events (SAEs), assessments of clinically significant changes in vital signs, physical examinations, clinical investigational

findings, and laboratory findings. AEs were recorded and classified using the Medical Dictionary for Regulatory Activities (MedDRA v24.1) terminology.

2.4 Statistical Analysis

The familywise type I error rate for testing the primary and key secondary endpoints was controlled at 5% using a sequential step-down closed testing procedure and the Bonferroni method. The order of testing was as follows:

1. Flare-free maintenance up until the onset of the first flare during the maintenance period.
2. Number of flare-free days over 52 weeks.
3. Number of flares over 52 weeks.
4. Maintenance of pruritus response up until the onset of first flare.

Flare-free maintenance (primary endpoint) and maintenance of pruritus response (key secondary endpoint) were analyzed using a log-rank test, stratified by age group (aged 3 months to < 12 years or ≥ 12 years), duration of the BID treatment in the open-label period (≤ 4 weeks or > 4 weeks), and ISGA score (0 [clear] or 1 [almost clear]) at randomization.

Other key secondary endpoints were analyzed using an analysis of covariance model (number of flare-free days) or Wilcoxon rank sum test (number of flares) accounting for age group (aged 3 months to < 12 years or ≥ 12 years), duration of the BID treatment in the open-label period (≤ 4 weeks or > 4 weeks), and ISGA score (0 [clear] or 1 [almost clear]) at randomization.

For the primary endpoint (flare-free maintenance until onset of first flare during the 52-week double-blinded period), and the key secondary endpoints (number of flare-free days and number of flares) during the 52-week double-blinded period, the significance level was defined as $p = 0.05$. Statistical significance could only be claimed for a given endpoint if the prior endpoint was significant in the order of testing as stated.

For the key secondary endpoint, maintenance of pruritus response until onset of first flare during the 52-week double-blind period, the Bonferroni method was used to adjust the significance level. The significance level was defined as $p = 0.01$ for each pruritus subgroup. Only the subgroup(s) with a p value of ≤ 0.01 could claim significance after the primary endpoint and other two secondary endpoints were found to be statistically significant. The five subgroups were as follows:

1. ≥ 12 years of age: ≥ 3 points reduction for responders
2. ≥ 12 years of age: ≥ 4 points reduction for responders
3. 6–11 years of age: ≥ 2 points reduction for responders
4. 3 months to 5 years of age: ≥ 3 points reduction for responders
5. 3 months to 5 years of age: ≥ 4 points reduction for responders

2.5 Ethical Approval

The final protocol, any amendments, and informed consent/assent documentation were reviewed and approved by the institutional review boards or institutional ethics committees at each of the investigational centers participating in the study. All patients or parent(s)/guardian(s) provided written informed consent, including age-appropriate assent, for participation in the study. This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines.

3 Results

3.1 Baseline Characteristics

Overall, 497 patients entered the open-label run-in period, of which 270 patients were enrolled into the 52-week double-blind maintenance period. Of 270 patients, 135 were randomly assigned to the crisaborole group and 135 were randomly assigned to the vehicle group (Fig. 1). Sixteen patients were randomly assigned but excluded from the efficacy analysis because they did not meet responder criteria (ISGA success and EASI-50) at randomization. This included ten patients in the crisaborole-treated group and six patients in the vehicle-treated group. All other patients who were randomly assigned were included in the efficacy analysis. The 270 patients who entered the double-blind maintenance period were included in the double-blind period safety analysis. Demographic and baseline characteristics between the two randomized groups were balanced and are shown in Table 1.

The study population comprised mostly pediatric patients aged < 18 years. In the vehicle-treated group, 57 patients (42.2%) and 23 patients (17%) were aged 2 to < 12 years and 12 to < 18 years, respectively. In the crisaborole-treated group, 46 patients (34.1%) and 32 patients (23.7%) were aged 2 to < 12 years and 12 to < 18 years, respectively. The mean (SD) duration of disease of all patients was 10.3 years (10.2) and 9.0 years (9.7) for the crisaborole- and vehicle-treated groups, respectively.

The crisaborole-treated group comprised 55 White patients (40.7%), 42 Black patients (31.1%), and 28 Asian patients (20.7%). The vehicle-treated group comprised

Table 1 Patient demographic and baseline disease characteristics

	Treated in OL period $N = 497$	Randomly assigned to DB period $N = 270$	Vehicle QD $N = 135$	Crisaborole QD $N = 135$
Age, *n* (%)				
3 to < 24 months	20 (4.0)	8 (3.0)	4 (3.0)	4 (3.0)
2 to < 12 years	202 (40.6)	103 (38.1)	57 (42.2)	46 (34.1)
12 to < 18 years	105 (21.1)	55 (20.4)	23 (17.0)	32 (23.7)
≥ 18 years	170 (34.2)	104 (38.5)	51 (37.8)	53 (39.3)
Age, mean (SD), years	19.9 (18.4)	22.2 (20.2)	21.8 (20.4)	22.6 (20.2)
Female, *n* (%)	283 (56.9)	147 (54.4)	76 (56.3)	71 (52.6)
Race,[a] *n* (%)				
White	204 (41.0)	109 (40.4)	54 (40.0)	55 (40.7)
Black	161 (32.4)	89 (33.0)	47 (34.8)	42 (31.1)
Asian	101 (20.3)	55 (20.4)	27 (20.0)	28 (20.7)
Other[b]	31 (6.2)	17 (6.3)	7 (5.2)	10 (7.4)
Duration of disease, mean (SD), years	9.6 (9.9)	9.6 (10.0)	9.0 (9.7)	10.3 (10.2)
ISGA score,[c] *n* (%)				
0 (clear)	0	104 (38.5)	56 (41.5)	48 (35.6)
1 (almost clear)	0	162 (60.0)	78 (57.8)	84 (62.2)
2 (mild)[d]	167 (33.6)	1 (0.4)	0	1 (0.7)
3 (moderate)[d]	329 (66.2)	3 (1.1)	1 (0.7)	2 (1.5)
4 (severe)[e]	1 (0.2)	0	0	0
EASI,[c] mean (SD)	10.30 (7.43)	1.67 (2.22)	1.53 (2.10)	1.81 (2.33)
%BSA,[c] mean (SD)	19.61 (16.81)	5.46 (8.81)	5.18 (9.38)	5.73 (8.23)
Most commonly affected AD %BSA, *n*		269	134	135
Mean (SD)		12.41 (12.25)	13.93 (13.81)	10.91 (10.3)
PP-NRS score,[c,f] *n*	247	155	73	82
Mean (SD)	4.79 (2.66)	2.09 (1.70)	2.01 (1.59)	2.15 (1.80)
PRIS score,[c,g] *n*	98	44	23	21
Mean (SD)	3.13 (1.15)	2.10 (0.80)	2.09 (0.82)	2.11 (0.80)
ORIS score,[c,h] *n*	105	64	36	28
Mean (SD)	5.87 (2.29)	2.66 (1.86)	2.49 (1.86)	2.88 (1.87)

AD atopic dermatitis, *BSA* body surface area, *DB* double blind, *EASI* Eczema Area Severity Index, *ISGA* Investigator's Static Global Assessment, *OL* open label, *ORIS* Observer Reported Itch Severity scale, *PP-NRS* Peak Pruritus Numerical Rating Scale, *PRIS* Patient Reported Itch Severity scale, *QD* once daily

[a]Data were obtained from the patients directly and/or hospital records

[b]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and other or not reported

[c]OL run-in baseline for all treated participants and DB randomization baseline for all randomly assigned participants

[d]Protocol deviation for the DB period

[e]Protocol deviation for the OL period

[f]For patients aged ≥ 12 years

[g]For patients aged 6 to < 12 years

[h]For patients aged 3 months to < 6 years

54 White patients (40%), 47 Black patients (34.8%), and 27 Asian patients (20.0%).

The mean %BSA at randomization was similar between the groups. In the crisaborole group, 48 patients (35.6%) had ISGA scores of 0 (clear) and 84 patients (62.2%) had ISGA scores of 1 (almost clear). In the vehicle-treated group, 56 patients (41.5%) had ISGA scores of 0 (clear) and 78 patients (57.8%) had ISGA scores of 1 (almost clear). The mean EASI, Peak Pruritus Numerical Rating Scale, Patient-Reported Itch Severity, and Observer-Reported Itch Severity scores were similar for the crisaborole- and vehicle-treated groups (Table 1).

During the 52-week double-blind maintenance period of the study, ~ 40% of the patients discontinued treatment. The most common reason for discontinuation was lack of efficacy (18 patients [13.3%] in the crisaborole-treated group and 23 patients [17.0%] in the vehicle-treated group). Discontinuation due to TEAEs was minimal in both groups. Overall, there was one patient (0.7%) in the crisaborole-treated group and three patients (2.2%) in the vehicle-treated group who discontinued because of a TEAE. During the 52-week double-blind maintenance period of the study, 11 (8.1%) of the crisaborole-treated patients and six (4.4%) of the vehicle-treated patients were lost to follow-up (Fig. 2).

3.2 Efficacy Endpoints

The median Kaplan-Meier estimate of flare-free maintenance was significantly longer with crisaborole versus vehicle (111 days, 95% confidence interval [CI] 56–224, vs 30 days, 95% CI 28–56, respectively; $p = 0.0034$ [Fig. 3]). Crisaborole-treated patients showed a longer duration of flare-free maintenance versus patients treated with vehicle when the analysis was stratified by age group, race (except the group categorized as "other"), ethnicity, ISGA score at

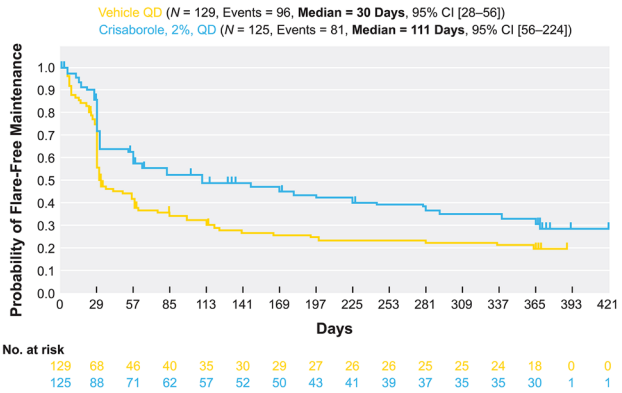

Fig. 3 Flare-free maintenance until onset of the first flare during the double-blind period. *CI* confidence interval, *QD* once daily

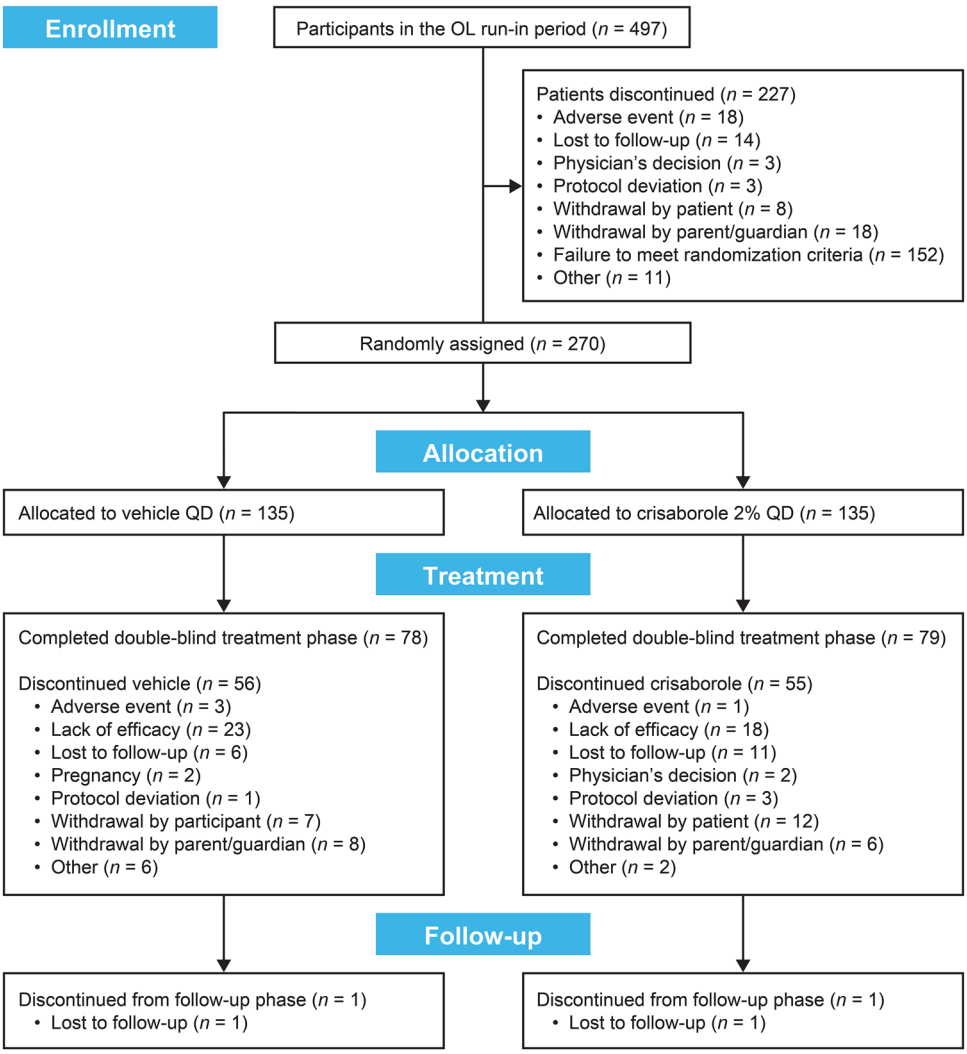

Fig. 2 Patient disposition of the CONTROL study. *OL* open label, *QD* once daily

Table 2 Flare-free maintenance subgroup analyses

	Vehicle QD		Crisaborole QD	
	Patients who experienced a flare *n* (%)	Median days (95% CI)	Patients who experienced a flare *n* (%)	Median days (95% CI)
Study population	96/129 (74.4)	30 (28–56)	81/125 (64.8)	111 (56–224)
Subgroup analyses				
Age				
3 months to < 12 years	48/60 (80.0)	28 (28–56)	35/47 (74.5)	56 (30–224)
≥ 12 years	48/69 (69.6)	31 (28–84)	46/78 (59.0)	175 (79–364)
ISGA score at randomization				
0 (clear)	38/56 (67.9)	56 (28–194)	29/48 (60.4)	111 (56–NA)
1 (almost clear)	58/73 (79.5)	29 (28–35)	52/77 (67.5)	111 (30, 224)
Race				
White	41/50 (82.0)	28 (27–31)	39/49 (79.6)	56 (30–111)
Black	29/45 (64.4)	57 (29–280)	19/38 (50.0)	365 (33–NA)
Asian	21/27 (77.8)	29 (27–98)	18/28 (64.3)	230 (69–NA)
Other	5/7 (71.4)	84 (8–NA)	5/10 (50.0)	56 (14–NA)
Ethnicity				
Hispanic or Latino	5/9 (55.6)	198 (22–NA)	10/18 (55.6)	242 (28–NA)
Not Hispanic or Latino	86/115 (74.8)	29 (28–54)	66/101 (65.3)	111 (56–278)
Number of run-in weeks				
≤ 4 weeks	33/41 (80.5)	28 (28–54)	27/36 (75.0)	84 (30–287)
> 4 weeks	63/88 (71.6)	48 (28–75)	54/89 (60.7)	169 (56–280)

CI confidence interval, *ISGA* Investigator's Static Global Assessment, *NA* not available, *QD* once daily

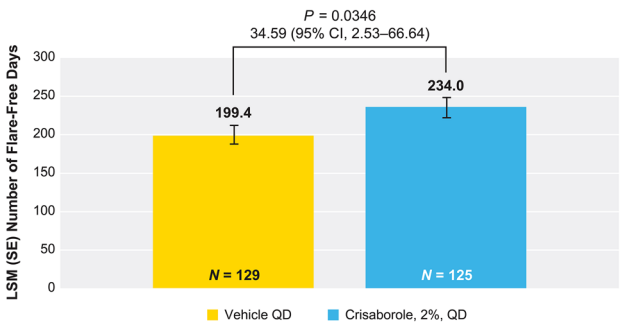

Fig. 4 Number of flare-free days during the double-blind maintenance period. *CI* confidence interval, *LSM* least squares mean, *QD* once daily, *SE* standard error

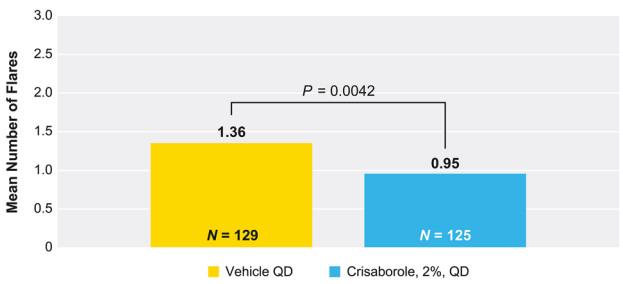

Fig. 5 Number of flares during the double-blind maintenance period. *QD* once daily

randomization, and duration of open-label run-in treatment (Table 2).

The mean number of flare-free days was significantly greater for patients treated with crisaborole versus vehicle (234.0 days vs 199.4 days, respectively; $p = 0.0346$), with a difference of 34.6 days (95% CI 2.53–66.64) (Fig. 4).

The mean number of flares was significantly lower for patients treated with crisaborole versus vehicle (0.95 vs 1.36, respectively; $p = 0.0042$) (Fig. 5). There was a greater proportion of patients having no flares in the crisaborole-treated group (44 [35.2%]) versus the vehicle-treated group (33 [25.6%]). The proportion of patients experiencing a single flare was greater in the crisaborole group (55 [44.0%]) versus the vehicle-treated group (51 [39.5%]). However, in the vehicle-treated group, a greater proportion of patients experienced two or more flares compared to the crisaborole-treated group.

No clear trend was observed in the maintenance of pruritus response until the onset of first flare between crisaborole- and vehicle-treated patients.

A diverse racial population was recruited for the CONTROL study, giving further insight into the efficacy profile of crisaborole in White, Black, and Asian patients. Favorable results were observed in the analysis of the primary efficacy endpoint in Black as well as Asian patients. The median number of days of flare-free maintenance until the onset of first flare during the 52-week double-blind period was higher among crisaborole- versus vehicle-treated Black patients (365 vs 57 days; $p = 0.09$) and Asian patients (230 vs 29 days; $p = 0.017$), respectively (Table 2).

3.3 Safety

During the open-label run-in period of the study, 109 patients (21.9%), all receiving crisaborole BID for up to 8 weeks, experienced 166 all-causality TEAEs. A total of 51 patients (10.3%) experienced 66 TRAEs. The most frequent TEAEs (all causality) were application site pain (5.6% for all TRAEs) and AD (2.4%; none were treatment related) (Table 3). Three patients experienced SAEs during this period; one SAE was considered treatment related (Tables 3, 4). This patient experienced AD with an application site infection. The event resolved; however, the patient was withdrawn from the study.

During the 52-week double-blind maintenance period of the study, 36 patients (26.7%) and 49 patients (36.3%) who received crisaborole QD and vehicle QD, respectively, experienced all-causality TEAEs. Overall, two patients (1.5%) and four patients (3.0%) reported TRAEs in the crisaborole and vehicle groups, respectively. In the crisaborole-treated group, one patient (0.7%) discontinued the study because of AEs, whereas three patients (2.2%) in the vehicle-treated group discontinued due to AEs. Two patients experienced SAEs in the crisaborole-treated group (one patient experienced congestive cardiac failure and one developed osteomyelitis). In the vehicle-treated group, three patients experienced SAEs. None of the SAEs were considered treatment related (Tables 3, 4).

During the 52-week double-blind maintenance period of the study, TEAEs of application site pain and AD did not occur in any of the crisaborole-treated patients. However, in vehicle-treated patients, application site pain and AD were present in two patients (1.5%) and three patients (2.2%), respectively. The only TEAEs that occurred in ≥ 2% of the crisaborole-treated patients during the 52-week double-blind maintenance period was upper respiratory tract infection (3%), influenza (2.2%), skin abrasion (2.2%), coronavirus disease 2019 (COVID-19)

Table 3 Safety summary

	OL, *n* (%)	DB maintenance, *n* (%)		Flare treatment period, *n* (%)
	Crisaborole BID *N* = 497	Vehicle QD *N* = 135	Crisaborole QD *N* = 135	Crisaborole BID *N* = 167
Patients who experienced ≥ 1 AE	109 (21.9)	49 (36.3)	36 (26.7)	37 (22.2)
Serious AEs	3 (0.6)	3 (2.2)	2 (1.5)	2 (1.2)
Severe AEs	6 (1.2)	1 (0.7)	2 (1.5)	1 (0.6)
AEs leading to study discontinuation or discontinuation of study drug[a,b]	30 (6.0)	3 (2.2)	1 (0.7)	3 (1.8)
AEs leading to dose reduction or temporary discontinuation due to AEs	3 (0.6)	1 (0.7)	1 (0.7)	1 (0.6)
AEs reported for ≥ 2% of patients in any group				
Application site pain	28 (5.6)	2 (1.5)	0	2 (1.2)
Dermatitis atopic	12 (2.4)	3 (2.2)	0	4 (2.4)
Upper respiratory tract infection	10 (2.0)	2 (1.5)	4 (3.0)	2 (1.2)
Application site infection	7 (1.4)	2 (1.5)	1 (0.7)	4 (2.4)
Nasopharyngitis	4 (0.8)	5 (3.7)	0	1 (0.6)
Influenza	4 (0.8)	1 (0.7)	3 (2.2)	0
Bronchitis	2 (0.4)	3 (2.2)	0	0
Skin abrasion	1 (0.2)	0	3 (2.2)	0
COVID-19	0	0	5 (3.7)	2 (1.2)
Headache	0	0	3 (2.2)	1 (0.6)

AE adverse event, *BID* twice daily, *COVID-19* coronavirus disease 2019, *DB* double blind, *OL* open label, *QD* once daily

[a]Patients who experienced an AE that caused the participant to be discontinued from the study

[b]Patients who experienced an AE for which the action taken was the withdrawal of the study treatment but for whom the AE did not result in discontinuation from the study

Table 4 Summary of treatment-related treatment-emergent adverse events

	OL	DB maintenance		Flare treatment period	DB total
	Crisaborole, 2%, BID *N* = 497	Vehicle QD *N* = 135	Crisaborole, 2%, QD *N* = 135	Crisaborole, 2%, BID *N* = 167	Total *N* = 270
Number of adverse events	66	6	2	3	11
Patients with adverse events, *n* (%)	51 (10.3)	4 (3.0)	2 (1.5)	3 (1.8)	9 (3.3)
Serious adverse events, *n* (%)	1 (0.2)	0	0	0	0
Severe adverse events, *n* (%)	4 (0.8)	1 (0.7)	0	0	1 (0.4)
Discontinued from study due to adverse events, *n* (%)	19 (3.8)	0	0	1 (0.6)	1 (0.4)
Dose reduction or temporary discontinuation due to adverse events, *n* (%)	2 (0.4)	0	0	0	0

BID twice daily, *DB* double blind, *OL* open label, *QD* once daily

(3.7%), and headache (2.2%) (Table 3). None were considered treatment related.

During the flare period (all received open-label crisaborole BID for 4, 8, or 12 weeks), 37 patients (22.2%) experienced TEAEs. Frequent TEAEs (occurring in ≥ 2% of patients) were AD (four patients [2.4%]) and application site infection (four patients [2.4%]); none were considered treatment related (Table 3).

No safety findings pertaining to class effect of PDE4 inhibition were observed. No new safety findings were identified in this study. The safety profile of crisaborole was found to be consistent across different races and ethnicities.

4 Discussion

Most guidelines have historically recommended using moderate-to-high potency TCS for acute treatment and low-to-moderate potency TCS as maintenance therapy [15]; however, current guidance documents and recent data recommend the use of TCSs, TCIs, or crisaborole as first-line treatment options for acute or maintenance treatment in AD [2].

The CONTROL study addressed the safety and efficacy of crisaborole QD maintenance use in patients with mild-to-moderate AD involving ≥ 5% treatable BSA who previously responded to crisaborole BID treatment. Crisaborole QD showed superior efficacy in the primary and first two key secondary endpoints versus vehicle QD. Crisaborole QD maintenance treatment delayed the onset of first flare, resulted in a greater number of flare-free days, and decreased the number of flares compared to vehicle in pediatric and adult patients with mild-to-moderate AD. In a vehicle-controlled study evaluating the use of TCSs (a more traditionally used maintenance treatment in AD of fluticasone propionate 0.05% cream or 0.005% ointment twice weekly) versus its placebo base (emollient as monotherapy), in patients with moderate-to-severe AD, the median flare-free period was 42 days for patients treated with emollient as monotherapy versus > 16 weeks (112 days) for patients treated with fluticasone propionate (the median time to relapse could not be determined as it extended beyond the EOS period) [29]. During the CONTROL study, the use of crisaborole QD as maintenance treatment achieved similar outcomes, with a significantly longer period of flare-free maintenance versus vehicle (111 days vs 30 days, respectively); however, the CONTROL study consisted only of patients with mild-to-moderate AD.

Maintenance of pruritus response until the onset of first flare showed no clear trend between crisaborole- and vehicle-treated patients. There were several possible reasons for this. First, the pruritus and observation of scratch assessments use three separate age-appropriate scales, and data from these three scales cannot be combined. Second, the baseline pruritus scores were low and relatively few patients met the pruritus response criteria during the open-label period. Note that the inclusion criteria did not enrich the population by including a minimal pruritus score for eligibility. For these reasons, the sample size for analyzing maintenance of pruritus response was small.

Notably, a diverse racial population was recruited for the CONTROL study, giving further insight into the efficacy and safety profile of crisaborole among White, Black, and Asian patients. Increased racial diversity in studies such as CrisADe CONTROL is important in gaining further insight into the likely differences in etiology, epidemiology, and presentation of AD of the different racial groups [30]. Skin lesions of non-White patients are more likely to be papular, follicular based, or lichenoid, whereas AD lesions in East Asian patients are more likely to be psoriasiform, and display lichenification, scaling, and clear demarcation [31, 32]. The prevalence of AD is high among Black and Asian patients, making the inclusion and assessment of these patient groups in clinical trials important [32]. Previous pooled post hoc

analyses by race and ethnicity of the two pivotal trials and a long-term safety extension trial reported that more crisaborole-treated than vehicle-treated patients achieved improvements in global disease severity among White as well as Asian/native Hawaiian/other Pacific Islander, Black/African American, and other/American Indian/Alaskan native patient groups [30]. Favorable results were observed in the analysis of the primary efficacy endpoint in Black as well as Asian patients. In addition, in accordance with the findings of the previous pooled analyses mentioned, the CONTROL study found the safety profile of crisaborole to be consistent across different races and ethnicities.

Safety results demonstrated that BID and QD crisaborole treatment regimens were consistent with the known safety profile of crisaborole. During the open-label run-in period, the most frequently reported TEAE was application site pain, which was reported by 28 patients (5.6%). In the pivotal CORE 1 (NCT02118766) and CORE 2 (NCT02118792) studies, application site pain was reported in 4.4% of crisaborole-treated patients and in 2.3% of crisaborole-treated patients in CORE 3 [25, 28]. From these studies, it is evident that the incidence of application site pain decreases with time. No application site pain or any other application site reactions were reported by crisaborole-treated patients during the maintenance period. TEAEs potentially attributable to systemic PDE4 inhibition, such as diarrhea, nausea, and vomiting, were reported infrequently. In addition, no treatment-related safety findings pertaining to systemic PDE4 inhibition were observed in this long-term study. No new or unexpected safety findings were identified with long-term use of crisaborole in this study. These safety results thus support the long-term use of crisaborole.

During this study, crisaborole was used as monotherapy. No TCSs or other topical treatments were used as rescue therapy. During any flare treatment period, crisaborole BID was used as rescue therapy. The results of this study support the role of crisaborole as monotherapy during both acute as well as long-term maintenance treatment.

4.1 Limitations

The pediatric population aged 3 to < 24 months in this study was small. In the open-label run-in period, only 20 patients (4%) were aged 3 to < 24 months. The protocol was amended late in the study to include this patient population, leaving a limited time to recruit patients in this age group. In the 52-week double-blind maintenance treatment period, only four patients (3%) in both the crisaborole- and vehicle-treated groups were aged 3 to < 24 months. Only a crisaborole QD maintenance regimen was used during the study. Future studies may evaluate the use of different regimens. There is no comparison of crisaborole to other first-line treatment options (TCS and TCIs) for AD as per the current treatment guidelines.

5 Conclusions

There is an unmet need for long-term topical treatment options for AD, especially considering the safety concerns and challenges in achieving lasting disease control noted with the current topical treatment options.

Crisaborole QD is effective as a long-term maintenance therapy, demonstrating a significant reduction in the incidence of AD-related flares compared to vehicle in pediatric (aged ≥ 3 months) and adult patients with mild-to-moderate AD. Furthermore, crisaborole QD as maintenance treatment was safe and well tolerated in this patient population. Crisaborole ointment, 2%, QD represents a potential long-term maintenance treatment option in pediatric (aged ≥ 3 months) and adult patients with mild-to-moderate AD who previously responded to crisaborole BID.

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Declarations

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Conflict of interest LFE has served as a scientific advisor, consultant, and/or clinical study investigator for Pfizer Inc., AbbVie, Almirall, Amgen, Arena, Aslan Dermavant, Eli Lilly and Company, Forté, Galderma, Incyte, LEO Pharma, Novartis, Ortho Dermatologics, Otsuka, Regeneron, and Sanofi-Genzyme. RGG has received research grants for Pfizer Inc. crisaborole clinical trials and consulting fees for participating on the Pfizer crisaborole advisory board as well as research grants from LEO Pharma and Incyte as an investigator. JX has received honoraria for serving as a speaker for Pfizer Inc., Novartis, and Sanofi. MSA has received research grants for her role as an investigator for AbbVie, Janssen, Novartis, and UCB; has received honoraria for serving on advisory boards for AbbVie, Novartis, and UCB; and has received honoraria for serving as a speaker for AbbVie. JCS has been a consultant/speaker/investigator for Pfizer Inc., AbbVie, Amgen, Bioderma, Bristol Myers Squibb, Ego Pharmaceuticals, Eli Lilly and Company, Janssen, LEO Pharma, L'Oreal, Mayne, Novartis, Pierre-Fabre, and Sanofi. DEM, PS, BV, CZ, JL, and JW are employees and shareholders of Pfizer Inc.

Availability of data and material Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Ethics approval The final protocol, any amendments, and informed consent/assent documentation were reviewed and approved by the institutional review boards or institutional ethics committees at each

of the investigational centers participating in the study. All patients or parent(s)/guardian(s) provided written informed consent, including age-appropriate assent, for participation in the study. This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines.

Consent to participate Informed consent and age-appropriate assents were obtained from all individual participants included in the study and/or their caregivers.

Consent to publish Not applicable.

Code availability Not applicable.

Author contributions All the authors were involved in the interpretation of the data, the draft preparation, writing, and approval of the final manuscript for submission. LFE, RG, JX, MSA, and JCS were involved in the methodology and investigation of the study. DEM, PS, BV, JL, and JW were involved in the conceptualization, methodology, formal analysis and investigation, and supervision of the study. CZ was involved in the conceptualization, methodology, and statistical analysis of the data.

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