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Authors

Eichenfield, Lawrence

Stein Gold, Linda

Lynde, Charles

et al.

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Maintenance of Investigator's Static Global Assessment Response with Once-Daily Crisaborole in Participants with Mild to Moderate Atopic Dermatitis

Lawrence F. Eichenfield (ID) · Linda F. Stein Gold · Charles Lynde ·

Lyn Guenther · Shoshana Greenberger · Chia-Yu Chu ·

Zara Ghodsi · Bonnie Vlahos · Paul Sanders · Amy Cha ·

Juliana M. Canosa

ABSTRACT

Introduction: Treatments for atopic dermatitis (AD) often fail to achieve lasting disease control. In the CrisADe CONTROL phase III study (ClinicalTrials.gov: NCT04040192), participants aged ≥ 3 months with mild to moderate AD

treated with once-daily (QD) crisaborole, following initial treatment success with crisaborole twice daily (BID), had longer periods of flare-free maintenance, a higher number of flare-free days, and a lower number of flares compared with those who received vehicle. The study was an exploratory analysis of data on the maintenance of response per Investigator's Static Global Assessment (ISGA; ISGA score of 0 [clear] or 1 [almost clear]) during the CrisADe CONTROL study through week 52.
Methods: Exploratory endpoints were the time to ISGA response during the open-label run-in

L. F. Eichenfield (✉)
UC San Diego and Rady Children's Hospital,
3020 Children's Way, Mail Code 5062,
San Diego, CA 92123, USA
e-mail: leichenfield@rchsd.org

L. F. Stein Gold
Henry Ford Hospital, Detroit, MI, USA

C. Lynde
University of Toronto, Toronto, ON, Canada

L. Guenther
Western University, London, ON, Canada

S. Greenberger
Sheba Medical Center, Ramat Gan, Israel

S. Greenberger
Tel Aviv University, Tel Aviv, Israel

C.-Y. Chu
Department of Dermatology, National Taiwan
University Hospital–National Taiwan University
College of Medicine, Taipei, Taiwan

Z. Ghodsi · P. Sanders
Pfizer R&D Ltd., Tadworth, Surrey, UK

B. Vlahos
Pfizer Inc., Collegeville, PA, USA

A. Cha
Pfizer Inc., New York, NY, USA

J. M. Canosa
Pfizer Brasil Ltd., São Paulo, Brazil

period, and the maintenance of ISGA response and the severity and duration of flares during the double-blind maintenance period. Outcomes were stratified by age (participants aged 3 months to < 12 years and ≥ 12 years) and duration of crisaborole BID treatment (< 4 weeks or ≥ 4 weeks) during the open-label run-in period.

Results: During the open-label run-in period, the median time to ISGA response was 41.5 days. From week 4 to week 52 of the double-blind maintenance period, the proportion of participants who maintained ISGA response was greater with crisaborole versus vehicle, and this difference was statistically significant up to week 36 ($P < 0.05$). Duration of flare periods during the maintenance period were 54.1 and 54.0 days for the vehicle and crisaborole-treated groups, respectively. Numerically fewer crisaborole-treated participants experienced a flare with an ISGA score of ≥ 2 compared with vehicle-treated participants (64.8% vs. 74.4%, respectively). Findings were comparable across most subgroups.

Conclusions: Adult and pediatric participants with mild to moderate AD at baseline who had achieved responder criteria (treatment success) with crisaborole BID during the run-in period maintained response per ISGA with crisaborole QD during the double-blind maintenance period through week 52.

Trial Registration: ClinicalTrials.gov: NCT04 040192.

PLAIN LANGUAGE SUMMARY

Atopic dermatitis is a skin disease that causes itchy, red, and dry patches of skin that can affect a person for a long time. Current treatments for atopic dermatitis often fail to keep the symptoms under control. Some creams and ointments applied to the skin (known as topical treatments) can ease the discomfort of atopic dermatitis. Crisaborole is a steroid-free ointment that has been shown to improve symptoms of atopic dermatitis in clinical studies. In a study called the CrisADe CONTROL trial, crisaborole was tested to see if it can keep atopic dermatitis symptoms under control. People who participated in the study were aged 3 months and older and they had mild-to-moderate atopic dermatitis. Participants were asked to use crisaborole on their itchy, red, and dry skin twice daily for 8 weeks. Patients were called "responders" if their symptoms became nearly clear or completely clear based on a doctor's assessment called the Investigator's Static Global Assessment, which rates atopic dermatitis between clear to severe. Some responders were asked to use crisaborole once daily for 52 weeks and another group of responders was asked to use a control (an ointment with no medicine) once daily for 52 weeks. Investigators looked at how long the skin remained nearly clear or completely clear during the 52 weeks. Results of this study showed that after initial treatment success with crisaborole twice daily, adult and pediatric participants who had mild-to-moderate atopic dermatitis were able to keep their skin nearly clear or completely clear with crisaborole once daily.

Key Summary Points

Why carry out the study?

Treatments for atopic dermatitis (AD) often fail to achieve long-term disease control.

The CrisADe CONTROL trial found that long-term maintenance treatment with crisaborole once daily (QD) 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 AD who responded to crisaborole twice daily (BID).

This exploratory analysis evaluated the maintenance of response per Investigator's Static Global Assessment (ISGA; ISGA score of 0 [clear] or 1 [almost clear]) during the CrisADe CONTROL trial through week 52.

What was learned from this study?

Participants achieving responder criteria (treatment success) with crisaborole BID during the run-in period maintained response per ISGA with crisaborole QD during the double-blind maintenance period through week 52.

Results were comparable among subgroups stratified by age (participants aged 3 months to < 12 years and ≥ 12 years) and duration of crisaborole BID treatment (< 4 weeks or ≥ 4 weeks) during the open-label run-in period.

INTRODUCTION

Atopic dermatitis (AD) is a complex chronic immuno-inflammatory skin disease characterized by dry skin, intense pruritus, and recurrent eczematous lesions [1–3]. Topical corticosteroids (TCSs) are traditionally considered the mainstay anti-inflammatory agent for AD flares, [1, 4, 5] although topical calcineurin inhibitors (TCIs) have demonstrated comparable efficacy to mild and moderate strength TCS [6, 7]. TCIs are approved for short-term and noncontinuous treatment in recalcitrant AD, and several guidelines have added TCIs as an alternative to TCSs [1, 4, 5].

Often, current treatments for AD do not achieve long-lasting disease control despite initial improvement [8, 9]. Patients often have a fluctuating clinical course characterized by periods of remission interrupted by acute exacerbations (flares) [9]. Moreover, treatment-related efficacy may vary according to several patient-specific factors, including age. Thus, studies evaluating efficacy outcomes among diverse populations are important to achieve a more targeted therapeutic approach in AD [10].

Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 (PDE4) inhibitor used for the treatment of mild to moderate AD [11]. Crisaborole has been shown to be effective and well tolerated in treating patients aged ≥ 3 months with mild to moderate AD [12–14]. The recent CrisADe CONTROL (ClinicalTrials.gov NCT04040192) trials evaluated the long-term efficacy and safety of crisaborole once daily (QD) versus vehicle as maintenance treatment to reduce the incidence of flares in participants aged ≥ 3 months with mild to moderate AD who previously responded to twice-daily (BID) treatment. Compared with vehicle, treatment with crisaborole QD resulted in a longer median time of flare-free maintenance, a higher mean number of flare-free days, and a lower mean number of flares through 52 weeks [15].

In this exploratory analysis of the CrisADe CONTROL trial, we evaluated the proportion of crisaborole- versus vehicle-treated participants who maintained response per Investigator's Static Global Assessment (ISGA; ISGA score of 0 [clear] or 1 [almost clear]) during the double-blind maintenance period through week 52. In addition, time to ISGA response during the open-label run-in period as well as the severity and duration of flare during the double-blind maintenance period were evaluated.

METHODS

Study Design

This analysis used data from the randomized, double-blind, vehicle-controlled, 52-week, phase 3 CrisADe CONTROL trial [15]. The final protocol for the CrisADe CONTROL trial and 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. Details of the study design have been reported previously [15].

In brief, eligible participants received crisaborole BID during an open-label run-in period of up to 8 weeks. Participants who achieved ISGA success (ISGA score of 0 [clear] or 1 [almost clear] with a $\geq$ 2-grade improvement from baseline) and $\geq$ 50% improvement in the Eczema Area and Severity Index (EASI-50) total score from baseline were defined as responders. Responders were randomized to the double-blind maintenance period in a 1:1 ratio to receive either crisaborole or vehicle QD for 52 weeks. Participants were assessed every 4 weeks during the maintenance period for efficacy and safety. If a flare (ISGA score $\geq$ 2) occurred, the participant entered a flare treatment period, during which the participant was switched from their assigned study treatment to open-label crisaborole BID for up to 12 weeks. If a flare occurred outside of the study visits, participants or caregivers reported the flare directly or by means of an electronic diary; however, the resolution of a flare outside of the scheduled study visits was not reported. Participants were assessed every 4 weeks to ascertain if the flare had resolved (ISGA score $\leq$ 1), in which case the assigned treatment was resumed [15].

Participants and Treatment

At the time of informed consent/assent, participants were aged $\geq$ 3 months [15]. Participants had mild to moderate AD, defined as an ISGA score of 2 (mild) or 3 (moderate), as well as a percentage body surface area (%BSA) involved (excluding scalp) of $\geq$ 5% [15].

Participants and/or their parent(s)/legal guardian(s) were instructed to apply a layer of the study treatment to cover all treatable AD lesions (excluding the scalp), including newly identified lesions during both the open-label period and the double-blind maintenance period. During the open-label run-in period, participants were instructed to apply crisaborole BID throughout 8 weeks, even when the skin became clinically clear. Likewise, throughout the maintenance period, participants were instructed to continue to apply the QD study treatment to the most commonly affected skin areas. Crisaborole was applied BID during all flares occurring during the maintenance period [15].

Endpoints and Assessments

Primary and Key Secondary Endpoints

In the CrisADe CONTROL trial, the primary endpoint was flare-free maintenance until onset of the first flare. Secondary endpoints were number of flare-free days, number of flares, and maintenance of pruritus response until onset of the first flare [15].

Exploratory Assessments

Time to ISGA response was assessed during the open-label run-in period; ISGA response was assessed every 2 weeks. Maintenance of ISGA response (score of 0 [clear] or 1 [almost clear]) was evaluated during the double-blind maintenance period of the study through week 52. Response to study treatment QD per ISGA was assessed during scheduled in-clinic visits every 4 or 8 weeks and by phone at weeks 20, 28, 36, and 44. In the event of a flare during the double-blind maintenance period, the severity and time until flare resolution (ISGA score $\leq$ 1) was assessed [15]. Participants were assessed every 4 weeks for flare resolution [15]. For this exploratory analysis, endpoints were stratified by age (participants aged 3 months to < 12 years and $\geq$ 12 years) and duration of crisaborole BID treatment (< 4 weeks or $\geq$ 4 weeks) during the run-in period.

Statistical Analysis

The overall population consisted of all the participants from the CrisADe CONTROL study who were randomly assigned to a treatment group and met responder criteria. The *P*-value and estimate of treatment difference for maintenance of ISGA response during the 52-week double-blind maintenance period were calculated from Cochran–Mantel–Haenszel weight method stratified by age group (3 months to < 12 years and ≥ 12 years), duration of the BID treatment in the open-label period (≤ 4 weeks and > 4 weeks), and ISGA score (clear [0], or almost clear [1]) at randomization. The significance level was defined as *P* = 0.05. For the maintenance of ISGA response during the double-blind maintenance period, the stratified 95% confidence interval (CI) was constructed using the NewCombe method.

Ethical Approval

This planned exploratory analysis of data from the CrisADe CONTROL study was exempt from institutional review board approval. All participants or parents/guardians provided written informed consent for participation in the CrisADe CONTROL study. The CrisADe CONTROL study was approved by the Quorum Review Institutional Review Board and was conducted in accordance with the ethical principles originating in the Declaration of Helsinki.

RESULTS

Baseline Characteristics

A total of 497 participants were included in the open-label run-in period. Overall, 270 participants were enrolled into the 52-week double-blind maintenance period, of whom 135 were randomly assigned to the crisaborole group and 135 were randomly assigned to the vehicle group. However, ten participants in the crisaborole-treated group and six participants in the vehicle-treated group were ultimately excluded from the efficacy analysis because they did not meet responder criteria (ISGA success and EASI-50) at randomization [15].

Demographic and baseline characteristics between the two randomized groups [15] and subgroups (Table 1) were generally balanced; however, participants receiving crisaborole QD following > 4 weeks BID treatment during the open-label period had a numerically greater EASI total score, ISGA score, and %BSA at baseline versus participants who received ≤ 4 weeks BID treatment. Participants aged 3 months to < 12 years treated with crisaborole QD had a numerically greater EASI total score and %BSA at baseline versus participants aged ≥ 12 years treated with crisaborole QD at baseline. Furthermore, participants aged ≥ 12 years had a numerically greater duration of disease than participants aged 3 months to < 12 years. Similarly, participants who had received > 4 weeks of BID treatment during the open-label period had a numerically greater duration of disease than participants who had received ≤ 4 weeks of BID treatment (Table 1).

Primary and Key Secondary Endpoints

Median time of flare-free maintenance (the number of consecutive flare-free days) was longer for patients who received crisaborole versus vehicle (111 vs. 30 days, respectively; *P* = 0.0034). The mean number of flare-free days (the number of flare-free days throughout the study period) 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 flares, respectively; *P* = 0.0042) [15].

Time to ISGA Response During the Open-Label Run-In Period

During the open-label period, the median time to ISGA response was 41.5 days for the overall population. When stratified by age, the median time to ISGA response for participants aged 3 months to < 12 years and those aged ≥ 12 years was 31.0 and 42.0 days, respectively.

Table 1 Participant demographic and baseline disease characteristics stratified by age and duration of crisaborole twice daily during the open-label run-in period

Participant demographic and baseline disease characteristics	Population randomized to DB maintenance period (N = 254)		Age at baseline				Duration of crisaborole BID			
			3 months to < 12 years		≥ 12 years		≤ 4 weeks		> 4 weeks	
	Vehicle QD N = 129	Crisaborole QD N = 125	Vehicle QD n = 60	Crisaborole QD n = 47	Vehicle QD n = 69	Crisaborole QD n = 78	Vehicle QD n = 41	Crisaborole QD n = 36	Vehicle QD n = 88	Crisaborole QD n = 89
Female, n (%)	70 (54.3)	69 (55.2)	33 (55.0)	23 (48.9)	37 (53.6)	46 (59.0)	23 (56.1)	19 (52.8)	47 (53.4)	50 (56.2)
Mean (SD) ISGA	0.6 (0.5)	0.6 (0.5)	0.5 (0.5)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	0.5 (0.5)	0.5 (0.5)	0.6 (0.5)	0.7 (0.5)
Mean (SD) EASI score	1.5 (2.1)	1.5 (1.6)	1.5 (2.1)	1.6 (1.8)	1.5 (2.1)	1.4 (1.5)	0.8 (0.9)	1.2 (1.7)	1.8 (2.4)	1.6 (1.6)
Mean (SD) %BSA	5.2 (9.6)	5.2 (7.2)	4.4 (9.1)	5.9 (7.1)	6.0 (10.0)	4.8 (7.2)	2.6 (3.8)	3.5 (5.3)	6.5 (11.1)	5.9 (7.7)
Mean (SD) duration of disease (AD), years	8.8 (9.5)	10.2 (10.2)	3.8 (3.1)	4.4 (3.1)	13.2 (11.0)	13.7 (11.4)	7.7 (8.2)	9.3 (6.3)	9.3 (10.0)	10.6 (11.4)

AD atopic dermatitis, BID twice daily, BSA body surface area, DB double-blind, EASI Eczema Area and Severity Index, ISGA Investigator's Static Global Assessment, QD once daily, SD standard deviation
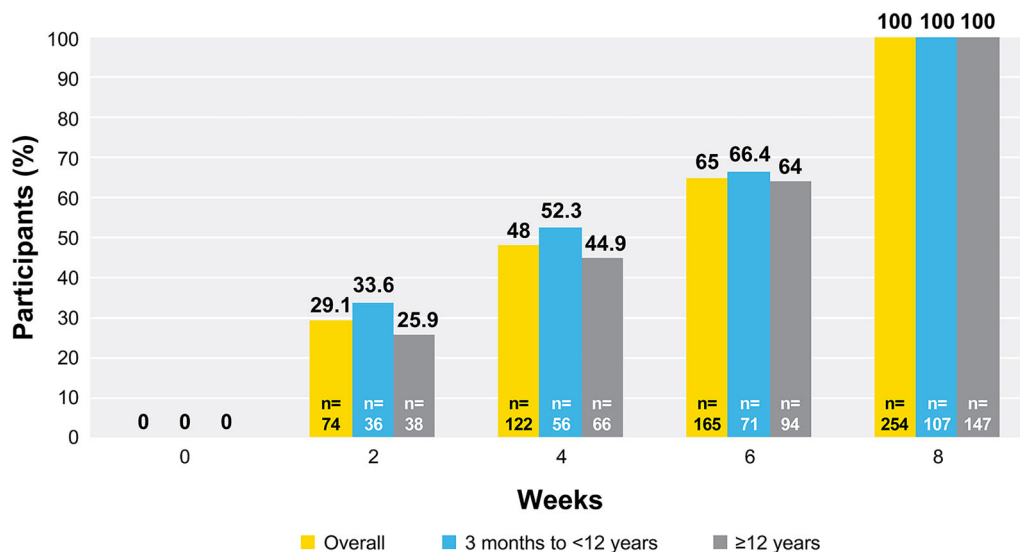
Fig. 1 Percentage of responders achieving ISGA response in the open-label period by age. *ISGA* Investigator's Static Global Assessment

A numerically greater proportion of participants aged 3 months to < 12 years achieved ISGA response from week 2 to week 6 versus the other age subgroup and the overall population (Fig. 1).

Maintenance of ISGA Response During the Double-Blind Maintenance period

Examples of AD lesions assessed throughout the CrisADe CONTROL trial are shown in Fig. 2. The proportion of participants who maintained ISGA score ≤ 1 (responders) was numerically greater in those treated with crisaborole versus those who received vehicle for up to 52 weeks (Fig. 3; Table 2). From week 4 to week 36, the proportion of participants maintaining ISGA score ≤ 1 was significantly greater ($P < 0.05$) in participants treated with crisaborole versus vehicle (Table 2).

When stratified by the duration of BID treatment in the open-label period (≤ 4 weeks and > 4 weeks), the proportion of crisaborole-versus vehicle-treated participants maintaining ISGA response was numerically greater in the ≤ 4 weeks subgroup throughout the 52-week maintenance period with the exception of week 20, when the adjusted difference was numerically greater in the > 4 weeks

subgroup and week 24 when the adjusted difference was the same for the two subgroups (Table 3). Statistically, the proportion of participants maintaining ISGA response was significantly greater in participants treated with crisaborole versus vehicle from weeks 4 to 8 and from weeks 28 to 44 for the ≤ 4 weeks subgroup, while for the > 4 week subgroup, the proportion of crisaborole versus vehicle-treated participants maintaining ISGA response was significantly greater from weeks 4 to 24 (Table 3).

Severity of Flare

Of the 254 participants assessed during the maintenance period, 96 in the vehicle-treated group and 81 in the crisaborole-treated group had at least 1 flare. In the overall population there was a numerically lower percentage of participants with flares having ISGA scores of ≥ 2 among the crisaborole-treated group compared to the vehicle-treated group (Table 4).

When stratified by age the percentage of participants with an ISGA score of two flares for the ≥ 12 years subgroup was numerically less in crisaborole-treated versus vehicle-treated participants; however, for the 3 months to < 12 years subgroup, the percentage was
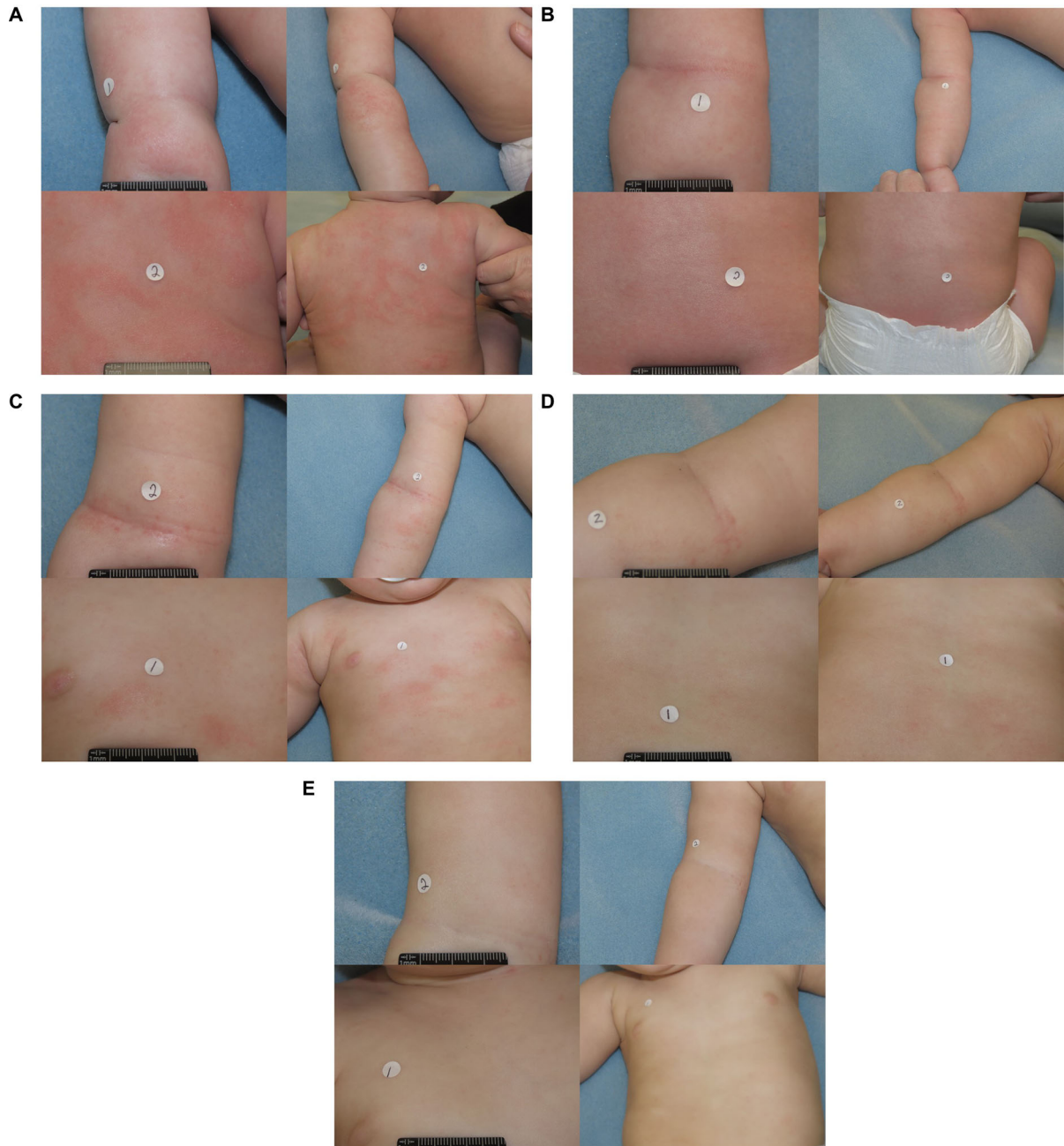
Fig. 2 Examples of AD lesions throughout the CrisADe CONTROL trial. **a** AD lesions on day 1/run-in baseline, **b** AD lesions at the end of the run-in period in participant classified as a responder, **c** flares during maintenance period, **d** resolved flares after treatment with crisaborole BID, **e** AD lesions at the end of the 52-week maintenance period. *AD* Atopic dermatitis, *BID* twice daily. Photographs were used with permission granted via informed consent/assent provided by each participant and/or their parent(s)/legal guardian(s)

numerically less in the vehicle-treated participants. The percentage of participants with an ISGA score of three flares for both age subgroups was numerically less in crisaborole-treated participants versus vehicle-treated participants. Across both treatment groups the incidence rate
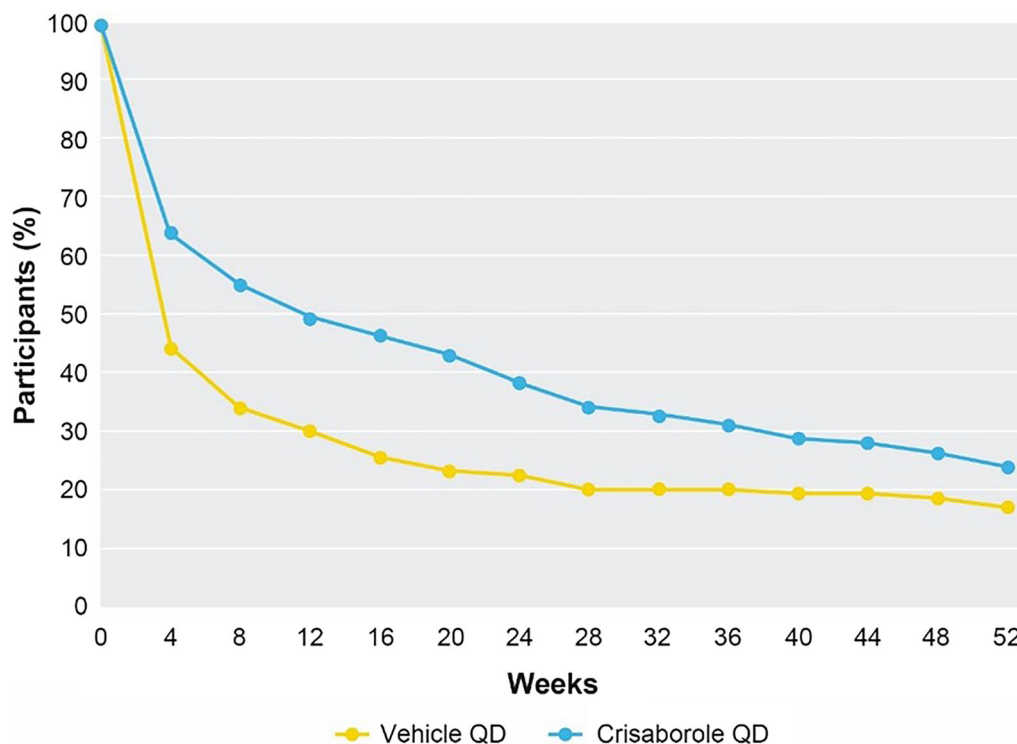
Fig. 3 Participants who maintained ISGA response during the 52-week double-blind maintenance period. *ISGA* Investigator's Static Global Assessment, *QD* once daily

of flares with an ISGA score of 2 or 3 was lower in the ≥ 12 years subgroup compared to the < 12 years subgroup (Table 4).

When stratified by the duration of BID treatment during the open-label treatment period, the percentage of participants having a flare (ISGA = 2) for the ≤ 4 weeks subgroup was numerically lower in the vehicle-treated subgroup versus the crisaborole-treated subgroup; however, for the > 4 weeks subgroup the percentage was numerically lower in the crisaborole-treated subgroup. The percentage of participants with a flare (ISGA = 3) for both the ≤ 4 weeks and > 4 weeks subgroups was numerically lower in the crisaborole-treated group. Overall, there was a trend towards a lower incidence rate of flares having an ISGA score of 2 among the > 4 weeks subgroup, while the ≤ 4 weeks subgroup had a trend towards a lower incidence rate of flares having an ISGA score of 3 (Table 4).

Duration of Flare Periods

The median time until flare resolution was comparable between the crisaborole-treated and vehicle-treated participants in the overall population (54.0 vs. 54.1 days, respectively) and was similar between subgroups (Fig. 4). When stratified by age, the median time until flare resolution for the 3 months to < 12 years subgroup was numerically less in crisaborole-treated versus vehicle-treated participants; however, the median time in the ≥ 12 years subgroup for crisaborole-treated participants was numerically greater than that for vehicle-treated participants (Fig. 4). When stratified by the duration of BID treatment during the open-label treatment period, the median time until flare resolution for the ≤ 4 weeks subgroup was numerically less in crisaborole-treated versus vehicle-treated participants. In contrast, the median time in the > 4 weeks subgroup for crisaborole-treated participants was numerically

Table 2 Proportion of participants who maintained Investigator's Static Global Assessment response during the 52-week maintenance period

Time point	Treatment	n (%)	Adjusted difference (95% CI)[a,b]	P-value[c]
Randomization	Vehicle	129 (100.0)		
	Crisaborole	125 (100.0)		
Week 4	Vehicle	57 (44.2)	19.2 (6.9, 30.8)	0.002
	Crisaborole	80 (64.0)		
Week 8	Vehicle	44 (34.1)	20.0 (7.8, 31.5)	0.0013
	Crisaborole	69 (55.2)		
Week 12	Vehicle	39 (30.2)	18.9 (6.8, 30.3)	0.0023
	Crisaborole	62 (49.6)		
Week 16	Vehicle	33 (25.6)	20.1 (8.2, 31.2)	0.0009
	Crisaborole	58 (46.4)		
Week 20	Vehicle	30 (23.3)	19.6 (8.0, 30.6)	0.0009
	Crisaborole	54 (43.2)		
Week 24	Vehicle	29 (22.5)	15.6 (4.2, 26.5)	0.0065
	Crisaborole	48 (38.4)		
Week 28	Vehicle	26 (20.2)	14.0 (2.9, 24.7)	0.0107
	Crisaborole	43 (34.4)		
Week 32	Vehicle	26 (20.2)	12.4 (1.5, 23.1)	0.0224
	Crisaborole	41 (32.8)		
Week 36	Vehicle	26 (20.2)	10.8 (0.04, 21.4)	0.043
	Crisaborole	39 (31.2)		
Week 40	Vehicle	25 (19.4)	9.1 (−1.6, 19.5)	0.0816
	Crisaborole	36 (28.8)		
Week 44	Vehicle	25 (19.4)	8.3 (−2.3, 18.7)	0.1102
	Crisaborole	35 (28.0)		
Week 48	Vehicle	24 (18.6)	7.1 (−3.3, 17.4)	0.1586
	Crisaborole	33 (26.4)		

Table 2 continued

Time point	Treatment	n (%)	Adjusted difference(95% CI)[a,b]	P-value[c]
Week 52	Vehicle	22 (17.1)	6.4 (−3.7, 16.4)	0.1919
	Crisaborole	30 (24.0)		

Number of participants in this analysis: $N = 125$ for the crisaborole 2% treatment group and $N = 129$ for vehicle treatment group

BID twice daily, CI confidence interval, ISGA Investigator's Static Global Assessment

[a]Calculated as crisaborole − vehicle

[b]The stratified CI was constructed using the Newcombe method

[c]The P-value and estimate of treatment difference were from the Cochran–Mantel–Haenszel weight method stratified by age group (3 months to < 12 years, ≥ 12 years), duration of the BID treatment in the open-label period (≤ 4 weeks, > 4 weeks) and ISGA score (clear [0] or almost clear [1]) at randomization

greater than for vehicle-treated participants (Fig. 4).

DISCUSSION

This exploratory analysis of the CrisADe CONTROL trial showed that adult and pediatric participants with mild to moderate AD at baseline who had achieved responder criteria (treatment success) with crisaborole BID during the run-in period maintained response per ISGA with crisaborole QD for ≤ 52 weeks during the double-blind maintenance period through week 52. Responses to crisaborole BID during the run-in period and to crisaborole QD during the maintenance period were similar between most subgroups.

From week 2 to week 6 of the open-label run-in period, ISGA response was achieved by a numerically greater proportion of participants in the age subgroup 3 months to < 12 years compared with the age subgroup ≥ 12 years and the overall population. This numerically greater response rate from week 2 to week 6 in younger patients may be explained by the difference in skin structure with age. Pediatric patients have a thinner stratum corneum than adults with increased permeability to topical agents [16–18] and a larger body surface area to weight ratio, both of which result in an increase

in the proportion of drug absorbed via the skin in the former patient group as compared to adults [18]. In addition, chronic lichenified AD lesions are typically less frequent in children as compared to adults, which may also reduce absorption [19, 20].

Relief from AD-related signs and symptoms, maintenance of response following initial improvement, and consistency among diverse populations are important factors to consider when determining the optimal treatment option for patients with AD. Although there are several treatment options which provide patients with AD relief from the signs and symptoms associated with this skin condition, AD is characterized by a chronic recurrent course, and initial success is often difficult to maintain long term [9]. The results of the CrisADe CONTROL trial showed that crisaborole QD was effective for long-term maintenance treatment and flare reduction in adult and pediatric patients with mild to moderate AD over a 52-week period [15]. The exploratory analysis of the CrisADe CONTROL trial presented here demonstrated that the favorable initial treatment-related success (following an initial run-in period of up to 8 weeks with crisaborole BID) was sustainable with crisaborole QD during the 52-week maintenance period. During the double-blind maintenance period, the proportion of crisaborole- versus vehicle-

Table 3 Participants who maintained Investigator's Static Global Assessment response during the 52-week maintenance period by duration of twice-daily treatment in the open-label period: ≤ 4 weeks and > 4 weeks

Time point	QD treatment during DB maintenance period	Number of weeks crisaborole BID treatment during open-label run-in period					
		≤ 4 weeks			> 4 weeks		
		n (%)	Adjusted difference (95% CI)[a,b]	*P*-value[c]	*n* (%)	Adjusted difference (95% CI)[a,b]	*P*-value[c]
Randomization	Vehicle	41 (100.0)			41 (100.0)		
	Crisaborole	36 (100.0)			36 (100.0)		
Week 4	Vehicle	15 (36.6)	24.9 (2.46, 44.35)	0.0322	42 (47.7)	16.8 (2.10, 30.52)	0.0230
	Crisaborole	22 (61.1)			58 (65.2)		
Week 8	Vehicle	12 (29.3)	26.2 (4.03, 45.34)	0.0232	32 (36.4)	17.4 (2.64, 31.15)	0.0190
	Crisaborole	20 (55.6)			49 (55.1)		
Week 12	Vehicle	11 (26.8)	21.3 (−0.17, 40.78)	0.0581	28 (31.8)	17.8 (3.21, 31.34)	0.0164
	Crisaborole	17 (47.2)			45 (50.6)		
Week 16	Vehicle	9 (22.0)	20.2 (−0.60, 39.28)	0.0635	24 (27.3)	20.0 (5.64, 33.27)	0.0060
	Crisaborole	15 (41.7)			43 (48.3)		
Week 20	Vehicle	8 (19.5)	15.6 (−4.14, 34.53)	0.1242	22 (25.0)	21.3 (7.10, 34.41)	0.0030
	Crisaborole	12 (33.3)			42 (47.2)		
Week 24	Vehicle	8 (19.5)	15.6 (−4.14, 34.53)	0.1242	21 (23.9)	15.6 (1.79, 28.70)	0.0246
	Crisaborole	12 (33.3)			36 (40.4)		
Week 28	Vehicle	5 (12.2)	20.4 (1.57, 38.18)	0.0275	21 (23.9)	11.2 (−2.34, 24.27)	0.0967
	Crisaborole	11 (30.6)			32 (36.0)		
Week 32	Vehicle	5 (12.2)	20.4 (1.57, 38.18)	0.0275	21 (23.9)	9.0 (−4.42, 22.00)	0.1788
	Crisaborole	11 (30.6)			30 (33.7)		
Week 36	Vehicle	5 (12.2)	20.4 (1.57, 38.18)	0.0275	21 (23.9)	6.7 (−6.54, 19.65)	0.3050
	Crisaborole	11 (30.6)			28 (31.5)		
Week 40	Vehicle	5 (12.2)	20.4 (1.57, 38.18)	0.0275	20 (22.7)	4.2 (−8.75, 16.92)	0.5055
	Crisaborole	11 (30.6)			25 (28.1)		
Week 44	Vehicle	5 (12.2)	17.7 (−0.66, 35.47)	0.0505	20 (22.7)	4.2 (−8.75, 16.92)	0.5055
	Crisaborole	10 (27.8)			25 (28.1)		
Week 48	Vehicle	5 (12.2)	12.0 (−5.47, 29.44)	0.1633	19 (21.6)	5.1 (−7.84, 17.70)	0.4174
	Crisaborole	8 (22.2)			25 (28.1)		

Table 3 continued

Time point	QD treatment during DB maintenance period	Number of weeks crisaborole BID treatment during open-label run-in period					
		≤ 4 weeks			> 4 weeks		
		n (%)	Adjusted difference(95% CI)[a,b]	*P*-value[c]	*n* (%)	Adjusted difference(95% CI)[a,b]	*P*-value[c]
Week 52	Vehicle	5 (12.2)	8.9 (−8.08, 26.06)	0.2848	17 (19.3)	5.4 (−7.16, 17.64)	0.3765
	Crisaborole	7 (19.4)			23 (25.8)		

For the ≤ 4 weeks duration, *N* = 36 for the crisaborole 2% treatment group and *N* = 41 for the vehicle treatment group.
For the > 4 weeks duration, *N* = 89 for the crisaborole 2% treatment group and *N* = 88 for the vehicle treatment group
BID twice daily, *CI* confidence interval, *DB* double-blind, *ISGA* Investigator's Static Global Assessment, *QD* once daily
[a]Calculated as crisaborole − vehicle
[b]The stratified CI was constructed using the Newcombe method
[c]The *P*-value and estimate of treatment difference were from the Cochran–Mantel–Haenszel weight method stratified duration of the BID treatment in the open-label period (≤ 4 weeks, > 4 weeks) and ISGA score (clear [0] or almost clear [1]) at randomization

treated participants maintaining ISGA response was generally numerically greater in participants who had an ISGA response in ≤ 4 weeks with BID treatment in the open-label period compared with those who took longer to have an ISGA response (> 4 weeks). A potential explanation would be that the subgroup with ≤ 4 weeks BID treatment had less severe AD at baseline.

The maintenance of ISGA response with crisaborole may be explained by the findings of a recent phase 2a, single-center, intrapatient, vehicle-controlled, proteomic analysis of 40 adults with mild to moderate AD and 20 healthy participants [21]. In that study, crisaborole induced normalization of the AD proteome towards a non-lesional non-AD normal skin molecular phenotype, supporting the role of topical PDE4 inhibition in the treatment of mild to moderate AD. Crisaborole may be useful as a broad-spectrum agent in AD management given its potential to target several general and immune pathways (e.g., Th2, Th17/Th22, and Th1 activation associated with AD pathogenesis in various stages and in different phenotypes of AD) [21–23].

The duration of flare periods during the maintenance period was found to be comparable for vehicle- and crisaborole-treated groups,

with a numerically lower proportion of crisaborole-treated participants experiencing a flare with an ISGA score of ≥ 2 compared with vehicle-treated participants. Findings were comparable across most subgroups, including age subgroups. Previous studies have shown crisaborole to be effective for treating AD in patients aged ≥ 3 months with mild to moderate AD [12–14]. Likewise, the present exploratory analysis of the CrisADe CONTROL trial showed that the crisaborole-treated participants in age subgroups had consistent but comparable efficacy, emphasizing crisaborole's consistency among different populations.

This study has a number of limitations. Firstly, the run-in period of the study was conducted in an open-label manner, which has the potential to introduce bias. Additionally, this study is limited by the lack of reporting on the resolution of flares between scheduled study visits, which might account for why the median time to flare resolution was similar in patients treated with crisaborole compared with those treated with vehicle. During flare treatment periods, participants were assessed every 4 weeks to determine if the flare had resolved (indicated by an ISGA score ≤ 1). However, in contrast to the process for detecting flares, instances of flare resolution occurring between

Table 4 Analysis of the severity of flares (Investigator's Static Global Assessment ≥ 2) during the 52-week maintenance period by age and duration of twice-daily treatment

| Severity of flares | Population randomized to DB maintenance period | | Age at baseline | | | | Duration of crisaborole BID | | | |
| | | | 3 months to < 12 years | | ≥ 12 years | | ≤ 4 weeks | | > 4 weeks | |
	Vehicle QD N = 129	Crisaborole QD N = 125	Vehicle QD n = 60	Crisaborole QD n = 47	Vehicle QD n = 69	Crisaborole QD n = 78	Vehicle QD n = 41	Crisaborole QD n = 36	Vehicle QD n = 88	Crisaborole QD n = 89
Participants evaluable for flare, n (%)	96 (74.4)	81 (64.8)	48 (80.0)	35 (74.5)	48 (69.6)	46 (59.0)	33 (80.5)	27 (75.0)	63 (71.6)	54 (60.7)
Number of flare events	175	119	93	62	82	57	51	37	124	82
Participants with ISGA = 2 flare, n (%)	62 (48.1)	53 (42.4)	31 (51.7)	28 (59.6)	31 (44.9)	25 (32.1)	23 (56.1)	22 (61.1)	39 (44.3)	31 (34.8)
Participants with ISGA = 3 flare, n (%)	54 (41.9)	34 (27.2)	29 (48.3)	14 (29.8)	25 (36.2)	20 (25.6)	14 (34.1)	7 (19.4)	40 (45.5)	27 (30.3)
Participants with ISGA = 4 flare, n (%)	5 (3.9)	1 (0.8)	0	0	5 (7.2)	1 (1.3)	2 (4.9)	0	3 (3.4)	1 (1.1)

One participant may be counted in multiple ISGA categories
DB double-blind, BID twice daily, QD once daily, ISGA Investigator's Static Global Assessment
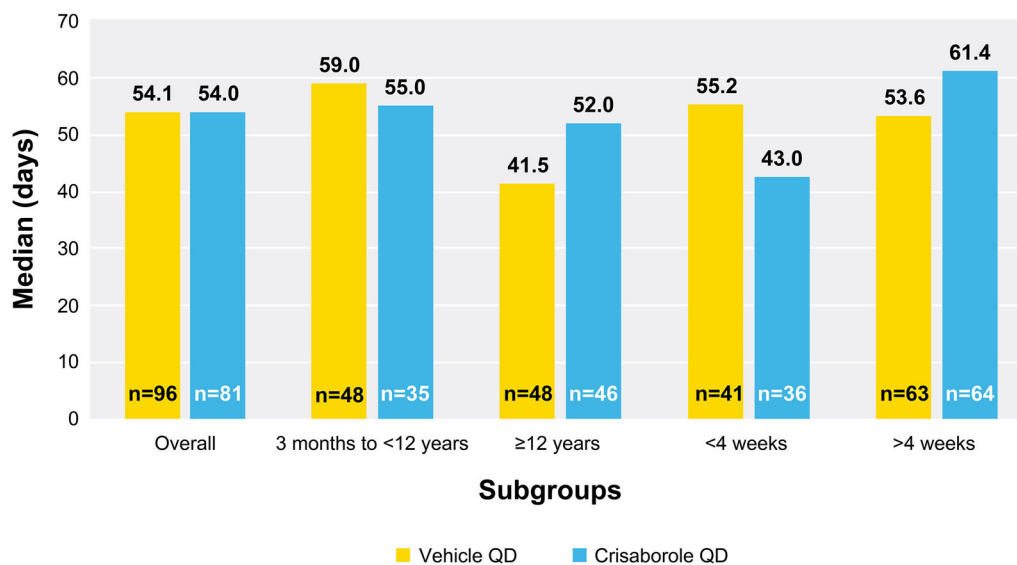
Fig. 4 Duration of flare period during the 52-week maintenance period by age and duration of BID treatment. *BID* twice daily, *QD* once daily

scheduled study visits were not documented by patients or caregivers through electronic diaries or direct reporting. This lack of reporting between scheduled study visits during the flare period may have led to an overestimation of the duration of the reported flare periods. The small sample size of some of the subgroups was a further limitation. Further evaluations of crisaborole across larger subgroups representing diverse populations would provide valuable support for its use in all patients with AD. Finally, the study involved only post hoc and exploratory analyses.

CONCLUSIONS

This exploratory analysis showed that after initial treatment success with crisaborole BID, crisaborole QD provides a durable and consistent maintenance treatment by maintaining ISGA response in adult and pediatric participants with mild to moderate AD. The results were comparable among the age subgroups analyzed. Head-to-head efficacy and safety studies comparing crisaborole to first-line treatment options for AD may still be needed; however, the data from this expanded analysis on prior research further substantiate the role of crisaborole as maintenance treatment in AD.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. 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.

Declarations

Conflict of Interest. Lawrence F. Eichenfield has served as a scientific advisor, consultant, and/or clinical trial investigator for Pfizer Inc., AbbVie, Amgen, Aslan Pharmaceuticals, Castle Biosciences, Dermavant, Eli Lilly and Company, Forté, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Ortho Dermatologics, Regeneron Pharmaceuticals, and Sanofi-Genzyme. Linda F. Stein-Gold has received grants from Pfizer Inc., Incyte, and LEO Pharma and has received payment for lectures from Pfizer Inc. and LEO Pharma. Charles Lynde has been a speaker, consultant, and/or principal investigator for Pfizer Inc., AbbVie, Amgen, Aralez, Arcutis, Bausch Health, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Cipher, Dermavant, Eli Lilly and Company, Fresnius Kabi, Galderma, GSK, InCyte, Innovaderm, Intega Skin, Janssen, Kyowa Kirin, La Roche-Posay, LEO Pharma, L'Oreal, Medexus, MedX, Merck, Novartis, P&G, Pediapharm, Regeneron, Roche, Sanofi-Genzyme, Sandoz, Sentrex, SunPharma, TEVA, Tribute, UCB, Valeant, Viatris, and Volo Health, and has served as a principal investigator for Acelyrin, Akros, Altius, Avillion, Celltrion, Concert, Devonian, Evelo, and MoonLake. Lyn Guenther has received consulting fees/honoraria from Pfizer Inc., Aralez, Bausch Health, BMS, Cipher, Eli Lilly and Company, GSK, Incyte, Janssen, Johnson and Johnson, La Roche-Posay, LEO Pharma, Merck, Miravo, Novartis, and UCB; has been a member of a Speaker's Bureau/advisory board member for Pfizer Inc., Abbvie, Actilion, Amgen, Altana, Aralez, Aslan, Bausch Health, Eli Lilly and Company, Galderma, Janssen, Johnson and Johnson, La Roche-Posay, LEO Pharma, Novartis, and Sanofi Aventis, UCB; and has received research grants from Pfizer Inc., Abbvie, Actilion, Amgen, Bausch Health, BMS, Boehringer Ingelheim, Celgene, Cipher, Eli Lilly and Company, Galderma, Innovaderm, Janssen, La Roche-Posay, LEO Pharma, Merck, Novartis, and UCB. Shoshana Greenberger served as an investigator for Pfizer Inc., AbbVie, Amgen, Eli Lilly and Company, and, Novartis; has served on a Speaker's Bureau/advisory board for Pfizer Inc., AbbVie, Sanofi, Pfizer, Padagis, and Dexcel Pharma; has provided investigator services for Pfizer Inc., AbbVie, Amgen, and Eli Lilly and Company; and has received research grants from Pfizer. Chia-Yu Chu has served as an investigator for Pfizer Inc., AbbVie, Amgen, Dermira, Eli Lilly and Company, Janssen, Novartis, Oneness Biotech, Regeneron, Roche, and Sanofi; has served as a consultant for Pfizer Inc., AbbVie, Eli Lilly and Company, Janssen, Novartis, Roche, and Sanofi; has served as a speaker for Pfizer Inc., AbbVie, Eli Lilly and Company, Janssen, Mylan, Novartis, Roche, Sanofi, and Viatris; and has served on the

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Ethical Approval. This planned exploratory analysis of data from the CrisADe CONTROL study was exempt from institutional review board approval. All participants or parents/guardians provided written informed consent for participation in the CrisADe CONTROL study. The CrisADe CONTROL study was approved by the Quorum Review Institutional Review Board and was conducted in accordance with the ethical principles originating in the Declaration of Helsinki.

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