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Evaluating the Efficacy of Crisaborole Using the Atopic Dermatitis Severity Index and Percentage of Affected Body Surface Area

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Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate atopic dermatitis. This *post hoc* analysis pools results from 2 phase 3 studies (ClinicalTrials.gov, NCT02118766 [AD-301]; NCT02118792 [AD-302]) to evaluate crisaborole efficacy in patients ≥ 2 years with mild-to-moderate atopic dermatitis (per Investigator's Static Global Assessment) using the Atopic Dermatitis Severity Index (ADSI) and percentage of treatable body surface area (%BSA). Patients were randomly assigned 2:1 to receive crisaborole (*n* = 1,016) or vehicle (*n* = 506) twice daily for 28 days. ADSI scores were the sum of pruritus, erythema, exudation, excoriation, and lichenification severity scores, each graded on a 4-point scale from none (0) to severe (3). Respective mean changes in ADSI score and %BSA at day 29 were (crisaborole vs. vehicle) −3.52 versus −2.42 (*p* < 0.0001) and −7.43 versus −4.44 (*p* < 0.0001). Crisaborole was effective in treating mild-to-moderate atopic dermatitis based on ADSI and %BSA.

SIGNIFICANCE

Crisaborole is a nonsteroidal topical treatment for mild-to-moderate atopic dermatitis. In 2 large, identically designed phase 3 studies of patients with mild-to-moderate atopic dermatitis, significantly more patients treated with crisaborole achieved treatment success per the Investigator's Static Global Assessment (ISGA) than patients treated with vehicle. This *post hoc* analysis confirms the effectiveness of crisaborole in alleviating atopic dermatitis severity using the measures Atopic Dermatitis Severity Index (ADSI) and percentage of treatable body surface area (%BSA).

Atopic dermatitis (AD) is a common chronic inflammatory skin disease associated with itch (pruritus) and eczematous lesions (1, 2). Many tools assess AD outcomes, signs, and symptoms; however, standardization is lacking (3, 4). Some of the most commonly used disease severity measures include SCORing of Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), Investigator's (Static) Global Assessment (I[S]GA), and Six Area, Six Sign Atopic Dermatitis (SASSAD) (4, 5). The I(S)GA is a physician-assessed outcome that evaluates overall disease severity on a 5- or 6-point scale ranging from clear (0) to severe (4) or very severe (5, 6). It provides a single assessment of disease severity based on visual signs of disease such as erythema, induration/papulation, and oozing/crusting (5, 6). However, it is limited in that it does not distinguish between individual AD signs or account for percentage of treatable body surface area (%BSA) or pruritus, one of the most prominent symptoms of AD (7). The Atopic Dermatitis Severity Index (ADSI) is a composite tool that uses the sum of 5 signs and symptoms of AD, each assessed globally and graded on a 4-point scale from none (0) to severe (3) for a maximum severity score of 15 (3). Unlike the I(S)GA, which uses a single score for a global assessment, the ADSI allows for a more detailed breakdown of the severity of individual signs of AD and includes pruritus, erythema, exudation, excoriation, and lichenification. However, it does not include an assessment of %BSA (3).

AD treatment guidelines primarily recommend topical agents, specifically topical corticosteroids, as first-line therapy, and topical calcineurin inhibitors as second-line options (8–11). Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD (12). In 2 large, identically designed phase 3 studies (AD-301: Clinical Trials.gov, NCT02118766; AD-302: ClinicalTrials.gov, NCT02118792), significantly more crisaborole-treated patients with mild-to-moderate AD achieved ISGA success (defined as clear [0] or almost clear [1] with a ≥2grade improvement from baseline) than vehicle-treated patients (6). In phase 2 studies, crisaborole was effective in improving ADSI score (13, 14). Although the components of ADSI were assessed in the phase 3 studies, ADSI score was not a prespecified outcome measure. In this *post hoc* analysis, the efficacy of crisaborole in the pooled phase 3 studies was evaluated using ADSI scores, calculated via the summation of pruritus and signs of AD scores, and by evaluating the effect of crisaborole on %BSA.

METHODS

Study designs

Study designs and methods have been published previously (6). Two multicenter, randomized, double-blind, vehicle-controlled phase 3 studies were performed to assess the efficacy and safety of crisaborole in patients ≥2 years with mild-to-moderate AD per ISGA. Patients were randomly assigned 2:1 to receive crisaborole or vehicle twice daily for 28 days. Both studies were conducted in accordance with Good Clinical Practice Guidelines and local regulatory requirements. The institutional review boards of participating centers approved the study protocols, and all participants provided informed consent.

Assessments

Prespecified efficacy measures included assessment of pruritus and signs of AD, including erythema, exudation, excoriation, and lichenification, each graded on a 4-point scale ranging from none (0) to severe (3). Pruritus was assessed twice daily by the patient or parent/caregiver via electronic diary using the validated Severity of Pruritus Scale (SPS) (15). For SPS, baseline values were based on the average of ≥2 assessments on day 1. For all other time points, SPS values were based on weekly average scores. Signs of AD were assessed by the investigator at each study visit. Other prespecified efficacy measures included %BSA, quality of life (QOL, as measured by the Dermatology Life Quality Index [DLQI] for patients ≥16 years and the Children's Dermatology Life Quality Index [CDLQI] for patients 2–15 years (16, 17)), and severity of AD as measured by ISGA (5-point scale ranging from clear [0] to severe [4] (6)). In this analysis, %BSA was categorized according to previously defined severity bands: clear (0%), mild (>0 to <16%), moderate (16 to <40%), and severe (40–100%) (18). These severity bands were chosen from among a number of different possible strata based on the highest κ-coefficient with a 4-point I(S)GA scale (κ=0.66) (18). Additional detail regarding scoring of these outcomes can be found in Paller et al. (6).

In this *post hoc* analysis, ADSI scores were calculated for each patient as the sum of the pruritus, erythema, exudation, excoriation, and lichenification scores that were collected prospectively in the phase 3 trials. ADSI scores were categorized according to previously defined (18) severity bands: clear/almost clear (0 to <2), mild (2 to <6), moderate (6 to <9), and severe (9–15) (**Fig. 1**). These severity bands were chosen from a number of different possible bands based on having the highest κ-coefficient with a 4-point I(S)GA scale (κ=0.55) (18).

Outcomes

Post hoc outcomes included change from baseline in ADSI scores at days 8, 15, 22, and 29; change from baseline in %BSA at day 29; proportion of patients who experienced ADSI improvement from baseline (de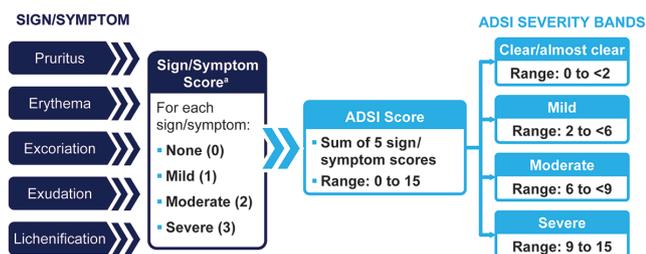fined as a change from moderate-severe to mild-clear/almost clear or from mild to clear/almost clear) and %BSA improvement from baseline (defined as a change from moderate-severe to mild-clear or from mild to clear) at day 29; proportion of patients who had an ADSI score of clear/almost clear at day 29 by baseline ADSI (among patients with baseline ADSI >1) and %BSA categories; and proportion of patients who achieved success in ISGA (defined as ISGA of clear [0] or almost clear [1] with ≥2-grade improvement from baseline), and ISGA of clear/almost clear at day 29 by baseline ADSI and %BSA categories. In addition, correlations between ADSI and ISGA, %BSA, DLQI, and CDLQI and between %BSA and ISGA, pruritus, DLQI, and CDLQI at baseline and day 29 were calculated.

Statistical analysis

Data from AD-301 and AD-302 were pooled for this analysis. ADSI scores were summarized using descriptive statistics. Comparisons between treatment groups for changes from baseline in ADSI and %BSA were analyzed using the Wilcoxon signed rank test. Proportions of patients with ADSI of clear/almost clear were compared between groups using normal approximation. Correlations and associated *p* values were calculated using Spearman rank correlations. Patients with missing data for any of the 5 signs/symptoms at any given time point were considered to have a missing ADSI score for that time point and, therefore, were not included in the efficacy analysis for that time point.

RESULTS

Demographics and baseline disease characteristics

The pooled intention-to-treat population for AD-301 and AD-302 included 1,016 patients treated with crisaborole and 506 treated with vehicle. Demographics and key baseline disease characteristics were balanced across treatment groups (**Table I** and **Fig. 2**). All patients had mild or moderate disease according to baseline ISGA; however, based on ADSI and %BSA severity bands, substantial proportions of patients were classified as having moderate or severe disease (Fig. 2). According to the ADSI, approximately 43% of patients had moderate disease and 33–34% had severe disease, whereas 23–28% had moderate disease and 10–12% had severe disease

Fig. 1. Atopic Dermatitis Severity Index (ADSI) score calculation and severity bands. [a]Additional detail regarding grading of signs/symptoms can be found in Paller AS, et al (6).

Table I. Demographics and baseline disease characteristics (pooled AD-301 and AD-302)

	Vehicle n = 506	Crisaborole n = 1016
Age, years, mean (SD)	12.1 (11.65)	12.3 (12.16)
Median (range)	9.0 (2–79)	9.0 (2–79)
Female, %	55.5	55.7
ISGA score, mean (SD)	2.6 (0.49)	2.6 (0.49)
DLQI score, n	92	192
Mean (SD)	9.3 (6.55)	9.7 (6.29)
CDLQI score, n	403	797
Mean (SD)	9.0 (6.02)	9.3 (5.99)
Severity of each ADSI component graded from none (0) to severe (3)		
Pruritus, mean (SD)[a]	1.8 (0.78)	1.8 (0.78)
Erythema, mean (SD)	1.6 (0.58)	1.7 (0.59)
Excoriation, mean (SD)	1.5 (0.70)	1.5 (0.71)
Exudation, mean (SD)	0.7 (0.84)	0.8 (0.80)
Lichenification, mean (SD)	1.5 (0.72)	1.5 (0.71)

[a]n = 368 for vehicle, n = 762 for crisaborole.
ADSI: Atopic Dermatitis Severity Index; CDLQI: Children's Dermatology Life Quality Index; DLQI: Dermatology Life Quality Index; ISGA: Investigator's Static Global Assessment; SD: standard deviation.
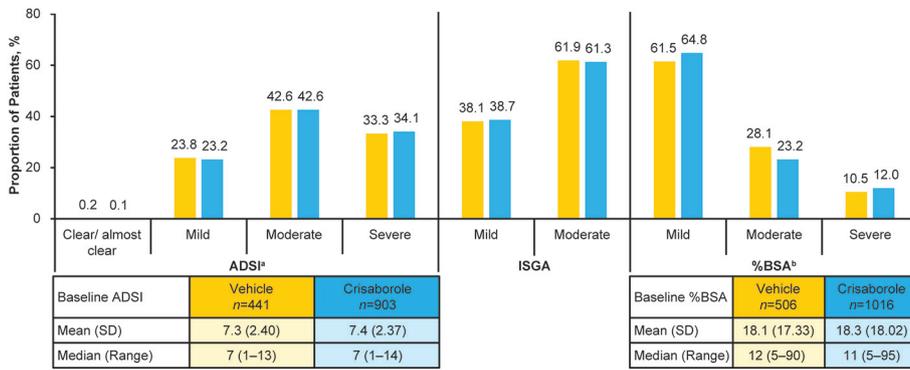
Fig. 2. Baseline atopic dermatitis (AD) severity by outcomes measure (pooled AD-301 and AD-302). [a]Severity bands for Atopic Dermatitis Severity Index (ADSI): clear/almost clear (0–<2), mild (2–<6), moderate (6–<9), severe (9–15) (18), [b]Severity bands for percentage of treatable body surface area (%BSA): clear (0), mild (>0–<16), moderate (16–<40), severe (40–100) (18). ISGA: Investigator's Static Global Assessment; SD: standard deviation.

according to %BSA (Fig. 2). When ADSI was deconstructed into its component signs and symptoms, the average score indicated that most signs and symptoms were mild to moderate except for exudation, which was mild, on average.

Atopic Dermatitis Severity Index

A decrease in ADSI score was observed in both treatment groups over time; a significantly greater reduction in mean ADSI score was observed in the crisaborole group compared with the vehicle group as early as day 8 and at days 15, 22, and 29 (**Fig. 3**). The proportion of patients who had improvement in ADSI score at day 29 was significantly greater for crisaborole-treated patients than vehicle-treated patients (62.7% vs. 48.4%; $p < 0.0001$). The proportion of patients with an ADSI score of clear/almost clear at day 29 was greater in the crisaborole-treated group than the vehicle-treated group across baseline disease severity as assessed by ADSI; however, these differences were only significant for baseline severe ADSI (**Fig. 4**A). Similarly, the proportion of patients with an ADSI score of clear/almost clear at day 29 was greater in the crisaborole-treated group than the vehicle-treated group across the baseline disease severity as assessed by %BSA; however, these differences were only significant for baseline severe %BSA (Fig. 4B). When analyzed by baseline lichenification, mean change
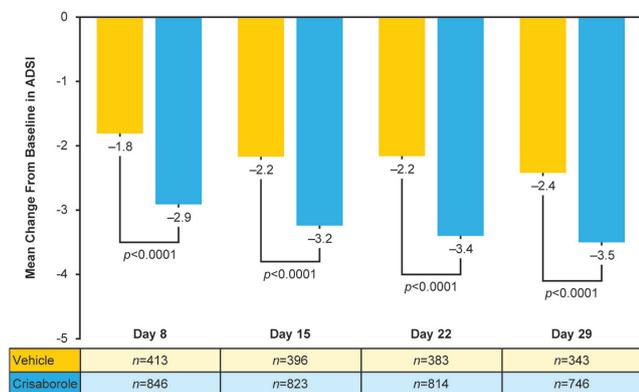
from baseline in ADSI score was greater for crisaborole-treated patients than vehicle-treated patients regardless of baseline score, with significant differences observed for all nonzero baseline scores (**Fig. 5**). When analyzing ISGA outcomes by baseline ADSI severity, significantly more crisaborole-treated patients achieved ISGA clear or almost clear at day 29 than vehicle-treated patients
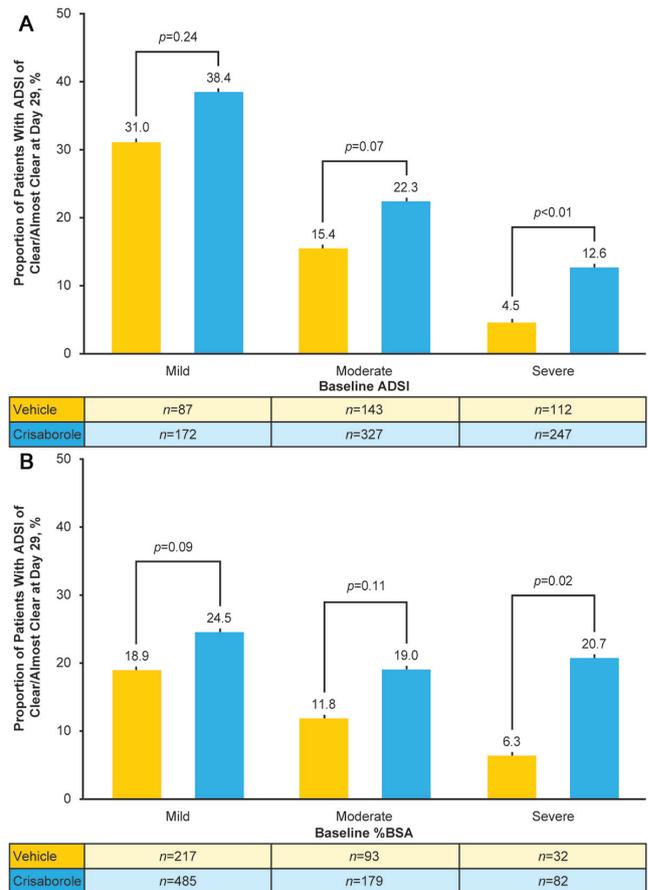

Fig. 4. Proportion of patients with Atopic Dermatitis Severity Index (ADSI) score of clear/almost clear at day 29 by baseline ADSI[a] (A) and baseline percentage of treatable body surface area (%BSA)[b] (B) (pooled AD-301 and AD-302). [a]ADSI scores were stratified according to following severity bands: clear/almost clear (0–<2), mild (2–<6), moderate (6–<9), and severe (9–15) (18). Analysis was conducted among patients with baseline ADSI >1. [b]%BSA was stratified according to the following severity bands: clear (0), mild (>0–<16), moderate (16–<40), and severe (40–100) (18).

Fig. 3. Mean change in Atopic Dermatitis Severity Index (ADSI) score from baseline over time (pooled AD-301 and AD-302).
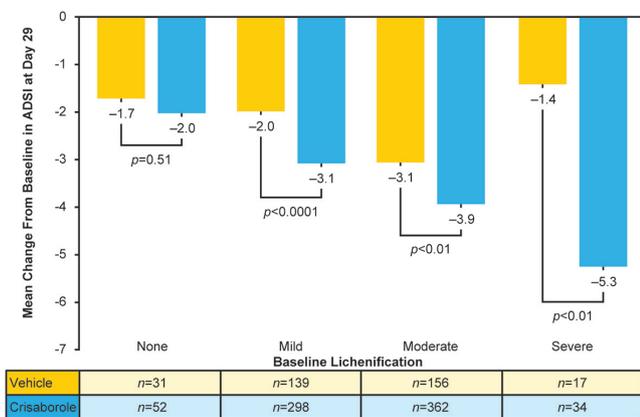
Fig. 5. Change from baseline in Atopic Dermatitis Severity Index (ADSI) score at day 29 by baseline lichenification (pooled AD-301 and AD-302).

regardless of baseline ADSI severity; however, for ISGA success, differences between crisaborole and vehicle were only observed for patients with severe baseline ADSI score (**Fig. 6**).

Percentage of treatable body surface area

Mean %BSA decreased from 18.3% at baseline to 10.6% at day 29 in crisaborole-treated patients and 18.1% to 13.6% in vehicle-treated patients. Mean change (95% CI) in %BSA at day 29 was significantly greater in crisaborole-treated patients than vehicle-treated patients (–7.43 [–8.22 to –6.64] vs. –4.44 [–5.55 to –3.33]; $p < 0.0001$). The proportion of patients with %BSA improvement at day 29 was significantly greater in the crisaborole-treated group than the vehicle-treated group (27.6% vs. 19.7%; $p < 0.001$). When analyzing ISGA outcomes by baseline %BSA severity, significantly more patients with mild or moderate baseline %BSA who were treated with crisaborole than those treated with vehicle achieved success in ISGA at day 29. Similarly, significantly more patients with baseline %BSA severity of mild or moderate treated with crisaborole compared with vehicle achieved ISGA clear or almost clear at day 29 (**Fig. 7**).

Correlations

ADSI score was significantly correlated with several treatment outcomes, such as ISGA, %BSA, SPS, DLQI, and CDLQI at baseline and at day 29 (**Table II**). Likewise, %BSA was significantly correlated with ISGA, SPS, DLQI, and CDLQI at baseline and day 29 (Table II).

DISCUSSION

In this *post hoc* analysis of pooled data from AD-301 and AD-302, crisaborole showed improvement in disease based on ADSI and %BSA. With use of crisaborole, greater decreases from baseline were seen in mean ADSI score and mean %BSA at day 29 compared with
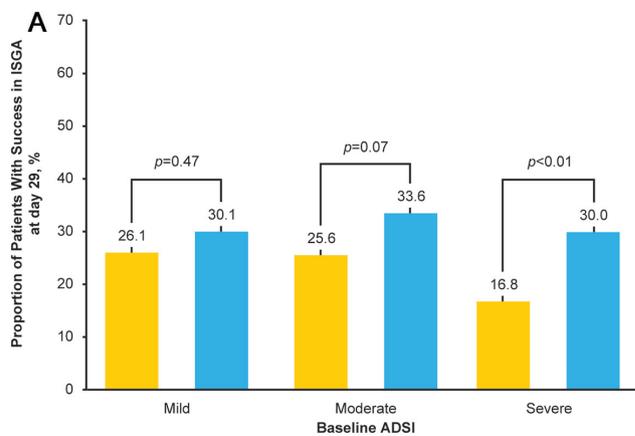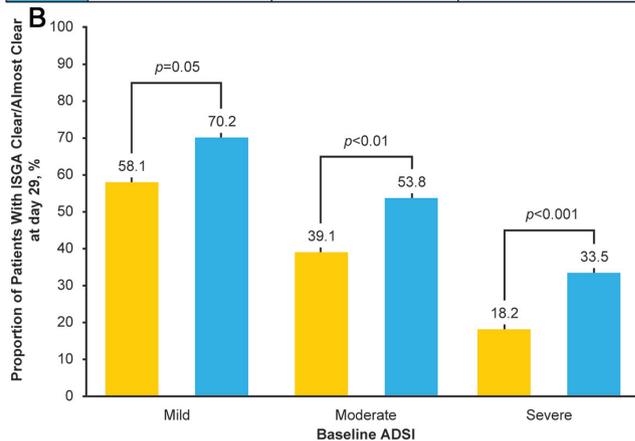
Fig. 6. Proportion of patients with (A) success in Investigator's Static Global Assessment (ISGA)[a] and (B) ISGA clear or almost clear at day 29 by baseline Atopic Dermatitis Severity Index (ADSI) severity[b] (pooled AD-301 and AD-302). [a]ISGA success was defined as achieving score of clear (0) or almost clear (1) with a 2-grade or more improvement from baseline. [b]ADSI scores were stratified according to following severity bands: clear/almost clear (0–<2), mild (2–<6), moderate (6–<9), and severe (9–15) (18).

vehicle, and greater proportions of patients treated with crisaborole experienced improvement in ADSI score and %BSA. Change from baseline in ADSI score was greater for crisaborole-treated patients than vehicle-treated patients, even with increasing levels of lichenification at baseline. Lichenification is often resistant to treatment (19) because it may contribute to poorer dermal penetration of topically applied drugs; however, in this analysis, crisaborole-treated patients with severe lichenification had the greatest improvement in ADSI score, whereas in those with no lichenification, no significant difference was observed. These results may also be influenced by lower ADSI overall scores at baseline for patients with no lichenification and/or small sample sizes. Nevertheless, the efficacy of crisaborole in patients with lichenification warrants further prospective study.

Many constructs are used to measure AD severity, such as SCORAD, EASI, I(S)GA, and SASSAD (4, 5). The
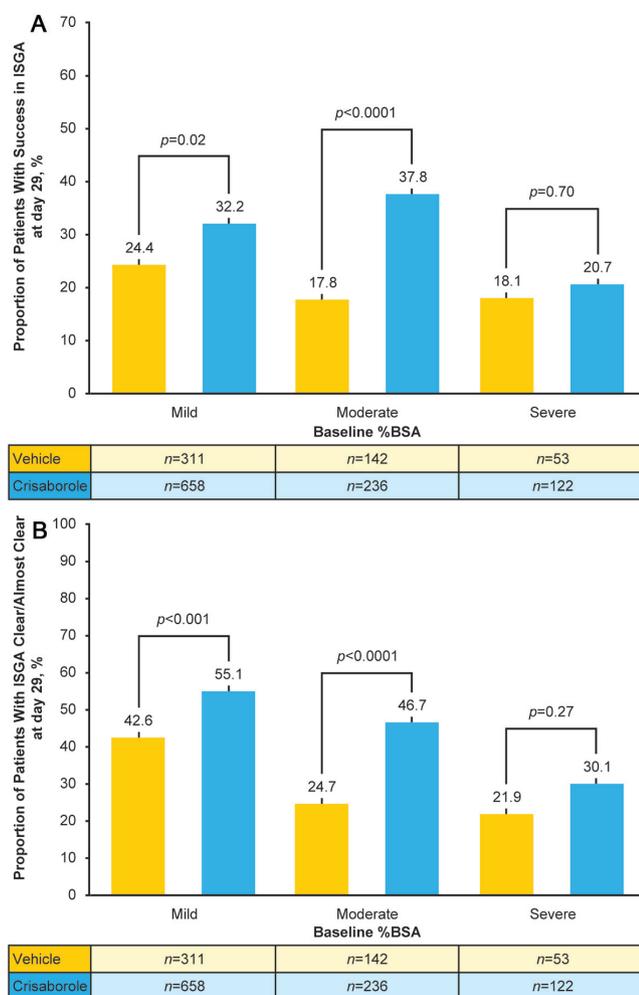
Fig. 7. Proportion of patients with (A) success in Investigator's Static Global Assessment (ISGA)[a] and (B) ISGA clear or almost clear at day 29 by baseline percentage of treatable body surface area (%BSA) severity[b]. [a]ISGA success was defined as achieving score of clear (0) or almost clear (1) with a 2-grade or more improvement from baseline, [b]%BSA was stratified according to the following severity bands: clear (0), mild (> 0–< 16), moderate (16–< 40), and severe (40–100) (18).

Table II. Spearman rank correlations for Atopic Dermatitis Severity Index (ADSI) and percentage of treatable body surface area (%BSA) with other outcomes

Outcome	Baseline			Day 29		
	n	Corr.	*p*-value	*n*	Corr.	*p*-value
ADSI correlation with						
ISGA	1,344	0.615	< 0.0001	1,238	0.852	< 0.0001
%BSA	1,344	0.264	< 0.0001	1,237	0.673	< 0.0001
SPS[a]	1,344	0.571	< 0.0001	1,238	0.680	< 0.0001
DLQI	248	0.377	< 0.0001	240	0.544	< 0.0001
CDLQI	1,062	0.376	< 0.0001	981	0.576	< 0.0001
%BSA correlation with						
ISGA	1,522	0.327	< 0.0001	1,415	0.727	< 0.0001
SPS[a]	1,344	0.167	< 0.0001	1,237	0.385	< 0.0001
DLQI	284	0.162	0.006	271	0.367	< 0.0001
CDLQI	1,200	0.161	< 0.0001	1,122	0.410	< 0.0001

[a]SPS correlations based on week 4 data.
CLDQI: Children's DLQI; DLQI: Dermatology Life Quality Index; ISGA: Investigator's Static Global Assessment; SPS: Severity of Pruritus Scale; Corr.: correlation.

Harmonising Outcomes in Eczema (HOME) Initiative recommends EASI followed by SCORAD as the preferred assessments of AD signs in clinical trials (20). However, the US Food and Drug Administration requires I(S)GA as the primary endpoint in clinical trials of treatments for AD (21); therefore, it was used in the primary analyses for AD-301 and AD-302. However, I(S)GA omits 2 of the most important aspects of the disease – pruritus and extent of disease (i.e., %BSA). The EASI includes a component that addresses %BSA but not pruritus. Although the ADSI does not include extent of disease, it includes an assessment of pruritus, is relatively simple to calculate, and correlated well with ISGA and %BSA in this analysis. Thus, in the absence of the EASI, the ADSI can be used to assess AD severity. AD-301 and AD-302 included patients with mild-to-moderate AD per ISGA assessment alone. However, our analysis showed that many patients could be classified as having more severe disease per the ADSI and/or %BSA, based on recently established severity bands (18). Because of the bands determined for the ADSI, a patient with moderate severity (score=2) in all 5 components of the ADSI would be considered to have an ADSI score of severe. This characteristic is similar to that seen with the EASI and SCORAD, where a patient with widespread or extensive disease may be classified as having severe disease even if individual symptoms are moderate. Despite the inclusion of patients with more severe disease per the ADSI or %BSA, the use of crisaborole triggered significant improvement in ADSI score and %BSA compared with vehicle at day 29. Similarly, a greater proportion of patients who received crisaborole experienced improvement in these measures than those who received vehicle, regardless of baseline disease severity measured by the ADSI or %BSA. Only crisaborole-treated patients with severe baseline ADSI scores had a significantly higher rate of achievement of ISGA success at day 29 than vehicle-treated patients, but not those with mild or moderate baseline ADSI score, whereas patients with mild or moderate baseline %BSA had higher rates of ISGA success with crisaborole, but not those with severe baseline %BSA. Possible explanations for these results could be the small sample sizes or challenges in adequately treating extensive disease with a topical medication, particularly for those with severe baseline %BSA. Considering the ≥ 2-grade improvement from baseline criteria included in the definition of ISGA success, it is more difficult for patients with mild disease (per ISGA) to achieve this endpoint than it is for those with moderate disease. This may translate to patients with mild or moderate ADSI scores at baseline also having more difficulty achieving ISGA success.

Use of crisaborole has previously shown improvement per the ADSI in other phase 2 trials (13, 14). In one of these, patients with AD lesions and ADSI scores ranging from 6 to 12 (moderate to severe with new ADSI severity

banding) experienced a 71% improvement from baseline after 29 days of treatment with crisaborole twice daily (13). Between those phase 2 studies, mean ADSI score with crisaborole was 8.2 at baseline and 2.4 at day 29 in one study (13) and 8.3 at baseline and 2.4 at day 28 in the other (14). Similarly, in this *post hoc* analysis of the AD-301 and AD-302 studies, mean ADSI score was 7.4 at baseline and 3.9 at day 29. However, these ADSI results from the phase 2 studies were for a target lesion rather than the whole-body assessment, as used in this analysis.

As with any *post hoc* analysis, these results are limited by not being powered a priori to detect a significant difference in ADSI scores between treatments. In addition, the ADSI has not been validated; however, pruritus was assessed using a validated measure (15).

This *post hoc* analysis confirms the effectiveness of crisaborole in alleviating AD severity as assessed by both the ADSI and %BSA and allows the results to be put into context of the previous phase 2 trials. This analysis also supports the use of the ADSI to measure AD severity, although further psychometric evaluation is necessary.

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