Relationship Among Treatment, Pruritus, Investigator's Static Global Assessment, and Quality of Life in Patients with Atopic Dermatitis

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ABSTRACT

Introduction: The Investigator's Static Global Assessment (ISGA) is a 5-point rating scale that is recommended by the US Food and Drug Administration for assessing the severity of atopic dermatitis (AD), and ISGA success is a widely used endpoint in AD clinical studies. In this study, we seek to interpret the relationship of ISGA with treatment, pruritus, and quality of life (QoL) by conducting post hoc analyses of pooled data from two phase 3 crisaborole studies.

Methods: Patients aged $\geq$ 2 years with baseline ISGA of 2 (mild) or 3 (moderate) were randomly assigned 2:1 to receive crisaborole or vehicle for 28 days. Disease severity, pruritus severity, and QoL were assessed with the ISGA, Severity of Pruritus Scale (SPS), and Dermatology Life Quality Index (DLQI; patients aged $\geq$ 16 years), or Children's Dermatology Life Quality Index (CDLQI; patients aged 2–15 years), respectively. The effect of treatment on ISGA and the relationship between ISGA and QoL were analyzed using a longitudinal repeated-measures model. The interrelationship between treatment, disease severity, pruritus, and QoL was analyzed with a mediation model.

Results: Overall, 1522 patients (crisaborole, $n = 1016$; vehicle, $n = 506$) were included. Estimated longitudinal profiles indicated changes

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in ISGA by day 8 were large for crisaborole (effect size [ES]: − 0.68) and small for vehicle (ES: − 0.34). There was a direct relationship between ISGA and DLQI and CDLQI severity bands in the longitudinal repeated-measures model. For both QoL mediation models, treatment effects on QoL were mediated indirectly by reduction in pruritus (DLQI, 42.4%; CDLQI, 58.1%) and disease severity (DLQI, 12.2%; CDLQI, 33.1%).

Conclusions: These post hoc analyses suggest that ISGA success is a clinically meaningful endpoint associated with reduction in the severity of pruritus and improvement in QoL.

Keywords: Atopic dermatitis; Children's Dermatology Life Quality Index; Crisaborole; Dermatology Life Quality Index; Investigator's Static Global Assessment; Pruritus; Quality of life

Key Summary Points

Why carry out this study?

Although the US Food and Drug Administration's preferred assessment of atopic dermatitis (AD) severity is Investigator's Static Global Assessment (ISGA) success (clear [0] or almost clear [1] with ≥ 2-grade improvement from baseline), no studies explore the relevance of this endpoint in clinical practice.

The objective of these post hoc analyses was to interpret the relationship of ISGA with treatment, pruritus, and quality of life (QoL) using pooled data from two identically designed phase 3 clinical studies of crisaborole ointment, 2%, versus vehicle in patients aged ≥ 2 years with mild-to-moderate AD.

What was learned from the study?

An approximately linear relationship exists between ISGA and QoL for patients with mild-to-moderate AD treated with crisaborole ointment, 2%.

The effect of crisaborole treatment on QoL was mostly mediated indirectly through reduction of pruritus, along with a smaller indirect contribution from reduction in AD severity, with differences in the magnitude of the effects among patients aged 2–15 years and patients aged ≥ 16 years.

The results of these post hoc analyses suggest that ISGA success is a clinically meaningful endpoint.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14035295.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by eczematous lesions and pruritus; it occurs in 15–30% of children and 2–10% of adults worldwide [1, 2]. AD is associated with substantial comorbidity and impairment in patient and caregiver quality of life (QoL) [3, 4].

The Investigator's Static Global Assessment (ISGA), a 5-point rating scale that measures overall disease severity from clear (0) to severe (4) [5], is recommended by the US Food and Drug Administration for the assessment of AD severity [6]. ISGA success, commonly defined as clear (0) or almost clear (1) skin with ≥ 2-grade improvement from baseline, is a widely used endpoint in AD clinical studies [5, 7]. However, this measure does not account for pruritus, one of the most prominent and bothersome symptoms of AD, or for percentage of affected body surface area (%BSA) [8, 9].

The ISGA has been used to assess the efficacy of crisaborole ointment, 2%, a nonsteroidal phosphodiesterase 4 inhibitor, in patients aged ≥ 2 years with mild-to-moderate AD. In two

identically designed phase 3 clinical studies (CrisADe CORE 1: AD-301, NCT02118766; CrisADe CORE 2: AD-302, NCT02118792), more crisaborole-treated than vehicle-treated patients achieved the primary endpoint of ISGA success at day 29, defined as clear or almost clear skin with $\geq$ 2-grade improvement from baseline. Similarly, more crisaborole-treated than vehicle-treated patients achieved the secondary endpoint of ISGA clear or almost clear at day 29 [5]. Furthermore, significantly greater proportions of crisaborole-treated patients experienced improvement in pruritus compared with vehicle-treated patients through week 4 as assessed by the Severity of Pruritus Scale (SPS), a 4-point rating scale that measures pruritus severity from none (0) to severe (3) [10]. Treatment with crisaborole has also improved QoL [11].

Although crisaborole-treated patients attained ISGA success in a statistically significant manner compared with vehicle-treated patients, to date no studies have explored the relevance of this endpoint in clinical practice. A better understanding of how the ISGA relates to the various domains of AD burden would improve a clinician's ability to interpret and communicate study results in a more meaningful way. The objective of the post hoc analyses reported here was to interpret the relationship of ISGA with treatment, pruritus, and QoL using pooled data from the two phase 3 crisaborole studies.

METHODS

Study Design

CrisADe CORE 1 and CrisADe CORE 2 were identically designed, vehicle-controlled, double-blind, phase 3 trials to assess the efficacy and safety of crisaborole in patients aged $\geq$ 2 years with mild-to-moderate AD [5]. Eligible patients had a clinical diagnosis of AD, %BSA involvement $\geq$ 5 (excluding the scalp), and baseline ISGA of mild (2) or moderate disease severity (3). Patients were randomly assigned 2:1 to receive crisaborole or vehicle, with instructions to apply the study drug to affected skin twice daily for 28 days. Efficacy and safety

were assessed during study visits on days 1 (baseline), 8, 15, 22, and 29 (end of treatment). Disease severity was assessed at baseline and at each study visit with the ISGA (Table 1) [5]. Pruritus severity was recorded via electronic diary twice daily by the patient or caregiver from baseline through day 29 before the study drug was applied, using the SPS (Electronic Supplementary Material [ESM] Table S1) [5, 10]. QoL was measured at baseline and day 29 using the Dermatology Life Quality Index (DLQI) in patients aged $\geq$ 16 years or the Children's Dermatology Life Quality Index (CDLQI) in patients aged 2–15 years; the DLQI and CDLQI are 10-item questionnaires that measure impact on QoL, from not at all (0) to very much (3), with a final total score ranging from 0 to 30 and higher scores indicating greater impairment in QoL (ESM Table S2) [12, 13].

This was a post hoc analysis of previously conducted studies and was exempt from institutional review board approval. All patients or parent(s)/guardian(s) provided written informed consent for participation in the studies. The studies were approved by Quorum Review Institutional Review Board and were conducted in accordance with the ethical principles originating in the Declaration of Helsinki.

Longitudinal Analysis

To further elucidate the effect of crisaborole treatment on ISGA, an analysis using longitudinal repeated-measures models for individual studies and pooled data was conducted [14, 15]. Standardized effect size (ES) was used to gauge the strength of the treatment effect (i.e., the difference in the mean for crisaborole vs. vehicle, or the difference from baseline for crisaborole or vehicle expressed in standard deviation [SD] units). ISGA was the main entry criteria in these studies and inevitably attenuated the SD for the ISGA score. As such, ES was calculated by dividing the mean change from baseline by the largest SD across studies and time points [16]. The largest SD came from the vehicle arm of both studies at day 29. A standardized ES of 0.1 was considered to be trivial, 0.2 to be small, 0.5 to be medium, and 0.8 to be

Table 1 Investigator's Static Global Assessment [5] (Reprinted from [5]; copyright 2016; with permission from Elsevier)

Scale	Grade	Definition
0	Clear	Minor residual hypopigmentation/hyperpigmentation; no erythema or induration/papulation; no oozing/crusting
1	Almost clear	Trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting
2	Mild	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate	Pink-red erythema with moderate induration/papulation with or without oozing/crusting
4	Severe	Deep or bright red erythema with severe induration/papulation and with oozing/crusting

large [17, 18]. Midpoints between values of 0.1, 0.2, 0.5, and 0.8 were used to create categorization intervals for ES.

Relationship Between ISGA and QoL

To interpret the relationship between ISGA and QoL, established DLQI and CDLQI severity bands ranging from "no effect on a patient's life" to an "extremely large effect on a patient's life" [19, 20] were used. All analyses were performed on the pooled intent-to-treat population of both studies, which included all patients who were randomly assigned to receive and were dispensed study drug. A longitudinal repeated-measures model [14, 15] was used to estimate relationships between ISGA as the predictor and QoL as the outcome using data from baseline and day 29 (with DLQI and CDLQI in separate analyses). To study the appropriateness of the linear approximation of the relationship between predictor and outcome, a model in which the predictor (ISGA) was used as a categorical variable was performed as a sensitivity analysis. This model did not impose any functional relationship between outcome and predictor.

Mediation Modeling

To determine the impact of treatment on QoL, a statistical mediation model was used and measured with DLQI or CDLQI (ESM Fig. S1) [14, 21]. In this mediation model, the independent variable was crisaborole treatment; the mediator variables were pruritus severity measured with SPS and disease severity measured with ISGA (day 29); the outcome variable was QoL measured with DLQI or CDLQI (day 29; 1-week recall). The mediation model also included a direct effect of crisaborole on QoL, which represented all of the effects of crisaborole on DLQI or CDLQI other than those mediated via pruritus or disease severity. SPS was calculated as an average of all available scores for every patient during week 4 to be consistent with the 1-week recall period of DLQI/CDLQI. All available data were used, and no imputation of missing data was performed.

RESULTS

Patient Demographics and Disposition

In total, 1522 patients were included in both studies, of whom 1016 were randomly assigned to receive crisaborole and 506 were randomly assigned to receive vehicle. Demographics and baseline disease characteristics were balanced between the pooled treatment arms (Table 2). The mean age of patients in both groups was approximately 12.2 years; most patients (80.2% for crisaborole and 81.4% for vehicle) were aged 2–15 years. Most patients (61.3% for crisaborole and 61.9% for vehicle) had moderate AD according to the ISGA. Overall, 903 and 441 patients had ≥ 2 available baseline pruritus measurements in the pooled crisaborole and

Table 2 Demographics and baseline disease characteristics

Demographics and baseline disease characteristics	Crisaborole arm ($N = 1016$)	Vehicle arm ($N = 506$)
Age, mean (range), years	12.3 (2–79)	12.1 (2–79)
Age group, n (%)		
2–15 years	815 (80.2)	412 (81.4)
$\geq$ 16 years	201 (19.8)	94 (18.6)
Sex, n (%)		
Male	450 (44.3)	225 (44.5)
Female	566 (55.7)	281 (55.5)
Race, n (%)		
White	617 (60.7)	306 (60.5)
Black or African American	285 (28.1)	139 (27.5)
Asian	52 (5.1)	27 (5.3)
American Indian or Alaskan Native	11 (1.1)	5 (1.0)
Hawaiian or other Pacific Islander	7 (0.7)	8 (1.6)
Other	44 (4.3)	21 (4.2)
Ethnicity, n (%)		
Hispanic or Latino	200 (19.7)	101 (20.0)
Not Hispanic or Latino	816 (80.3)	405 (80.0)
ISGA[a], n (%)		
Mild (score 2)	393 (38.7)	193 (38.1)
Moderate (score 3)	623 (61.3)	313 (61.9)
SPS score[b,c], n (%)	$N = 903$	$N = 441$
None (score 0)	35 (3.9)	19 (4.3)
Mild (score 1)	229 (25.4)	119 (27.0)
Moderate (score 2)	331 (36.7)	167 (37.9)
Severe (score 3)	308 (34.1)	136 (30.8)
%BSA, mean $\pm$ SD (range)	18.3 $\pm$ 18.02 (5–95)	18.1 $\pm$ 17.33 (5–90)
DLQI total score[d,e]	$N = 192$	$N = 92$
Mean $\pm$ SD	9.7 $\pm$ 6.29	9.3 $\pm$ 6.55
CDLQI total score[d,f]	$N = 797$	$N = 403$

Table 2 continued

Demographics and baseline disease characteristics	Crisaborole arm ($N = 1016$)	Vehicle arm ($N = 506$)
Mean ± SD	9.3 ± 5.99	9.0 ± 6.02

%BSA Percentage of treatable body surface area, *CDLQI* Children's Dermatology Life Quality Index, *DLQI* Dermatology Life Quality Index, *ISGA* Investigator's Static Global Assessment, *QoL* quality of life, *SPS* Severity of Pruritus Scale

[a] ISGA score ranges from clear (0) to severe (4)

[b] SPS score ranges from none (0) to severe (3)

[c] Baseline SPS was the mean of at least two SPS assessments on day 1. Patients with < 2 SPS assessments on day 1 were considered to have missing data

[d] DLQI and CDLQI scores range from 0 to 30, with a higher score indicating more impairment in QoL

[e] For patients aged ≥ 16 years

[f] For patients aged 2–15 years

vehicle groups, respectively. More than 60% of patients in the crisaborole and vehicle arms reported moderate (SPS score 2) or severe (SPS score 3) pruritus. Based on previously established severity bands for DLQI and CDLQI [19, 20], mean baseline DLQI and CDLQI scores indicated that patients in the pooled studies reported a moderate effect of AD on their QoL at baseline.

Longitudinal Analysis

Compared with vehicle, crisaborole resulted in a greater improvement from baseline in ISGA at all time points in both studies and in the pooled population (Table 3). Mean improve-ments from baseline were significantly greater and differences between crisaborole and vehicle were statistically significant starting at the first postbaseline assessment (day 8). These improvements were generally consistent between the two studies and in the pooled population of the studies (Table 3).

Crisaborole significantly reduced overall AD severity compared with vehicle, beginning at the first postbaseline assessment (day 8) and continuing through day 29 (Fig. 1). Using the largest SD of 1.06, the change from baseline in mean ISGA score for crisaborole on day 8 can be interpreted in terms of the ES as large and continued to improve through day 29; the improvement in mean ISGA score corresponded

Table 3 Least-squares mean change from baseline in ISGA

Postbaseline assessment	CORE 1 trial		CORE 2 trial		Pooled results	
	Crisaborole arm	Vehicle arm	Crisaborole arm	Vehicle arm	Crisaborole arm	Vehicle arm
Day 8	− 0.73*[†]	− 0.36*	− 0.71*[†]	− 0.35*	− 0.72*[†]	− 0.36*
Day 15	− 0.97*[†]	− 0.58*	− 0.82*[†]	− 0.42*	− 0.89*[†]	− 0.51*
Day 22	− 1.05*[†]	− 0.68*	− 0.91*[†]	− 0.46*	− 0.98*[†]	− 0.57*
Day 29 (end of treatment)	− 1.08*[†]	− 0.77*	− 0.98*[†]	− 0.49*	− 1.03*[†]	− 0.63*

*Significant difference at $p < 0.0001$ vs. baseline; [†]Significant difference at $p < 0.0001$ vs. vehicle
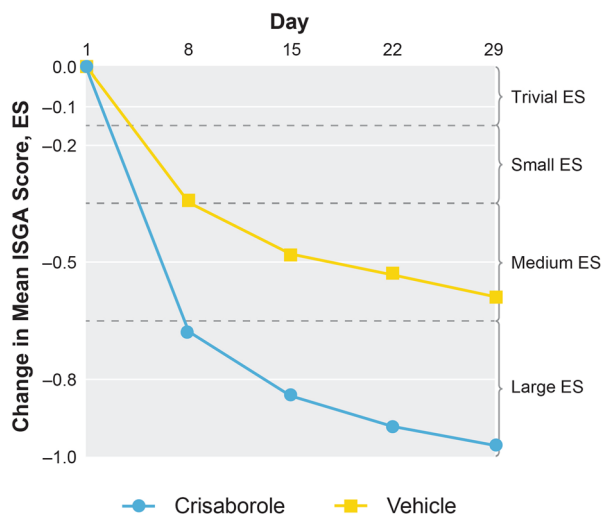
Fig. 1 Effect size (*ES*) of the mean change from baseline in the Investigator's Static Global Assessment (*ISGA*) score (CORE 1 and CORE 2 data pooled).[a] A standardized ES of 0.1 was considered to be trivial, 0.2 to be small, 0.5 to be medium, and 0.8 to be large. Midpoints between values of 0.1, 0.2, 0.5, and 0.8 were used to create categorization intervals for ES. [a]Least-squares means are statistically significant ($p < 0.0001$)

to an ES of − 1.0 by day 29. The change from baseline in mean ISGA score in the vehicle arm on day 8 can be interpreted in terms of the ES as small, improving to medium by day 29; the

improvement in mean ISGA score corresponded to an ES of − 0.6 by day 29.

Relationship of ISGA and QoL

There was an approximately linear relationship between ISGA and DLQI or CDLQI total scores (Fig. 2a, b). The sensitivity analysis using ISGA as a categorical variable confirmed the results of the continuous model (Fig. 2a, b). The relationship between ISGA and patient QoL was nearly identical for DLQI and CDLQI (Fig. 2c).

Linking of severity bands for DLQI and CDLQI with ISGA demonstrated that greater global disease severity was associated with worse QoL (Fig. 3a, b). For DLQI, an ISGA of clear (0) corresponded to "no negative effect on patient's life," an ISGA of almost clear (1) corresponded to "small effect on patient's life," an ISGA of mild (2) or moderate (3) corresponded to "moderate effect on patient's life," and an ISGA of severe (4) corresponded to "very large effect on patient's life" (Fig. 3a). For CDLQI, an ISGA of clear (0) corresponded to "no negative effect on patient's life," an ISGA of almost clear (1) or mild (2) corresponded to "small effect on patient's life," and an ISGA of moderate (3) or severe (4) corresponded to "moderate effect on patient's life" (Fig. 3b).
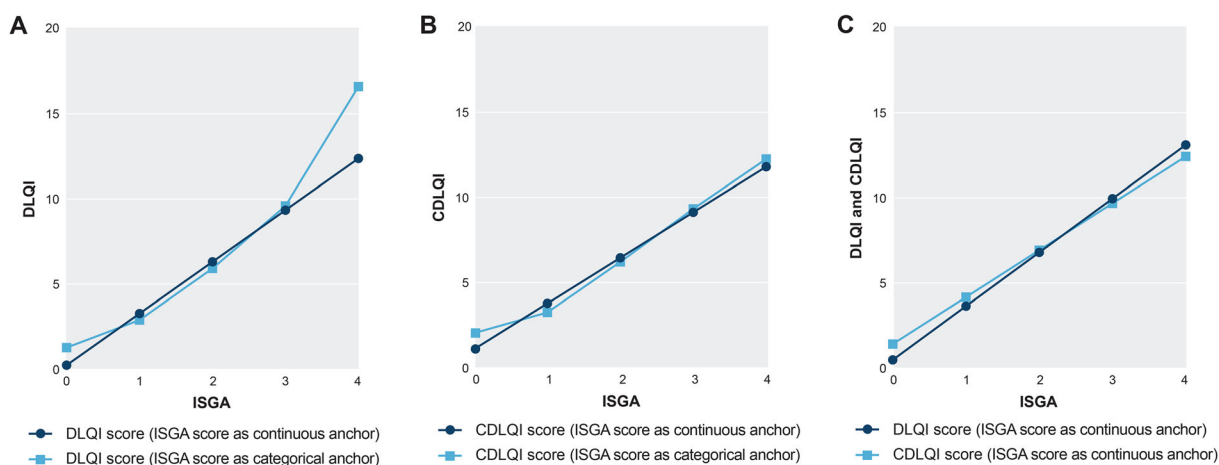
Fig. 2 Relationship between the ISGA and **a** the Dermatology Life Quality Index (*DLQI*) (with ISGA as continuous and categorical anchor) and **b** the Children's Dermatology Life Quality Index (*CDLQI*) (with ISGA as continuous and categorical anchor), and **c** comparison between DLQI and CDLQI (with ISGA as continuous anchor)
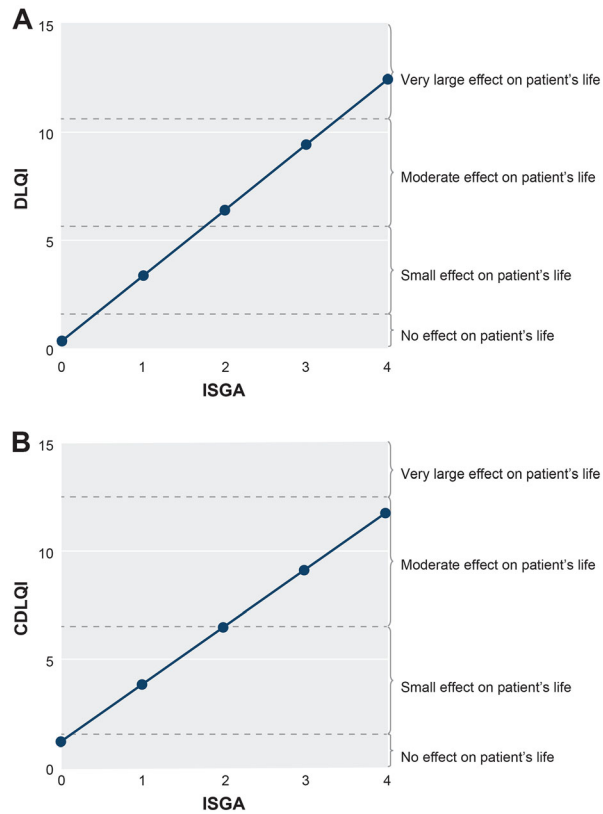
Fig. 3 Effect of ISGA on quality of life (*QoL*) as measured by **a** DLQI and **b** CDLQI severity bands

Mediation Modeling

In the DLQI-based mediation model ($N = 266$), 54.6% of the treatment effect on QoL was mediated indirectly by the reduction in severity of pruritus (42.4%; $p = 0.03$; as measured by SPS) and disease severity (12.2%; $p = 0.17$; as measured by ISGA); the direct effect of treatment on DLQI was 45.4% ($p = 0.06$) (Fig. 4a). In the CDLQI-based mediation model ($N = 1112$), 91.2% of the treatment effect on QoL was mediated indirectly by the reduction in severity of pruritus (58.1%; $p < 0.0001$) and disease severity (33.1%, $p < 0.0001$); the direct effect of treatment on CDLQI was 8.9% ($p = 0.6$) (Fig. 4b).
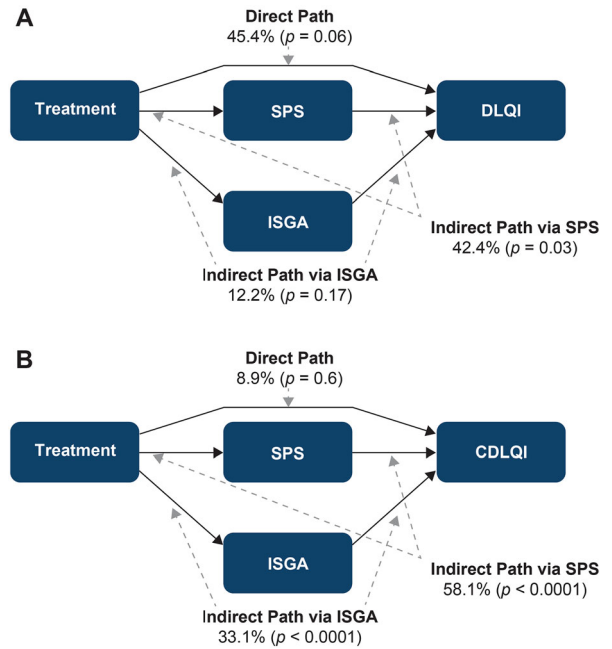
Fig. 4 Mediation models for the relationship between crisaborole treatment, ISGA, Severity of Pruritus Scale (*SPS*), and **a** DLQI or **b** CDLQI

DISCUSSION

Crisaborole improved AD severity, pruritus, and QoL in significantly more patients than vehicle in both phase 3 studies [5, 10, 11]. The post hoc analyses presented herein suggest that ISGA success is a clinically meaningful endpoint. The patients who reached this endpoint in the CORE 1 and CORE 2 studies experienced significant reductions in itch and impact on QoL. Although not all patients achieved ISGA success, our analyses reveal that patients can have an average reduction of 1 point on the ISGA scale with crisaborole use; this is clinically meaningful and corresponds to a large ES in statistical terms. Finally, we show that improvement in QoL with crisaborole occurs primarily via itch and reduction of signs of AD. These data improve our understanding of the ISGA and help translate clinical trial data into AD patient-centric outcomes, which can be used to engage patients in shared decision-making.

In the longitudinal analysis, ISGA improved significantly from baseline with both

crisaborole and vehicle. Some effect from vehicle alone is anticipated because vehicles can have properties that lead to improvement of signs and symptoms of AD. However, the change from baseline in mean ISGA for crisaborole in terms of ES was large, starting at the first postbaseline assessment (day 8) and continuing through day 29 (end of treatment), whereas, in the vehicle group, the ES was small at day 8 and medium by day 29. These findings were consistent with the significant improvement in SPS observed with crisaborole treatment at all weekly time points of the CORE 1 and CORE 2 studies; effect sizes at week 4 for CORE 1 and CORE 2 (0.40 and 0.33, respectively) suggested a small to medium effect [10].

There was an approximately linear relationship between ISGA and QoL as measured by DLQI or CDLQI, suggesting that improvements in ISGA for crisaborole treatment were related to improvements in QoL. The departures from linearity for ISGA of clear (0) or severe (4) relate to the small number of available observations. Although patients had an ISGA of mild or moderate at baseline, a few patients experienced deterioration of AD symptoms during the study ($n = 67$, 4.7%), which explains why patients with an ISGA of severe (4) were observed in this analysis. Although the relationship between ISGA and patient QoL was nearly identical for DLQI and CDLQI, the interpretation of ISGA scores based on DLQI and CDLQI severity bands were different. In the DLQI severity band analysis, an ISGA of mild or moderate corresponded to a "moderate effect on patient's life," whereas an ISGA of severe corresponded to "very large effect on patient's life." However, in the CDLQI severity band analysis, an ISGA of mild corresponded to a "small effect on patient's life," whereas an ISGA of moderate or severe corresponded to a "moderate effect on patient's life." DLQI and CDLQI also have different cutoff scores to represent the same severity categories. This difference in the relationship between disease severity and QoL in patients aged 2–15 years versus patients aged $\geq$ 16 years could be related to differences in personal relationships, leisure, sleep, and daily activity scales of DLQI and CDLQI and their impact on severity bands; a different capacity of younger versus older patients to cope with AD; or a combination of the two. Taken together, these results provide a qualitative and quantitative assessment of how reduction in AD severity (as measured by ISGA) improves patient QoL and adds to our current understanding of the linear relationship between pruritus severity (measured with SPS) and QoL [22]. The results of these analyses also suggest a direct relationship between reduction of disease severity (measured by ISGA) and improvement of QoL (measured with DLQI or CDLQI). Direct factors may also include psychosocial factors, soreness, pain, stinging, and treatment challenges.

In mediation analysis, the overall indirect effect of treatment on QoL was largely mediated via reduction in pruritus (measured with SPS), with a smaller contribution from reduction in disease severity (measured with ISGA). Previous mediation modeling in the CORE 1 and CORE 2 studies showed that crisaborole improved QoL by an indirect effect through the reduction in severity of pruritus (measured with SPS) [23]. These analyses highlight the interplay between patient- and caregiver-reported assessments of QoL and pruritus and clinician-reported global assessment of AD severity.

Differences in results between the DLQI and CDLQI mediation models suggest that AD treatment impacts patients aged 2–15 years and patients aged $\geq$ 16 years in different ways. In both mediation models, the greatest contribution to improvement in QoL was the indirect effect from reduction in severity of pruritus, with a smaller indirect contribution from reduction in disease severity. However, the impact of the indirect effect of disease severity was larger in the CDLQI-based model than in the DLQI-based model, suggesting that, for patients aged 2–15 years, improvement in disease severity has a larger indirect effect on QoL than for patients aged $\geq$ 16 years.

These analyses were limited by their post hoc nature. The patient population was limited to those with mild-to-moderate AD at baseline. Therefore, results may not be generalizable to patients with severe AD, although the analysis included a limited number of patients who experienced deterioration of their symptoms to severe AD during the course of the study.

Furthermore, mediation models and other forms of structural equation models cannot prove causation and can only determine whether the hypothesized causal inferences by a researcher are consistent with the data. In addition, CDLQI is validated for patients aged 4–16 years; in this study, it was used in patients aged 2–16 years.

CONCLUSION

These analyses explored the relationship between patient- and caregiver-reported assessments of QoL (DLQI and CDLQI) and pruritus (SPS) with a clinician-reported global assessment of severity of AD (ISGA). An approximately linear relationship exists between ISGA and QoL for patients with mild-to-moderate AD treated with crisaborole. However, the effect of crisaborole treatment on QoL was mostly mediated indirectly through a reduction in the severity of pruritus (SPS), along with a smaller indirect contribution from reduction in AD severity (ISGA). Differences in the magnitude of the effects were noted in patients aged 2–15 years and patients aged ≥ 16 years.

ACKNOWLEDGEMENTS

parent(s)/guardian(s) provided written informed consent for participation in the studies. The studies were approved by Quorum Review Institutional Review Board and were conducted in accordance with the ethical principles originating in the Declaration of Helsinki.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available. Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the USA and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

REFERENCES

1. Bieber T. Atopic dermatitis. N Engl J Med. 2008;358(14):1483–94.

2. Blume-Peytavi U, Metz M. Atopic dermatitis in children: management of pruritus. J Eur Acad Dermatol Venereol. 2012;26(Suppl 6):2–8.

3. Carroll CL, Balkrishnan R, Feldman SR, Fleischer AB Jr, Manuel JC. The burden of atopic dermatitis: impact on the patient, family, and society. Pediatr Dermatol. 2005;22(3):192–9.

4. Ronnstad ATM, Halling-Overgaard AS, Hamann CR, Skov L, Egeberg A, Thyssen JP. Association of atopic dermatitis with depression, anxiety, and suicidal ideation in children and adults: a systematic review and meta-analysis. J Am Acad Dermatol. 2018;79(3):448-56.e30.

5. Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. J Am Acad Dermatol. 2016;75(3):494-503.e6.

6. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. Ann Allergy Asthma Immunol. 2018;120(1):10-22.e2.

7. Hanifin JM, Ellis CN, Frieden IJ, et al. OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): a phase-II randomized, double-blind, placebo-controlled study. J Am Acad Dermatol. 2016;75(2):297–305.

8. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? Clin Rev Allergy Immunol. 2016;51(3):263–92.

9. Silverberg JI, Gelfand JM, Margolis DJ, et al. Patient burden and quality of life in atopic dermatitis in US adults: a population-based cross-sectional study. Ann Allergy Asthma Immunol. 2018;121(3):340–7.

10. Yosipovitch G, Simpson EL, Tan H, et al. Effect of crisaborole topical ointment, 2%, on atopic dermatitis–associated pruritus: an extended analysis of

2 phase 3 clinical trials. Itch. 2018;3:e12 (erratum published in: Itch. 2019;4:e21).

11. Simpson EL, Paller AS, Boguniewicz M, et al. Crisaborole ointment improves quality of life of patients with mild to moderate atopic dermatitis and their families. Dermatol Ther. 2018;8(4):605–19.

12. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)–a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210–6.

13. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol. 1995;132(6): 942–9.

14. Cappelleri JC, Zou KH, Bushmakin AG, Ma J, Alemayehu D, Symonds T. Patient-reported outcomes: measurement, implementation and interpretation. Boca Raton: Chapman and Hall/CRC Press; 2013.

15. Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. 2nd ed. Hoboken: Wiley; 2011.

16. Pinkerton JV, Bushmakin AG, Abraham L, Cappelleri JC, Komm BS. Most bothersome symptom in women with genitourinary syndrome of menopause as a moderator of treatment effects. Menopause. 2016;23(10):1092–101.

17. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale: Lawrence Erlbaum Associates; 1988.

18. Fayers PM, Machin D. Quality of life: the assessment, analysis and reporting of patient-reported outcomes. 3rd ed. Chichester: Wiley; 2016.

19. Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Investig Dermatol. 2005;125(4):659–64.

20. Waters A, Sandhu D, Beattie P, Lewis-Jones S. Severity stratification of Children's Dermatology Life Quality Index (CDLQI) scores. Br J Dermatol. 2010;163(Suppl 1):121.

21. Mackinnon DP. Introduction to statistical mediation analysis. 1st ed. New York: Taylor Francis; 2008.

22. Ständer S, Yosipovitch G, Bushmakin AG, et al. Examining the association between pruritus and quality of life in patients with atopic dermatitis treated with crisaborole. J Eur Acad Dermatol Venereol. 2019;33(9):1742–6.

23. Simpson EL, Yosipovitch G, Bushmakin AG, et al. Direct and indirect effects of crisaborole ointment on quality of life in patients with atopic dermatitis: a mediation analysis. Acta Derm Venereol. 2019;99(9):756–61.