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ORIGINAL ARTICLES

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Improvement in disease severity and pruritus outcomes with crisaborole ointment, 2%, by baseline atopic dermatitis severity in children and adolescents with mild-to-moderate atopic dermatitis

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Abstract

Background/Objectives: Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate atopic dermatitis (AD). This pooled post hoc analysis of two phase 3 trials (NCT02118766, NCT02118792) assessed improvement and time to improvement in Investigator's Static Global Assessment (ISGA) and Severity of Pruritus Scale (SPS) outcomes in pediatric patients with mild-to-moderate AD.

Methods: Patients aged ≥2 years were randomly assigned 2:1 to receive twice-daily crisaborole or vehicle for 28 days. Patients aged 2-17 years were pooled for this analysis. Proportions of patients and time to achieving ISGA success (clear [0] or almost clear [1] with ≥2-grade improvement from baseline), ISGA clear/almost clear, ≥1-grade improvement in ISGA, SPS success (SPS score ≤1 with ≥1-grade improvement), or ≥1-grade improvement in SPS score were analyzed and stratified by baseline ISGA.

Results: At first postbaseline assessment (day 8), significantly higher proportions of crisaborole- than vehicle-treated patients achieved ISGA success, ISGA clear/almost clear, ≥1-grade ISGA improvement, SPS success, or ≥1-grade improvement in SPS regardless of baseline ISGA. Differences were significantly greater over time for all outcomes for patients with moderate baseline ISGA and numerically greater for those with mild baseline ISGA. Median times to ISGA and SPS outcomes were shorter for crisaborole versus vehicle.

Conclusion: Improvement in ISGA and SPS outcomes were observed with crisaborole in pediatric patients with mild-to-moderate baseline AD.

KEYWORDS

atopic dermatitis, pruritus, therapy-topical

1 | INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by acute flares of eczematous pruritic lesions. AD affects as many as 20% of children worldwide[1] and usually begins during the first 5 years of life. Disease presentation has a characteristic age-dependent distribution, with facial, scalp, and extensor involvement seen in infants and young children and predominant flexural involvement occurring in older children.[2] AD is a complex condition that includes interplay of impaired skin barrier function, immune dysregulation, genetic susceptibility, and environmental factors.[2] AD often has long-term implications for physical and mental health.[3,4] The management of AD presents a clinical challenge. Topical treatment options range from the use of creams and emollients to improve skin hydration to the use of topical anti-inflammatory agents to reduce skin inflammation and improve skin barrier function.[5]

Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase4 inhibitor for the treatment of mild-to-moderate AD.[6] In two identically designed phase 3 studies (CrisADe CORE 1: AD-301, NCT02118766; CrisADe CORE 2: AD-302, NCT02118792), twice-daily application of crisaborole for 4 weeks was well tolerated and effective in patients aged ≥2 years with mild-to-moderate AD. In both studies, most (86.0%) crisaborole-treated patients were aged 2-17 years. Within this age group, 38.1% of patients had a mild Investigator's Static Global Assessment (ISGA) at baseline, and 61.9% of patients had a moderate ISGA at baseline.

In the overall populations of the studies, significantly greater proportions of crisaborole-treated than vehicle-treated patients achieved the primary end point of ISGA success (clear [0] or almost clear [1] with ≥2-grade improvement from baseline) at the end of 4 weeks, and significantly greater proportions achieved the secondary end point of an ISGA score of clear or almost clear.[7] More crisaborole-treated patients also experienced improvement in pruritus as assessed by the Severity of Pruritus Scale (SPS),[7] a 4-point rating scale (none [0], mild [1], moderate [2], severe [3]) validated to assess pruritus severity in AD.[8] SPS success (SPS score ≤1 with ≥1-grade improvement from baseline) was achieved by significantly greater proportions of crisaborole-treated than vehicle-treated patients in both studies.[9] In crisaborole-versus-vehicle-treated patients, the incidence of treatment-emergent adverse events (TEAEs) and treatment discontinuation because of adverse events (AEs) were similar. Most TEAEs were mild to moderate in severity, and there were no reports of treatment-related serious AEs.[7]

ISGA success is the primary end point preferred by the US Food and Drug Administration for AD trials.[10] However, this end point excludes many patients with mild AD (ie, to attain ≥2-grade improvement, patients with mild ISGA [2] at baseline must achieve clear ISGA [0], whereas patients with moderate ISGA [3] at baseline only need to achieve almost clear ISGA [1]). Even mild AD imparts a substantial burden, both in terms of impact on patient quality of life because of itching and sleep difficulties that can affect social functioning and mental health, and in terms of economic costs associated with the reduced work productivity that caregivers may experience as well as outpatient expenses.[11] Hence, even smaller improvements in ISGA score may be important to physicians, patients, and caregivers. For these reasons, it is important to assess the efficacy of crisaborole using smaller improvements in ISGA score, especially among children and adolescents, who are most often affected by AD.

This post hoc analysis of pooled data from two phase 3 trials was designed to assess improvement in disease severity (ISGA) and pruritus (SPS) outcomes and the time to achieve these outcomes by baseline AD severity in pediatric patients with mild-to-moderate AD treated with crisaborole or vehicle.

2 | METHODS

2.1 | Study design and population

In these two identically designed, multicenter, randomized, double-blind, vehicle-controlled phase 3 studies, patients aged ≥2 years with mild-to-moderate AD were randomly assigned 2:1 to receive crisaborole or vehicle twice daily applied to all affected treatable areas of the body (except the scalp) for 28 days.[7] There was no upper limit to the percentage of treatable body surface area (%BSA) patients could have. This post hoc analysis included pooled data from patients 2-17 years of age.

The studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization Good Clinical Practice Guidelines. All local regulatory requirements were followed. The studies were approved by institutional review boards or ethics committees at each study site. An internal review committee monitored the safety of patients throughout the studies. All patients provided written informed consent.

2.2 | Outcomes

ISGA outcomes included the proportion of patients achieving ISGA success (defined as clear [0] or almost clear [1] with ≥2-grade improvement from baseline) and time to ISGA success. Additionally, the proportion of patients achieving ISGA clear or almost clear and/or ≥1-grade improvement in ISGA from baseline were evaluated by the investigator at days 8, 15, 22, and 29. SPS outcomes included the proportion of patients achieving SPS success (defined as SPS score ≤1 with ≥1-grade improvement from baseline) and time to SPS success. Additionally, the proportion of patients achieving ≥ 1-grade improvement in SPS score from baseline was evaluated at weeks 1, 2, 3, and 4. SPS was evaluated twice daily through day 29 by the patient or caregiver via electronic diary.

2.3 | Statistical analysis

The proportions of patients achieving ISGA or SPS outcomes were compared via normal approximation.[12] Time-to-event analyses were

assessed using Kaplan-Meier methods and compared using log-rank tests.[12] The proportions of patients achieving SPS outcomes were based on weekly average values using all available SPS scores for the corresponding week. Only patients with both a mean baseline value and a postbaseline assessment were included. The times to SPS outcomes were based on daily average SPS scores, calculated as the mean of at least two SPS assessments on that day. Patients with fewer than two SPS assessments on day 1 were considered to have missing baseline data and were excluded from the analysis set. Patients with fewer than two SPS assessments on a given day were considered to have missing data for that day. Patients who did not experience improvement in pruritus were censored (labeled as not experiencing improvement in pruritus) before the first missing SPS value up to day 32.

3 | RESULTS

3.1 | Study population

Most patients included in the phase 3 studies (86.0% [874/1016] of crisaborole-treated patients and 86.8% [439/506] of vehicle-treated patients) were aged 2-17 years and were included in this post hoc subanalysis. No significant differences were observed in demographics or baseline disease characteristics across treatment groups (Table 1). Overall, 38.1% and 61.9% of crisaborole-treated patients had mild or moderate baseline ISGA, respectively; baseline ISGA distribution was similar in vehicle-treated patients (mild, 38.0%; moderate, 62.0%). Crisaborole-treated patients with mild baseline ISGA had mean SPS scores (standard deviation [SD]) of 1.59 (0.78), and those with moderate baseline ISGA had mean (SD) SPS scores of 1.95 (0.78). Similarly, vehicle-treated patients with mild or moderate baseline ISGA had mean (SD) SPS scores of 1.57 (0.71) and 1.86 (0.78), respectively. The median (range) %BSA was 12.0 (5.0-95.0) in the crisaborole-treated group and 12.0 (5.0-90.0) in the vehicle-treated group.

TABLE 1 Demographics and baseline disease characteristics for patients aged 2-17 y

	Vehicle n = 439	Crisaborole n = 874
Age group, n (%)		
2-6 y	171 (39.0)	335 (38.3)
7-11 y	144 (32.8)	292 (33.4)
12-17 y	124 (28.2)	247 (28.3)
Female, n (%)	232 (52.9)	466 (53.3)
White, n (%)	273 (62.2)	536 (61.3)
%BSA, median (range)	12.0 (5.0-90.0)	12.0 (5.0-95.0)
ISGA score, n (%)		
Mild (2)	167 (38.0)	333 (38.1)
Moderate (3)	272 (62.0)	541 (61.9)
SPS score, mean (SD) [n][a]		
Overall	1.80 (0.76) [322]	1.80 (0.79) [662]
For baseline ISGA mild (2)	1.57 (0.71) [119]	1.59 (0.78) [250]
For baseline ISGA moderate (3)	1.86 (0.78) [200]	1.95 (0.78) [411]

Note: There were no significant differences between the vehicle and crisaborole groups at baseline.

Abbreviations: %BSA, percentage of treatable body surface area; ISGA, Investigator's Static Global Assessment; SD, standard deviation; SPS, Severity of Pruritus Scale.

[a]Baseline SPS scores were based on the average of at least two assessments on day 1; patients with fewer than two assessments on day 1 were considered to have a missing baseline SPS value.

3.2 | ISGA outcomes by baseline disease severity

At the first postbaseline assessment (day 8), significantly greater proportions of crisaborole-treated than vehicle-treated patients achieved ISGA success regardless of baseline disease severity. This difference continued to be significant ($P < .0001$) through day 29 for patients with moderate baseline ISGA. For patients with mild baseline ISGA, differences after day 8 were significant at day 22, with other days being only numerically greater (Figure 1A). Additionally, significantly greater proportions of patients receiving crisaborole achieved ISGA clear or almost clear than those receiving vehicle at the first postbaseline visit (day 8), continuing through day 29 in both baseline disease severity subgroups (Figure 1B). Likewise, significantly greater proportions of crisaborole-treated patients achieved ≥1-grade improvement in ISGA than vehicle-treated patients did in both disease severity groups at the first postbaseline visit (day 8), continuing through day 29 (Figure 1C). Patients treated with crisaborole achieved each of these ISGA outcomes significantly earlier than patients treated with vehicle ($P <.0001$ for all, except ISGA success for patients with mild baseline ISGA, for which $P = .0024$; Figure 2).

3.3 | SPS outcomes by baseline disease severity

Significantly greater proportions of crisaborole- than vehicle-treated patients achieved SPS success at week 1 in both disease severity subgroups (Figure 3A). These differences continued to be significant through week 4 in both disease severity subgroups, except at week 2 for patients with mild baseline ISGA, where a numerically greater proportion of crisaborole-treated patients achieved SPS success compared with vehicle-treated patients (Figure 3A). Similarly, significantly greater proportions of patients in both severity groups achieved ≥1-point improvement in SPS score at week 1, and this difference continued to be significant through week 4, except at week 2 for patients with mild baseline ISGA, where the difference was only numerically greater (Figure 3B). Among patients with moderate baseline ISGA, the median times to achieve SPS success and ≥1-point improvement in SPS score were significantly shorter for

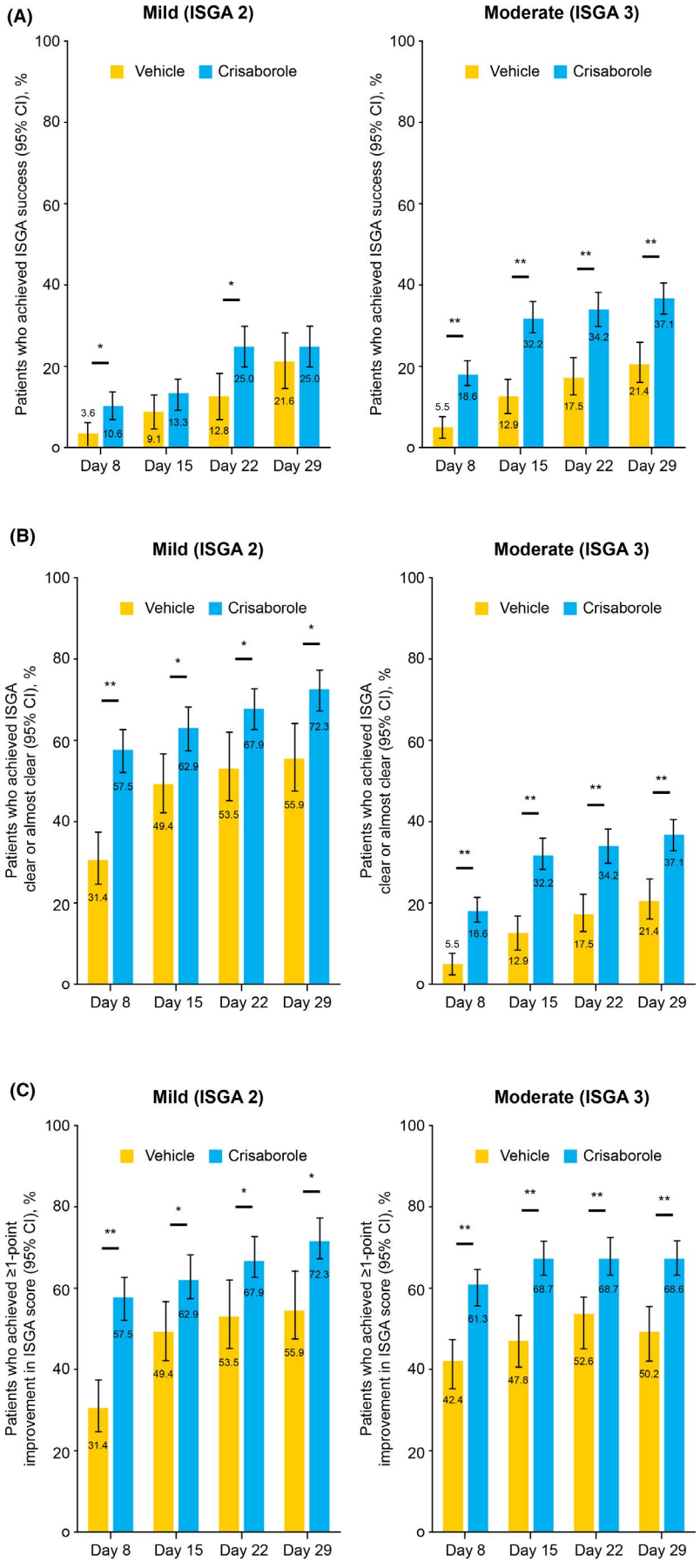

FIGURE 1 Patients achieving ISGA outcomes by baseline disease severity. A, ISGA success.[a] B, ISGA clear or almost clear. C, ≥1-grade improvement in ISGA. CI, confidence interval; ISGA, Investigator's Static Global Assessment. [a]ISGA success defined as clear (0) or almost clear (1) with ≥2-grade improvement from baseline. $^{*}P < .05$, $^{**}P < .0001$ compared with vehicle

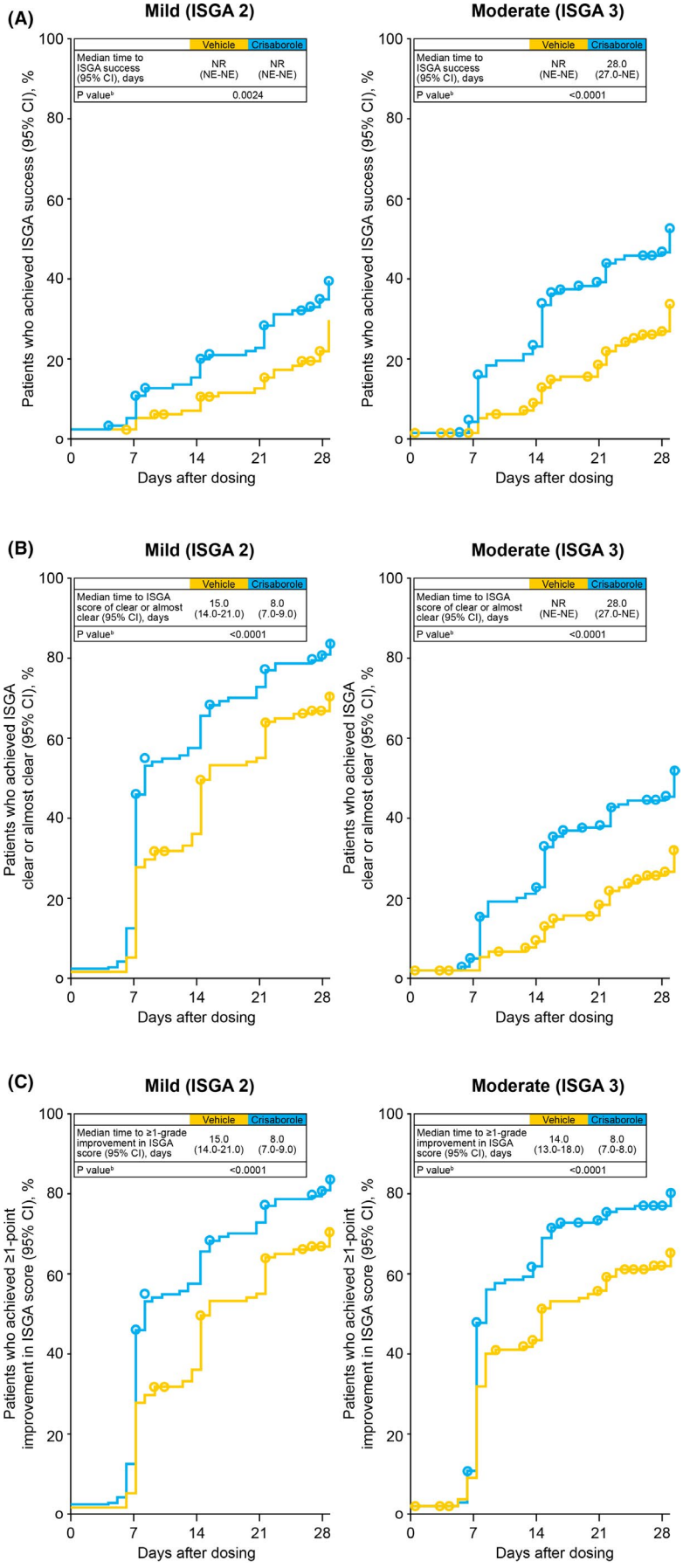

FIGURE 2 Time to achieving ISGA outcomes by baseline disease severity. A, ISGA success.[a] B, ISGA clear or almost clear. C, ≥1-grade improvement in ISGA. ISGA, Investigator's Static Global Assessment; NE, not evaluable; NR, not reached. [a]ISGA success defined as clear (0) or almost clear (1) with ≥2-grade improvement from baseline. [b]*P* value from log-rank test

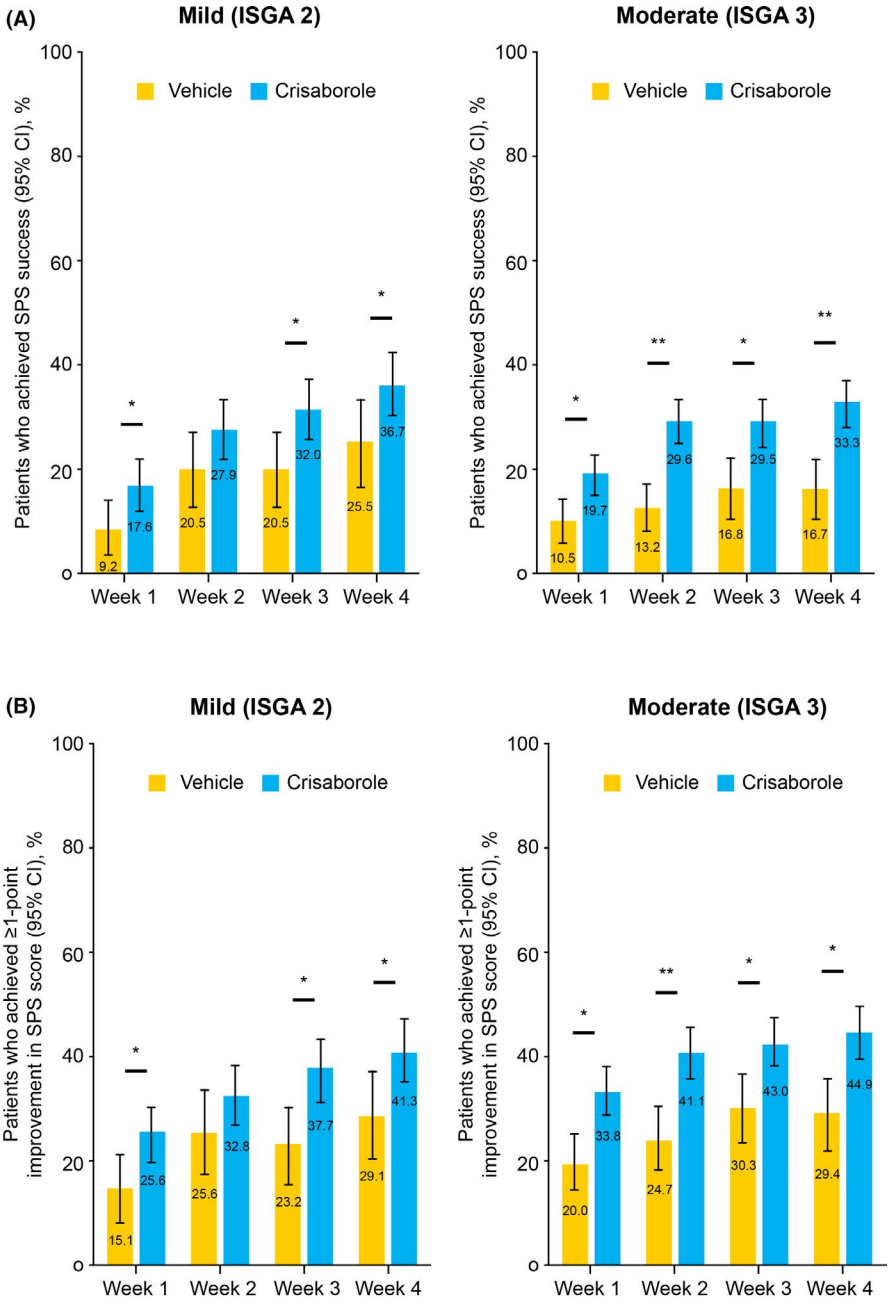

FIGURE 3 Patients achieving SPS outcomes by baseline disease severity. (A) SPS success.[a] (B) ≥1-grade improvement in SPS score. CI, confidence interval; ISGA, Investigator's Static Global Assessment; SPS, Severity of Pruritus Scale. [a]SPS success defined as SPS score ≤ 1 with ≥1-grade improvement from baseline. *$P < .05$, **$P < .0001$ crisaborole compared with vehicle

crisaborole-treated patients than vehicle-treated patients (Figure 4). In patients with mild baseline ISGA, a numerically shorter time to SPS success was observed between crisaborole- and vehicle-treated patients (Figure 4A). The median time to achieve ≥1-point improvement in SPS score was significantly shorter among crisaborole-treated patients than in vehicle-treated patients in both subgroups (Figure 4B).

4 | DISCUSSION

Crisaborole treatment resulted in greater proportions of patients achieving ISGA outcomes among those aged 2-17 years with mild or moderate AD at baseline, including ISGA success, ISGA clear or almost clear, and ≥1-grade improvement in ISGA. ISGA success was defined as a score of clear (0) or almost clear (1) with ≥2-point improvement from baseline. For patients with mild AD at baseline (ISGA 2), this meant clear disease (ISGA 0) at day 8, 15, 22, or 29, whereas for patients with moderate AD at baseline (ISGA 3), success meant almost clear (ISGA 1) or clear (ISGA 0) disease at these time points. Consequently, it is more difficult for a patient with mild baseline ISGA to achieve ISGA success than a patient with moderate baseline ISGA. Patients with moderate baseline ISGA only need to achieve a state of almost clear disease, whereas patients with mild baseline ISGA must achieve clear ISGA. For this reason, smaller improvements in ISGA that may also be relevant to patients with AD were assessed as well: ISGA clear or almost clear and ≥1-grade improvement in ISGA. Greater proportions of patients achieving SPS

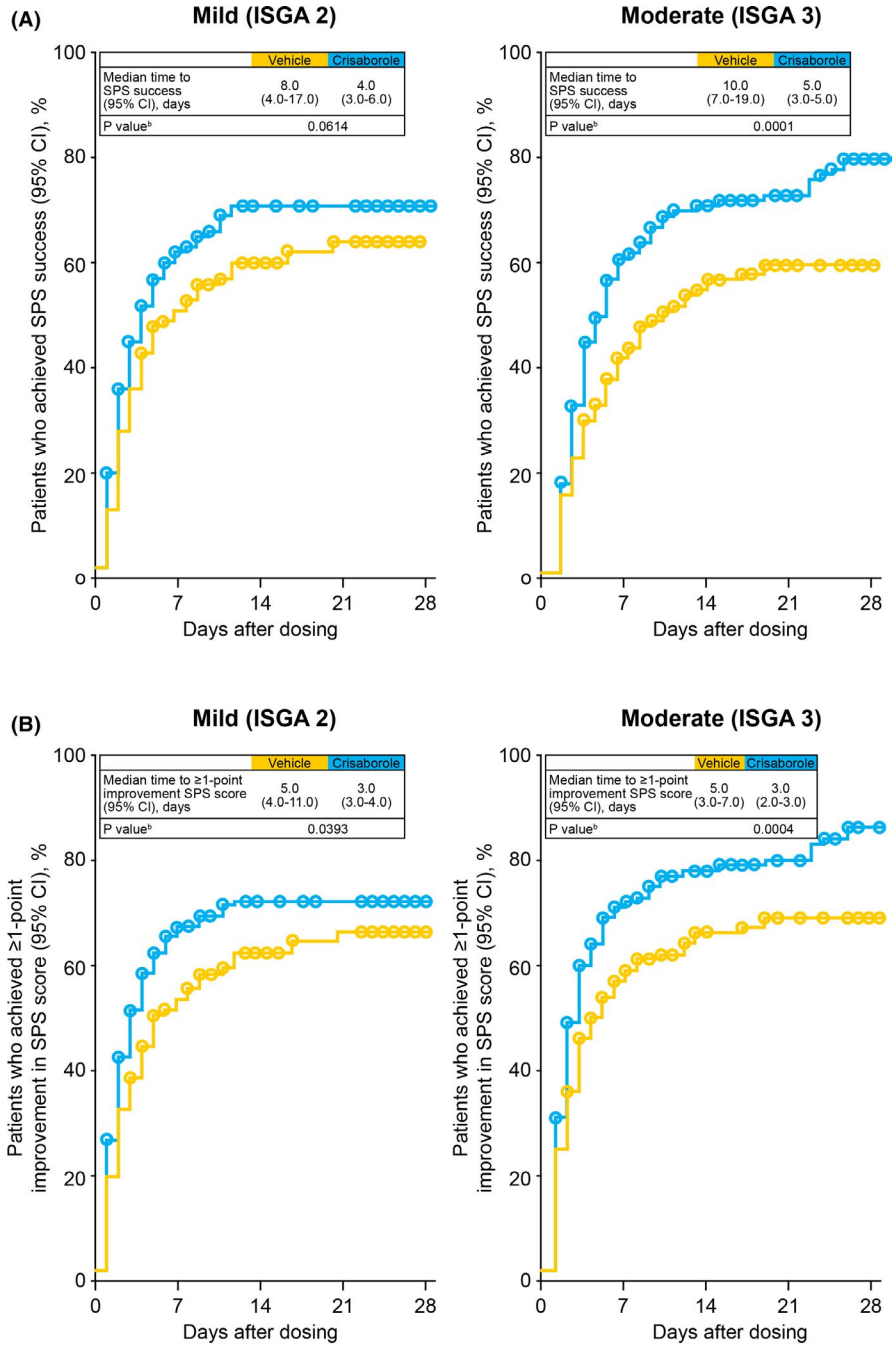

FIGURE 4 Time to achieving SPS outcomes by baseline disease severity. A, SPS success.[a] B, ≥1-grade improvement in SPS score. ISGA, Investigator's Static Global Assessment; SPS, Severity of Pruritus Scale. [a]SPS success defined as SPS score ≤ 1 with ≥ 1-grade improvement from baseline. [b]*P* value from log-rank test

outcomes (SPS success and ≥1-point improvement in SPS score) were also seen in patients aged 2-17 years who were treated with crisaborole compared with patients treated with vehicle, irrespective of baseline disease severity. Differences between crisaborole- and vehicle-treated patients in both the ISGA and the SPS outcomes were seen as early as day 8 or week 1, respectively.

These results are in line with earlier analyses of time to improvement in disease severity and time to pruritus relief in the overall study populations of CORE 1 and CORE 2.[7] Significant differences in proportions of patients achieving ISGA success between the crisaborole- and vehicle-treated groups were observed at day 8 for the overall populations in both CORE 1 and CORE 2 ($P < .001$).[7] In addition, in the overall populations, significantly greater proportions of crisaborole-treated patients achieved SPS success than vehicle-treated patients did at week 1 ($P < .05$) and continued through week 4 ($P < .001$), and times to SPS success were shorter with crisaborole than with vehicle in the overall study population ($P < .05$).[9]

The results of CORE 1 and CORE 2 were limited by the short duration of treatment. This analysis was post hoc and was not powered to detect differences between mild and moderate baseline ISGA subgroups or the 2-17 age group, thereby limiting the interpretation of the results. However, the improvements in disease severity and pruritus that were observed for patients with mild or moderate baseline ISGA in this subgroup analysis continue to support the use of crisaborole in pediatric patients across the spectrum of mild-to-moderate AD.

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CONFLICTS OF INTEREST

Lawrence F. Eichenfield has been an investigator for Pfizer Inc, AbbVie, Eli Lilly, Galderma, LEO Pharma, Medimetriks, Sanofi-Regeneron, and Valeant/Ortho Dermatologics and a consultant or participant in a data safety monitoring board for Almirall, Amgen, Asana, Dermavant, Dermira, Eli Lilly, Forte Biosciences, Galderma, LEO Pharma, Matrisys, Novartis, Sanofi-Regeneron and Valeant/Ortho Dermatologics. Gil Yosipovitch has been a member of scientific advisory boards for Pfizer Inc, Bayer, CeraVe, Eli Lilly, Galderma, Kiniksa, Menlo Therapeutics, Novartis, Sanofi-Regeneron, Trevi Therapeutics, and Sienna Biopharmaceuticals and a principal investigator for Pfizer Inc, Kiniksa, LEO Pharma, Menlo Therapeutics, Sun Pharmaceutical Industries, and Vanda Pharmaceuticals. 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. Mizuho Kalabis and Melissa Olivadoti were employees and stockholders of Pfizer Inc at the time of this analysis. Chuanbo Zang, Bonnie Vlahos, Paul Sanders, Daniela E. Myers, Andrew G. Bushmakin, and Joseph C. Cappelleri are employees and stockholders of Pfizer Inc. Amy S. Paller has been an investigator for AbbVie, AnaptysBio, Eli Lilly, Galderma, Incyte, LEO Pharma, Janssen, Novartis, and Sanofi-Regeneron and has been a consultant with honoraria for Pfizer Inc, Amgen, Asana BioSciences, Dermavant, Dermira, Galderma, Eli Lilly, Forte Biosciences, LEO Pharma, Menlo Pharmaceuticals, MorphoSys/Galapagos, Novartis, and Sanofi-Regeneron.

ETHICAL APPROVAL

These studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization Good Clinical Practice Guidelines. All local regulatory requirements were followed. The studies were approved by institutional review boards or ethics committees at each study site. An internal review committee monitored the safety of patients throughout the studies.

REFERENCES

1. Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab*. 2015;66(suppl 1):8-16.
2. Lyons JJ, Milner JD, Stone KD. Atopic dermatitis in children: clinical features, pathophysiology, and treatment. *Immunol Allergy Clin North Am*. 2015;35(1):161-183.
3. Barnetson RS, Rogers M. Childhood atopic eczema. *BMJ*. 2002;324(7350):1376-1379.
4. Howlett S. Emotional dysfunction, child-family relationships and childhood atopic dermatitis. *Br J Dermatol*. 1999;140(3):381-384.
5. Akdis CA, Akdis M, Bieber T, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol*. 2006;118(1):152-169.
6. *Eucrisa (crisaborole) ointment, 2%, package insert*. New York, NY: Pfizer Labs; 2017. http://labeling.pfizer.com/ShowLabeling.aspx?id=5331. Accessed September 18, 2020.
7. 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.
8. Yosipovitch G, Simpson EL, Bushmakin AG, et al. Assessment of pruritus in atopic dermatitis: validation of the Severity of Pruritus Scale (SPS). *Itch*. 2018;3:e13.
9. 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(2):e12.
10. 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.
11. Hebert AA, Stingl G, Ho LK, et al. Patient impact and economic burden of mild-to-moderate atopic dermatitis. *Curr Med Res Opin*. 2018;34(12):2177-2185.
12. van Belle G, Fisher LD, Heagerty PJ, Lumley T. *Biostatistics: A Methodology for the Health Sciences*, 2nd edn. New Jersey, NJ: John Wiley & Sons; 2004.

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