



## Early Relief of Pruritus in Atopic Dermatitis with Crisaborole Ointment, A Non-steroidal, Phosphodiesterase 4 Inhibitor

Gil YOSIPOVITCH<sup>1</sup>, Linda F. STEIN GOLD<sup>2</sup>, Mark G. LEBWOHL<sup>3</sup>, Jonathan I. SILVERBERG<sup>4</sup>, Anna M. TALLMAN<sup>5</sup> and Lee T. ZANE<sup>6</sup>  
<sup>1</sup>University of Miami Miller School of Medicine, Miami, FL, <sup>2</sup>Henry Ford Health System, Detroit, MI, <sup>3</sup>Icahn School of Medicine at Mount Sinai, New York, NY, <sup>4</sup>Northwestern University Feinberg School of Medicine, Chicago, IL, <sup>5</sup>Pfizer Inc., New York, NY, and <sup>6</sup>Anacor Pharmaceuticals Inc., acquired by Pfizer Inc., New York, NY, USA

**Pruritus occurs in all patients with atopic dermatitis and requires quick relief to reduce disease exacerbation and improve quality of life. Crisaborole ointment is a non-steroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate atopic dermatitis. This *post hoc* analysis explores crisaborole ointment for early relief of pruritus in patients with mild to moderate atopic dermatitis from 2 phase III studies. Patients received crisaborole or vehicle twice daily for 28 days. Pruritus was graded on a 4-point scale of none (0) to severe (3). Early improvement in pruritus required a score of none (0) or mild (1), with a  $\geq 1$ -grade improvement from baseline on day 6. Significantly more patients experienced early improvement in pruritus with crisaborole than with vehicle (56.6% vs 39.5%;  $p < 0.001$ ), including at earliest assessment (day 2, 34.3% vs 27.3%;  $p = 0.013$ ). Crisaborole is a topical treatment option that can rapidly relieve atopic dermatitis-associated pruritus.**

*Key words:* atopic dermatitis; pruritus; crisaborole; phosphodiesterase 4 inhibitor.

Accepted Jan 23, 2018; Epub ahead of print Jan 24, 2018

Acta Derm Venereol 2018; 98: 484–489.

*Corr:* Gil Yosipovitch, MD, Department of Dermatology and Itch Center, University of Miami Hospital, 1600 NW 10th Avenue, Miami, FL 33136, USA. E-mail: yosipog@gmail.com

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects approximately 15–30% of children and 2–10% of adults; up to 90% of cases present as mild or moderate (1–3). Hallmarks of AD include pruritus and pruritus-induced scratching, which lead to exacerbation of symptoms and worsening of disease (4). Although the pathophysiology behind AD-associated pruritus is under investigation, it is believed to be a complex pathway that involves the interaction of neuropeptides with keratinocytes, immune cells and nerve fibres (5).

AD-associated pruritus often results in sleep disturbance, psychosocial morbidity and reduced quality of life (QoL) for patients and caregivers. Elevated stress levels and sleep problems can exacerbate pruritus pathways (4, 6, 7). The “itch-scratch cycle” describes the pattern of pruritus that leads to scratching, and the scratching that leads to further inflammation (8). Patients may be unaware they are scratching during sleep, and young patients may additionally experience sleep dysfunction,

which can lead to emotional and psychological issues in adolescence (5, 8). Stress and anxiety have been associated with neuropeptides that can induce further pruritus and subsequent scratching (5). In addition, the damage to skin because of scratching can lead to skin infection and scarring and possibly contribute to the risk for ‘atopic march’, which is the progression to other atopic diseases, such as allergic rhinitis and asthma (5, 9, 10). Treatments that provide rapid relief and control of pruritus are important parts of therapy to reduce the occurrence of exacerbation of disease and improve sleep and QoL (4). Treatment guidelines from the American Academy of Dermatology (AAD) and the American Academy of Allergy, Asthma & Immunology (AAAAI)/American College of Allergy, Asthma & Immunology (ACAAI) do not provide specific guidance for addressing AD-associated symptoms such as pruritus (4, 11). However, it is important that therapy reduces pruritus quickly, regardless of disease or pruritus severity or other demographics or characteristics.

Both the AAD and AAAAI/ACAAI guidelines recommend topical pharmacological agents such as topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs) to treat AD, while noting the potential of these agents to reduce the severity of pruritus (4, 11). Although TCIs and TCSs have been shown to reduce the severity of pruritus (5, 12, 13), they are associated with a range of adverse effects, such as burning and stinging (TCIs) and skin atrophy (TCSs), although skin atrophy is rare with appropriate use of low- or mid-potency TCSs (4, 11, 14). A boxed warning for TCIs indicates a theoretical risk for malignancy, and superpotent TCSs have been associated with lymphoma (11, 15). Consequently, additional topical non-steroidal medications are needed that provide rapid relief of pruritus in AD with minimal adverse effects.

Crisaborole ointment is a non-steroidal phosphodiesterase 4 (PDE4) inhibitor for the treatment of mild-to-moderate AD (16). Results of several early phase II trials evaluating crisaborole demonstrated an improvement in pruritus in patients with AD (17–19). Crisaborole was later evaluated in 2 large, identically designed, double-blind, vehicle-controlled, phase III studies (AD-301: NCT02118766; AD-302: NCT02118792). In these studies, patients  $\geq 2$  years old with mild or moderate AD were randomly assigned 2:1 to receive crisaborole or vehicle ointment twice daily for 28 days (20). Significantly more crisaborole-treated than vehicle-treated patients achieved the primary endpoint of

success in Investigator's Static Global Assessment [ISGA] score (AD-301: 32.8% vs 25.4%,  $p=0.038$ ; AD-302: 31.4% vs 18.0%,  $p<0.001$ ), where success was defined as a score of clear [0] or almost clear [1], with a  $\geq 2$ -grade improvement from baseline at day 29 (20). Improvement in severity of pruritus at day 29 was a secondary endpoint. Significantly more crisaborole-treated patients than vehicle-treated patients experienced improvement in pruritus (pooled data: 63% vs 53%,  $p=0.002$ ), which was defined as achievement of a pruritus severity score of none [0] or mild [1], with a  $\geq 1$ -grade improvement from baseline (20). Crisaborole was well-tolerated; application site pain (primarily burning or stinging) was the most common treatment-related adverse effect (crisaborole 4.4%; vehicle 1.2%) (20). Because the primary analysis of these studies evaluated relief of pruritus at the end of treatment, the objective of the *post hoc* analysis presented herein was to explore the impact of crisaborole treatment on achievement of early relief of pruritus from the pooled results of the 2 phase III studies.

## METHODS

### Study design and treatment

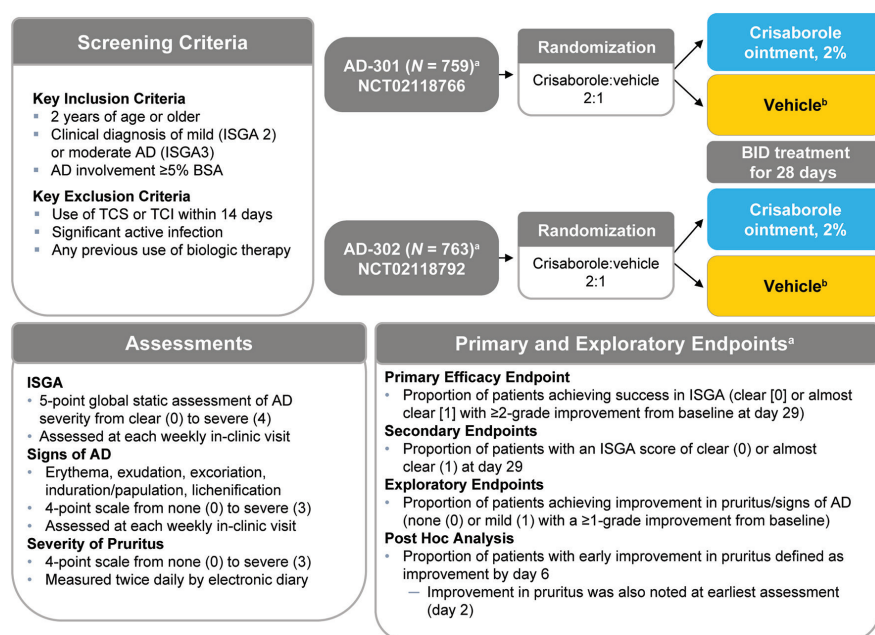
The study design and methods of the 2 phase III studies have been published previously (20). Briefly, 2 multicentre, randomised, double-blind, vehicle-controlled phase III studies were performed to assess the efficacy and safety of crisaborole in patients  $\geq 2$  years old with mild-to-moderate AD. Patients were randomly assigned 2:1 to receive either crisaborole ointment 2% or vehicle ointment. Treatments were then applied twice daily for 28 days (Fig. 1). Study protocols were developed and conducted in accordance with the principles of Good Clinical Practice and local country-specific regulatory requirements. An institutional review board approved all study protocols, informed consent/assent forms and relevant supporting data at each investigational centre.

### Endpoints and assessments

The primary endpoint of the studies was success in ISGA, which was defined as achieving a score of 0 or 1, with a 2-grade improvement from baseline at day 29, based on a 5-point scale of clear [0] to severe [4]. The secondary endpoint was the proportion of patients with an ISGA score of clear [0] or almost clear [1] at day 29.

Exploratory endpoints included pruritus and signs of AD, which were both assessed on 4-point scales of none [0] to severe [3]. Improvement in pruritus or signs of AD were defined as none [0] or mild [1], with a  $\geq 1$ -grade improvement from baseline. Pruritus data were measured twice daily by the patient or parent/caregiver using an electronic diary. Additional endpoints such as QoL measures included the Children's Dermatology Life Quality Index (CDLQI) (patients 2–15 years of age), and the Dermatology Life Quality Index (DLQI) (patients  $\geq 16$  years of age) (21, 22).

In this *post hoc* analysis, early improvement of pruritus was defined as experiencing improvement at day 6 using the morning assessment. Endpoints in the *post hoc* analysis include the proportion of patients who experienced early improvement of pruritus, the proportion who experienced pruritus symptom improvement at earliest assessment (day 2) and the percentage reduction in pruritus severity over the first 6 days of treatment. The likelihood of early improvement in pruritus based on baseline demographics and disease characteristics was also evaluated. QoL scores for CDLQI and DLQI used in the correlation with early improvement of pruritus were based on the established minimal clinically important difference (MCID) for each scale (CDLQI:  $\geq 2.5$ -point change from baseline; DLQI:  $\geq 3.3$ -point change from baseline) (23, 24). The MCID is the smallest change in QoL score that patients perceive as beneficial and that would result in a change in patient therapy, in the absence of troublesome side effects and excessive cost (25). The correlation between early improvement in pruritus and treatment outcomes such as improvement in ISGA, QoL measures, other signs of AD and higher sleep scores (as a component of CDLQI) at day 29 were examined in crisaborole-treated patients. This analysis also evaluated the proportion of patients who began the study with itch and became itch free (defined as achieving a pruritus severity score of 0 among patients with baseline pruritus severity of mild or worse [score  $\geq 1$ ]) on days 2, 6 and 29, and the proportion of patients who experienced early improvement in pruritus and maintained improvement at day 29.



**Fig. 1. Study design, treatment, and assessments.** <sup>a</sup>Intent-to-treat population. <sup>b</sup>Proprietary vehicle developed by Anacor Pharmaceuticals, Inc., which was acquired by Pfizer Inc., June 2016. AD: atopic dermatitis; BID: twice daily; BSA: body surface area; ISGA: Investigator's Static Global Assessment; TCI: topical calcineurin inhibitor; TCS: topical corticosteroid.

## Statistical analysis

Populations from both studies were pooled for this analysis. Pruritus and other baseline characteristics were evaluated by use of descriptive statistics. Differences in proportions between treatment groups for improvement in pruritus were compared using the Fisher exact test. Differences in proportions between treatment groups for patients who became itch free were compared using normal approximation to binomial proportions. Differences in percentage change were compared using analysis of variance with a factor of treatment. Odds ratios with corresponding confidence intervals and *p*-values were found from a logistic regression with a factor of treatment. The missing observations were not imputed, statistical significance was set at a 0.05 level, and nominal *p*-values were displayed.

## RESULTS

## Patient population

The pooled population from both studies included 1,016 patients treated with crisaborole and 506 patients given vehicle ointment. No significant differences were observed in the key baseline demographics across treatment groups (Table I). No significant differences were observed across treatment groups for baseline disease severity or baseline severity of pruritus.

## Pruritus outcomes

A significantly greater proportion of patients treated with crisaborole demonstrated improvement at earliest assessment (day 2;  $p=0.013$ ) and early improvement of pruritus at day 6 ( $p<0.001$ ) than patients given vehicle (Fig. 2a). Additionally, a significantly greater percentage reduction in pruritus severity was observed on days 2–6 in patients treated with crisaborole than in those given vehicle (Fig. 2b). Early pruritus relief also persisted in most patients. Among 474 patients treated with crisaborole who experienced early improvement in pruritus (day 6), 321 (67.7%) still reported improvement at day 29. Also, most of the vehicle-treated patients who experienced early relief of pruritus still reported improvement at day 29 ( $n=103/163$  [63.2%]). More crisaborole patients with pruritus severity of mild or greater at baseline became

Table I. Baseline patient characteristics

Patient demographics and disease characteristics	AD-301/AD-302 pooled	
	Crisaborole ointment <i>n</i> = 1,016	Vehicle <i>n</i> = 506
Age, years, mean $\pm$ SD	12.3 $\pm$ 12.16	12.1 $\pm$ 11.65
Median (range)	9.0 (2–79)	9.0 (2–79)
Age group, %		
2–6 years	33	33.8
7–11 years	28.7	28.5
12–17 years	24.3	24.5
$\geq$ 18 years	14.0	13.2
Sex, %		
Male	44.3	44.5
Female	55.7	55.5
Ethnicity, %		
Hispanic or Latino	19.7	20.0
Not Hispanic or Latino	80.3	80.0
Race, %		
American Indian or Alaskan native	1.1	1.0
Asian	5.1	5.3
Black or African American	28.1	27.5
Hawaiian or other Pacific Islander	0.7	1.6
White	60.7	60.5
Other	4.3	4.2
ISGA, <i>n</i> (%)		
Mild – 2	393 (38.7)	193 (38.1)
Moderate – 3	623 (61.3)	313 (61.9)
Severity of pruritus, <i>n</i> (%)		
None – 0	35 (3.9)	19 (4.3)
Mild – 1	229 (25.4)	119 (27.0)
Moderate – 2	331 (36.7)	167 (37.9)
Severe – 3	308 (34.1)	136 (30.8)
Treatable % BSA, mean $\pm$ SD	18.3 $\pm$ 18.02	18.1 $\pm$ 17.33
Min–Max	5–95	5–90

SD: standard deviation; BSA: body surface area; ISGA: Investigator's Static Global Assessment.

itch free over the course of the study. The proportion of patients with itch at baseline who became itch free over the course of the study generally increased in both study arms. No difference was observed at day 2; however, significantly more patients receiving crisaborole became itch free at day 6 and day 29 (Fig. 3).

Treatment with crisaborole increased the likelihood of early improvement in pruritus in patients, regardless of varying baseline disease characteristics and demographics. For example, early improvement in pruritus was more likely with crisaborole treatment regardless of baseline pruritus severity (mild,  $p=0.008$ ; moderate,  $p=0.002$ ; severe,  $p=0.001$ ) (Fig. 4a). Patients receiving crisaborole were also more likely to experience early improvement in pruritus regardless of their baseline ISGA (Fig. 4b)

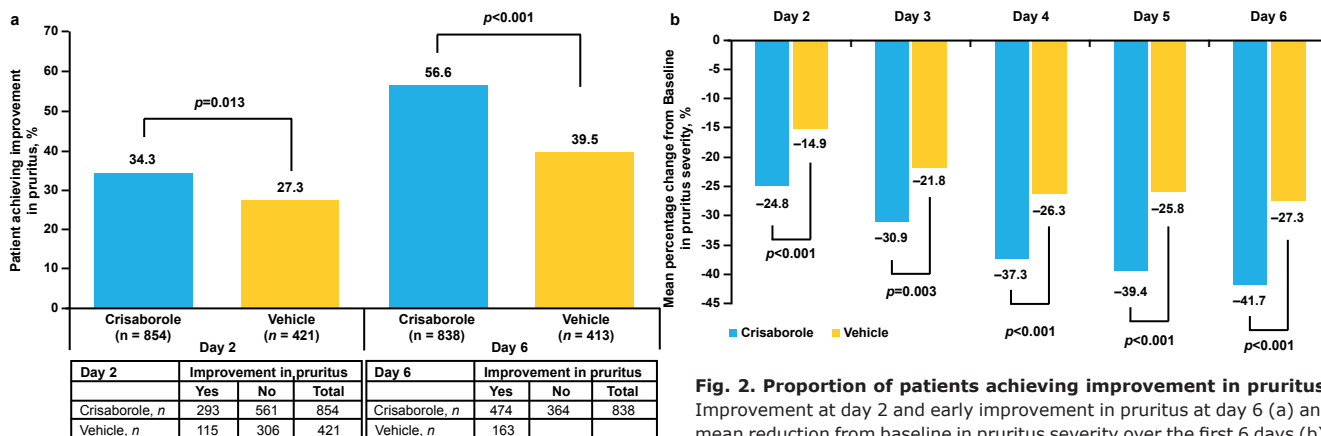
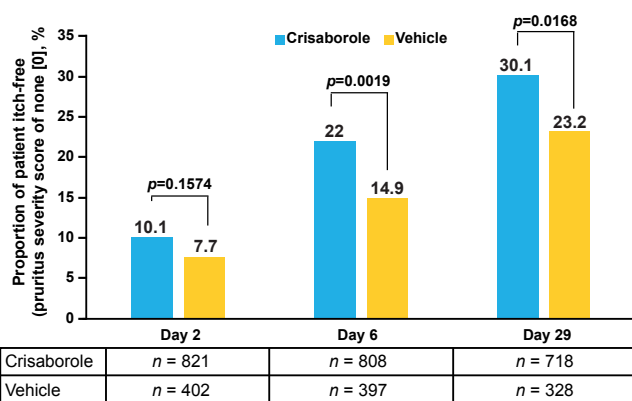


Fig. 2. Proportion of patients achieving improvement in pruritus. Improvement at day 2 and early improvement in pruritus at day 6 (a) and mean reduction from baseline in pruritus severity over the first 6 days (b).

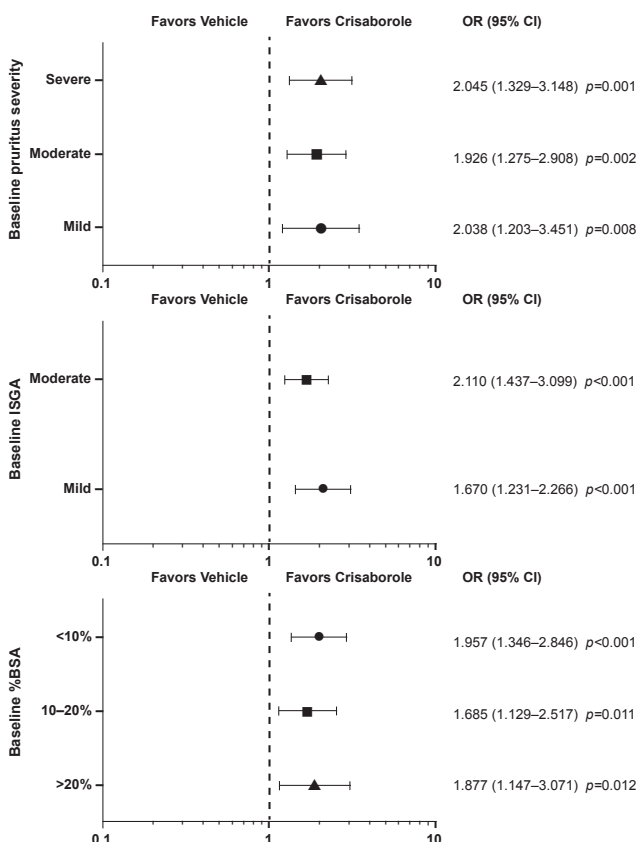




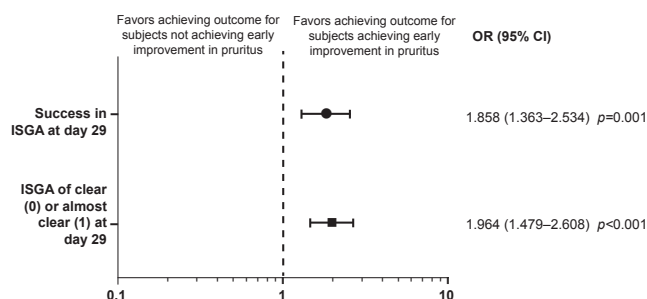
**Fig. 3.** Proportion of patients who became itch free (pruritus severity score – none [0]) over time among patients with mild (1) to severe (3) pruritus severity at baseline.

and percentage of affected body surface area (BSA) at baseline (Fig. 4c).

Patients receiving crisaborole were significantly more likely to achieve early improvement in pruritus among most age groups ( $p < 0.05$ ), except for patients aged 12–17 years, though there was a trend towards early pruritus improvement with crisaborole in this age group (odds ratio: 1.502; 95% CI 0.931–2.423;  $p = 0.096$ ) (Fig. S1a<sup>1</sup>). Crisaborole demonstrated a significant likelihood of a patient



**Fig. 4.** Odds ratio for achieving early improvement in pruritus. Per baseline pruritus severity (a), IGSA (b) and percentage affected BSA (c). BSA: body surface area; CI: confidence interval; IGSA: Investigator’s Static Global Assessment; OR: odds ratio.



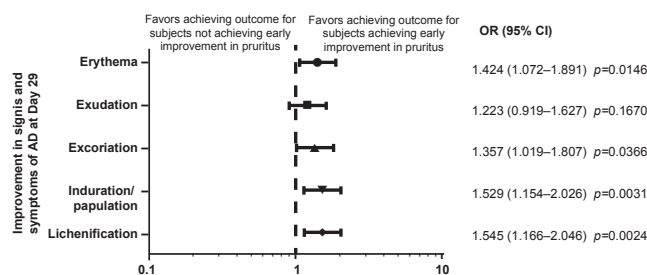
**Fig. 5.** Odds ratio (OR) of achieving outcome (success in Investigator’s Static Global Assessment [ISGA] at day 29 OR ISGA of clear [0] or almost clear [1] at day 29) based on achieving early improvement in pruritus (day 6) among crisaborole-treated patients. CI: confidence interval.

experiencing early improvement in pruritus regardless of sex (male,  $p = 0.009$ ; female,  $p < 0.001$ ) (Fig. S1b<sup>1</sup>).

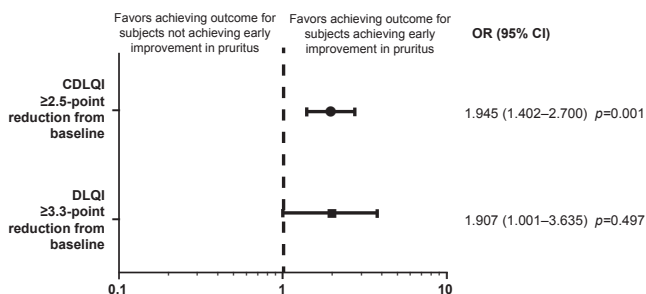
Among crisaborole-treated patients, early improvement in pruritus was more likely to be correlated with improvement in disease. For example, patients who experienced early improvement in pruritus were significantly more likely to have experienced treatment success ( $p < 0.0001$ ) and an ISGA score of clear (0) or almost clear (1) ( $p < 0.0001$ ) at day 29 than those who did experience early pruritus improvement (Fig. 5). Similarly, crisaborole-treated patients who experienced early improvement in pruritus were more likely to have experienced improvement in most signs of AD by day 29 with the exception of exudation (Fig. 6).

Correlations were also observed between early relief of pruritus and some QoL measures in crisaborole-treated patients. Crisaborole-treated patients experiencing early improvement in pruritus were significantly more likely to experience an MCID in CDLQI and DLQI scores at day 29 than those who did not see early improvement in pruritus ( $p < 0.0001$  and  $p = 0.0497$ , respectively) (Fig. 7). Early improvement in pruritus in crisaborole-treated patients was also associated with better scores in certain QoL components, particularly sleep, which is a component of the CDLQI. More patients who had early improvement in pruritus while receiving crisaborole reported that their pruritus had

<sup>1</sup><https://doi.org/10.2340/00015555-2893>



**Fig. 6.** Odds ratio (OR) of improvement in other signs of atopic dermatitis (AD) based on achieving early improvement in pruritus (day 6) among crisaborole-treated patients. CI: confidence interval.



**Fig. 7. Odds ratio (OR) of improvement in quality of life measures based on achieving early improvement in pruritus (day 6) among crisaborole-treated patients.** CDLQI: Children's Dermatology Life Quality Index; CI: confidence interval; DLQI: Dermatology Life Quality Index.

affected their sleep “only a little” or “not at all” at day 29 than those who did not have early improvement in pruritus (odds ratio: 2.656; 95% CI 1.708–4.130;  $p < 0.0001$ ).

## DISCUSSION

In this *post hoc* analysis that evaluated the effect of crisaborole on early relief of pruritus, improvement in pruritus was observed in significantly more patients treated with crisaborole than in those given vehicle as early as day 2 of the study. Most crisaborole-treated patients also experienced improvement in pruritus at day 6, regardless of baseline pruritus severity. In addition, more crisaborole-treated patients who had pruritus at baseline became itch free, with more than 20% experiencing complete relief of pruritus by day 6. Crisaborole treatment was more likely to lead to early improvement in pruritus regardless of various baseline characteristics, including baseline pruritus severity, disease severity (by ISGA) and percentage of affected BSA.

Rapid relief of pruritus is necessary to break the itch-scratch cycle and associated atopic march and to prevent chronicity, learned defective sleep patterns and negative physical and psychological complications and sequelae (5, 26–28). Early and effective intervention is particularly important in preserving QoL in young patients with AD (28). In the current analysis, early improvement in pruritus after crisaborole treatment was more likely to be associated with improvement in disease, such as most signs of AD at day 29 and improvement in ISGA score. Crisaborole-treated patients seeing early improvement in pruritus were also more likely to have higher scores in QoL per DLQI and CDLQI at day 29 than those who did not experience early improvement in pruritus. Additionally, early improvement in pruritus among crisaborole-treated children was associated with better scores in sleep (based on a component of the CDLQI) at day 29 than in those who did not have early pruritus improvement. Although the mechanisms are complex and not fully elucidated, crisaborole is believed to relieve pruritus through inhibition of PDE4, which is involved in production of proinflammatory cytokines through degradation of cyclic adenosine monophosphate (cAMP) (29). Elevated cAMP-specific

PDE activity in mononuclear lymphocytes has been reported in patients with AD (30). Use of PDE4 inhibitors has shown that increased intracellular cAMP might contribute to the reduction of inflammation and itch (31). However, the exact mechanism is not clear and warrants further study based on the rapid relief observed in this analysis.

In addition to understanding the causes of pruritus, it is important to assess its severity because it is the cardinal symptom of AD. Various scales have been used to assess pruritus, including the verbal rating scale (VRS), the visual analogue scale (VAS) and the numeric rating scale (NRS) (32). Where the VRS uses a 4-point verbally administered scale from 0 to 3 with increasing intensity, the VAS and NRS are 11-point scales that grade severity from 0 to 10, increasing in intensity. An analysis comparing the use of these tests in chronic pruritus found that they all had high validity and concurrent validity in pruritus intensity assessment (32). The scale used to measure pruritus in this study was a 4-point scale administered via electronic diary (20). The mean percentage reduction from baseline at day 6 in crisaborole-treated patients in this analysis was 42%. Because different measuring scales were used in this study, it is difficult to compare itch reduction with that found in other studies because of differing definitions of pruritus severity and differences in how the scales were administered. In addition, a limitation of this analysis was that the pruritus severity scale had not been validated at the time of publication development.

Although it is difficult to directly compare the early reduction in pruritus after use of crisaborole with the reduction time with other topical agents such as TCSs and TCIs, this analysis shows that pruritus relief with crisaborole is at least comparable with what has been reported with those agents (12, 13, 33). It is also important to consider the highly tolerable safety profile of crisaborole. The most commonly reported adverse event from the phase III studies was application site pain (including skin burning or stinging), which was reported in 4.4% of crisaborole-treated patients (20). This is especially important to consider with younger patients because discomfort can lead to issues of adherence. Therefore, the combination of rapid relief of pruritus and its safety profile makes crisaborole a suitable non-steroidal topical therapy option for the management of mild-to-moderate AD.

In this *post hoc* analysis, a greater proportion of crisaborole-treated patients experienced early relief of pruritus. Crisaborole-treated patients were more likely to experience early relief of pruritus regardless of most baseline characteristics, and early relief of pruritus was associated with improved treatment outcome measures.

## ACKNOWLEDGEMENTS

The authors thank the study patients, investigators and investigational sites, whose participation made these studies possible. We also thank Huaming Tan, PhD, of Pfizer Inc for performing some

of the statistical analyses. Robert J. Schoen, PharmD, and Corey Mandel, PhD, of ApotheCom (Yardley/San Francisco) provided writing and editorial assistance, which was funded by Anacor Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer Inc.

This study was funded by Anacor Pharmaceuticals, Inc., a wholly owned subsidiary of Pfizer, Inc.

**Conflicts of interest:** GY conducted clinical trials or received honoraria for serving as a member of the scientific advisory boards of Opko, TREVI, Eli Lilly, Menlo, Regeneron, Sanofi, Galderma, Pfizer, Novartis and Sienna, and received research funds from Pfizer, Allergan, GSK/Stiefel and the Leo Foundation. LFSG has served as an investigator for Pfizer, Incyte, Leo and GSK; as an advisor for Pfizer, Medimetriks, Sanofi, Regeneron, Leo and GSK; and as a speaker for Pfizer, Sanofi-Aventis, Regeneron and Leo. ML received research funds from AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Incyte, Janssen, Johnson & Johnson, Leo, Medimmune/AstraZeneca, Novartis, Pfizer, Sciaderm, Valeant and ViDac; and has served as a consultant for Allergan and Dr. Reddy's Laboratories. JS has served as an investigator for Celgene, Eli Lilly, Menlo, Realm, Regeneron, Sanofi and F. Hoffmann-La Roche; as a consultant for AbbVie, Anacor Pharmaceuticals, Inc., Eli Lilly, Galderma, GSK, Incyte, Kiniksa, Menlo, Leo, Pfizer, Realm, Regeneron and Sanofi; and as a speaker for Regeneron and Sanofi. AMT is an employee and shareholder of Pfizer. LZ was an employee of Anacor Pharmaceuticals, Inc. during the conduct of these trials.

## REFERENCES

- Bieber T. Atopic dermatitis. *N Engl J Med* 2008; 358: 1483–1494.
- Bieber T. Atopic dermatitis. *Ann Dermatol* 2010; 22: 125–137.
- Arkwright PD, Motala C, Subramanian H, Spergel J, Schneider LC, Wollenberg A. Management of difficult-to-treat atopic dermatitis. *J Allergy Clin Immunol Pract* 2013; 1: 142–151.
- Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol* 2013; 131: 295–299.
- Blume-Peytavi U, Metz M. Atopic dermatitis in children: management of pruritus. *J Eur Acad Dermatol Venereol* 2012; 26: 2–8.
- Mollanazar NK, Smith PK, Yosipovitch G. Mediators of chronic pruritus in atopic dermatitis: getting the itch out? *Clin Rev Allergy Immunol* 2016; 51: 263–292.
- Hong J, Buddenkotte J, Berger TG, Steinhoff M. Management of itch in atopic dermatitis. *Semin Cutan Med Surg* 2011; 30: 71–86.
- Yosipovitch G, Papoiu AD. What causes itch in atopic dermatitis? *Curr Allergy Asthma Rep* 2008; 8: 306–311.
- Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab* 2015; 66: 8–16.
- Zheng T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy Asthma Immunol Res* 2011; 3: 67–73.
- Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014; 71: 116–132.
- Wahlgren CF, Hagermark O, Bergstrom R, Hedin B. Evaluation of a new method of assessing pruritus and antipruritic drugs. *Skin Pharmacol* 1988; 1: 3–13.
- Yentzer BA, Ade RA, Fountain JM, Clark AR, Taylor SL, Borgerding E, et al. Improvement in treatment adherence with a 3-day course of flucinonidic cream 0.1% for atopic dermatitis. *Cutis* 2010; 86: 208–213.
- Siegfried EC, Jaworski JC, Kaiser JD, Hebert AA. Systematic review of published trials: long-term safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic dermatitis. *BMC Pediatrics* 2016; 16: 75.
- Legendre L, Barnette T, Mazereeuw-Hautier J, Meyer N, Murrell D, Paul C. Risk of lymphoma in patients with atopic dermatitis and the role of topical treatment: a systematic review and meta-analysis. *J Am Acad Dermatol* 2015; 72: 992–1002.
- US Food and Drug Administration. FDA Approves Eucrisa for eczema. 14 December 2016. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm533371.htm>.
- Stein Gold LF, Spelman L, Spellman MC, Hughes MH, Zane LT. A phase 2, randomized, controlled, dose-ranging study evaluating crisaborole topical ointment, 0.5% and 2% in adolescents with mild to moderate atopic dermatitis. *J Drugs Dermatol* 2015; 14: 1394–1399.
- Tom WL, Van SM, Chanda S, Zane LT. Pharmacokinetic profile, safety, and tolerability of crisaborole topical ointment, 2% in adolescents with atopic dermatitis: an open-label phase 2a study. *Pediatr Dermatol* 2016; 33: 150–159.
- Murrell D, Gebauer K, Spelman L, Zane LT. Crisaborole topical ointment, 2% in adults with atopic dermatitis: a phase 2a, vehicle-controlled, proof-of-concept study. *J Drugs Dermatol* 2015; 14: 1108–1112.
- Paller AS, Tom WL, Lebwol MG, Blumenthal RL, Boguniewicz M, Call RS, 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: 494–503.e6.
- Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol* 1995; 132: 942–949.
- Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; 19: 210–216.
- Salek MS, Jung S, Brincat-Ruffini LA, MacFarlane L, Lewis-Jones MS, Basra MK, et al. Clinical experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995–2012. *Br J Dermatol* 2013; 169: 734–759.
- Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. *Dermatology* 2015; 230: 27–33.
- Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials* 1989; 10: 407–415.
- 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: 192–199.
- Chamlin SL, Mattson CL, Frieden IJ, Williams ML, Mancini AJ, Cella D, et al. The price of pruritus: sleep disturbance and cosleeping in atopic dermatitis. *Arch Pediatr Adolesc Med* 2005; 159: 745–750.
- Garcia PL, Ebert U. Frontiers of rapid itch relief: a review of methylprednisolone aceponate. *J Eur Acad Dermatol Venereol* 2012; 26(suppl 6): 9–13.
- Baumer W, Hoppmann J, Rundfeldt C, Kietzmann M. Highly selective phosphodiesterase 4 inhibitors for the treatment of allergic skin diseases and psoriasis. *Inflamm Allergy Drug Targets* 2007; 6: 17–26.
- Grewe SR, Chan SC, Hanifin JM. Elevated leukocyte cyclic AMP-phosphodiesterase in atopic disease: a possible mechanism for cyclic AMP-agonist hyporesponsiveness. *J Allergy Clin Immunol* 1982; 70: 452–457.
- Andoh T, Yoshida T, Kuraishi Y. Topical E6005, a novel phosphodiesterase 4 inhibitor, attenuates spontaneous itch-related responses in mice with chronic atopy-like dermatitis. *Exp Dermatol* 2014; 23: 359–361.
- Phan NQ, Blome C, Fritz F, Gerss J, Reich A, Ebata T, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol* 2012; 92: 502–507.
- Fleischer AB Jr, Boguniewicz M. An approach to pruritus in atopic dermatitis: a critical systematic review of the tacrolimus ointment literature. *J Drugs Dermatol* 2010; 9: 488–498.