The Effect of Crisaborole Ointment, 2%, on Pruritus in Patients With Atopic Dermatitis (AD): An Extended Analysis

Gil Yosipovitch,[1] Eric Simpson,[2] Huaming Tan,[3] Robert A. Gerber,[3] Thomas Luger,[4] Sonja Ständer,[4] Wynnis Tom,[5] Joseph C. Cappelleri,[3] Andrew G. Bushmakin,[3] William C. Ports,[3] Anna M. Tallman[6]

[1]*University of Miami, Miller School of Medicine, Miami, FL, USA;* [2]*Oregon Health and Science University, Portland, OR, USA;* [3]*Pfizer Inc., Groton, CT, USA;* [4]*University Hospital Münster, Münster, Germany;* [5]*Rady Children's Hospital-San Diego, San Diego, CA, USA;* [6]*ICON plc, Gaithersburg, MD, USA;* [4]*Pfizer Inc., New York, NY, USA*

BACKGROUND

- Crisaborole ointment is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild to moderate AD[1]
- The safety and efficacy of crisaborole was previously established in 2 identically designed, multicenter, randomized, double-blind, vehicle-controlled Phase 3 trials (AD-301: NCT02118766; AD-302: NCT02118792)[2]
- Within these trials, pruritus severity was measured using the Severity of Pruritus Scale (SPS), a 4-point rating scale ranging from (none: no itching) to 3 (severe: bothersome itching/scratching which disturbs sleep) adapted from the Atopic Dermatitis Severity Index[3] to quantify itch over a 24-hour recall period (**Table 1**)
- In the prespecified analysis, SPS data were analyzed using each SPS observation as a single measurement[2]
- Subsequent validation analysis has determined that the mean of at least 2 SPS observations is necessary to provide a reliable measure of pruritus severity

Table 1. Severity of Pruritus Scale (SPS)

Instructions: Please think about your itching (or your child's itching if you are completing for your child) over the past 24 hours and choose the category that best describes it.		
Score	Grade	Definition
0	None	No itching
1	Mild	Occasional, slight itching/scratching
2	Moderate	Constant or intermittent itching/scratching which is not disturbing sleep
3	Severe	Bothersome itching/scratching which is disturbing sleep

OBJECTIVES

- To conduct an extended analysis of the SPS data from the pivotal Phase 3 trials to assess the efficacy of crisaborole for treatment of AD-associated pruritus using the mean of at least 2 SPS observations to provide a reliable measure of pruritus

METHODS

Data Source

- Data were sourced from 2 identically designed, multicenter, vehicle-controlled, double-blind, Phase 3 crisaborole trials (AD-301: NCT02118766; AD-302: NCT02118792)[2]
  - Eligible patients were ≥2 years of age, with a clinical diagnosis of AD with ≥5% treatable body surface area involvement and a baseline Investigator's Static Global Assessment (ISGA) score of mild (2) or moderate (3) (the ISGA is a 5-point rating scale measuring overall disease severity from clear [0] to severe [4])
  - Patients were randomly assigned 2:1 to receive crisaborole or vehicle and instructed to apply the study drug to each lesion twice daily for 28 days
  - Pruritus severity was recorded twice daily using the SPS via electronic diary from baseline/day 1 through day 29

Analysis

- Improvement in pruritus was indicated by an SPS score ≤1, with at least a 1-grade improvement from baseline
- A minimum of 2 SPS observations were averaged for each analysis to meet the test-retest reliability threshold of acceptability (intraclass correlation coefficient ≥0.70)
  - Baseline for all analyses was the mean of ≥2 SPS measurements on day 1

Time to Improvement in Pruritus

- Based on daily SPS values, calculated as the mean of ≥2 SPS measurements on that day

Proportion of Patients Who Experienced Improvement in Pruritus

- Assessed at each weekly study visit and calculated using the mean of all available postbaseline SPS scores for the patient during the corresponding preceding week (generally up to 14 measurements)

Pruritus Score by Week

- Weekly SPS scores were calculated as the mean of all available postbaseline SPS scores for the patient during the corresponding preceding week (up to 14 measurements)
- Scores were analyzed using a repeated-measures longitudinal model with fixed effects for treatment, visit, treatment-by-visit interaction, and baseline value
- The previously estimated clinically important difference (CID) of 0.20 was used as a threshold to assess the clinical meaningfulness of the treatment effect

Proportion of Responders by Week

- Per the pruritus score by week analysis, weekly SPS scores were calculated as the mean of all available postbaseline SPS scores for the patient during the preceding corresponding week (up to 14 measurements)
- Responders were defined by a previously estimated clinically important response (CIR) of ≥0.19-point reduction in severity of pruritus from baseline

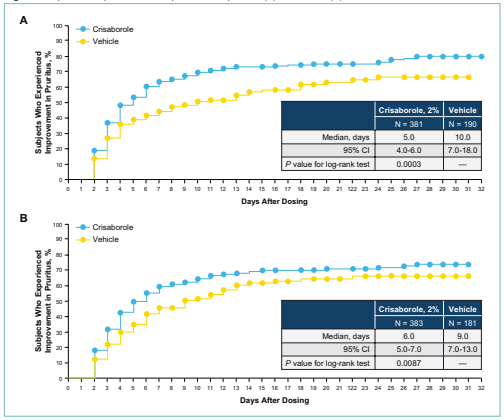
RESULTS

- The intent-to-treat population included 759 patients in AD-301 (503 crisaborole; 256 vehicle) and 763 patients in AD-302 (513 crisaborole; 250 vehicle)[2]
- The mean baseline SPS scores (standard deviation [SD]) were 1.83 (0.79) for crisaborole-treated patients and 1.75 (0.83) for vehicle-treated patients in AD-301 and were 1.81 (0.77) for crisaborole-treated patients and 1.79 (0.72) for vehicle-treated patients in AD-302

Time to Improvement in Pruritus

- Median time to improvement in pruritus was significantly less for crisaborole-treated patients than for vehicle-treated patients in both trials (**Figure 1**)
  - AD-301: 5.0 days (95% CI, 4.0-6.0 days) for crisaborole-treated patients compared with 10.0 days (95% CI, 7.0-18.0 days) for vehicle-treated patients ($P = 0.0003$) (**Figure 1A**)
  - AD-302: 6.0 days (95% CI, 5.0-7.0 days) for crisaborole-treated patients compared with 9.0 days (95% CI, 7.0-13.0 days) for vehicle-treated patients ($P = 0.0087$) (**Figure 1B**)

Figure 1. Kaplan-Meier plot of time to improvement in pruritus. (A) AD-301 and (B) AD-302.

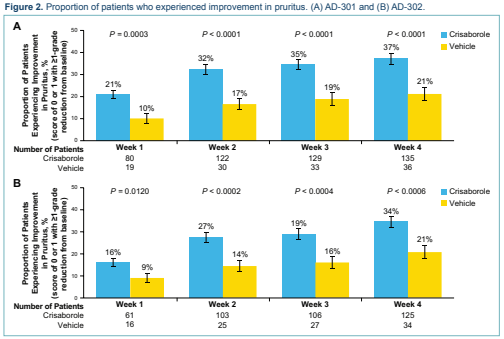


BID, twice daily; SPS, Severity of Pruritus Scale.
Improvement in pruritus was indicated by an SPS score ≤1, with at least a 1-grade improvement from baseline. Baseline was the mean of at least 2 SPS assessments on day 1. Patients with fewer than 2 SPS assessments on day 1 were considered to have missing data. SPS daily values were calculated as the mean of 2 or more assessments on that day. If fewer than 2 assessments were available, SPS was considered missing. Analysed using Kaplan-Meier methods and the log-rank test.

Proportion of Patients Who Experienced Improvement in Pruritus

- A significantly greater proportion of crisaborole-treated patients exhibited improvement in pruritus at each weekly time point than vehicle-treated patients in both trials (**Figure 2**)
  - AD-301 week 4: 37% (95% CI, 32%-42%) of crisaborole-treated patients compared with 21% (95% CI, 15%-27%) of vehicle-treated patients ($P < 0.0001$) (**Figure 2A**)
  - AD-302 week 4: 34% (95% CI, 30%-39%) of crisaborole-treated patients compared with 21% (95% CI, 14%-27%) of vehicle-treated patients ($P = 0.0006$) (**Figure 2B**)

Figure 2. Proportion of patients who experienced improvement in pruritus. (A) AD-301 and (B) AD-302.

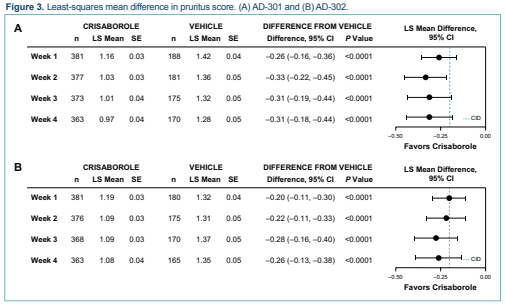


SPS, Severity of Pruritus Scale.
Improvement in pruritus was indicated by an SPS score ≤1, with at least a 1-grade improvement from baseline. Baseline was the mean of at least 2 SPS assessments on day 1. Patients with fewer than 2 SPS assessments on day 1 were considered to have missing data. Weekly SPS scores for each subject were calculated as the mean of all available postbaseline SPS scores for the subject during the corresponding week (generally up to 14 measurements). Only subjects with a mean baseline value and a postbaseline assessment were included. Error bars denote standard error.

Pruritus Score by Week

- Crisaborole-treated patients exhibited significantly lower mean pruritus scores than vehicle-treated patients at each weekly time point in both trials (**Figure 3**)
- The least-squares mean difference between pruritus scores for crisaborole-treated and vehicle-treated patients was ≥0.20 at all time points in both trials, which exceeded the CID previously identified (**Figure 3**)

Figure 3. Least-squares mean difference in pruritus score. (A) AD-301 and (B) AD-302.

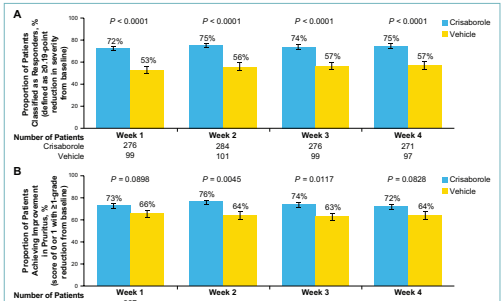


CID, clinically important difference; LS, least squares; SE, standard error; SPS, Severity of Pruritus Scale.
The dotted line represents the estimated CID of 0.20. Baseline was the mean of at least 2 SPS assessments on day 1. Subjects with fewer than 2 SPS assessments on day 1 were considered to have missing data. Weekly SPS scores for each subject were calculated as the mean of all available postbaseline SPS scores for the subject during the corresponding week (generally up to 14 measurements). Only subjects with nonmissing baseline scores were included. All statistics were derived from a repeated-measures model with fixed effects for treatment, visit, treatment-by-visit interaction, and baseline value. Error bars denote standard error of least-squares mean.

Proportion of Responders by Week

- A significantly greater proportion of crisaborole-treated patients experienced CIR (defined as ≥0.19-point reduction in severity of pruritus from baseline) than vehicle-treated patients at each time point in AD-301 and at weeks 2 and 3 in AD-302 (**Figure 4**)

Figure 4. Proportion of patients experiencing clinically important response. (A) AD-301 and (B) AD-302.



SPS, Severity of Pruritus Scale.
Responders were defined by a ≥0.19-point reduction in severity of pruritus from baseline. Baseline was the mean of at least 2 SPS assessments on day 1. Weekly SPS scores for each subject were calculated as the mean of all available postbaseline SPS scores for the subject during the corresponding week (generally up to 14 measurements). Only subjects with an average baseline and postbaseline assessments were included.

CONCLUSIONS

- **The results of this extended analysis confirm that crisaborole is effective in treating AD-associated pruritus**
  - **Patients treated with crisaborole experienced improvement in pruritus earlier than vehicle-treated patients**
  - **Crisaborole-treated patients exhibited significantly lower pruritus scores than vehicle-treated patients, with a difference that was considered clinically meaningful**
  - **A greater proportion of crisaborole-treated patients experienced improvement in severity of pruritus and CIR than vehicle-treated patients**

REFERENCES

1. Eucrisa (crisaborole) ointment, 2%, for topical use [prescribing information]. Palo Alto, CA: Anacor Pharmaceuticals, Inc.; 2016.
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