Pruritus Response and Skin Biomarkers of Atopic Dermatitis (AD) With Crisaborole Versus Vehicle in Patients With Mild-to-Moderate AD

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BACKGROUND

- AD is a highly prevalent, chronic inflammatory skin disease characterized by eczematous lesions and intense pruritus[1]
  - Pruritus is the most common and the most burdensome AD symptom and is associated with impaired quality of life[2]
  - Most patients have mild-to-moderate disease that can be managed with topical therapies[3-5]
- Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD
- In 2 identically designed pivotal phase 3 trials, crisaborole, compared with vehicle, significantly reduced pruritus from the first postbaseline assessment (day 2, after 1 day of treatment), continuing through the end of treatment (week 4)[6-8]
- The MOA of crisaborole on AD and pruritus is not well defined
- A single-center, vehicle-controlled, intrapatient, phase 2a study (NCT03233529) was designed to characterize the MOA of crisaborole through evaluation of changes in skin biomarkers and correlation of biomarker changes with measures of clinical improvement, including pruritus, in adults with mild-to-moderate AD[9]

OBJECTIVE

- **To assess the relationship between pruritus response and changes in key skin biomarkers in AD lesions treated with crisaborole versus vehicle**

METHODS

Study Design

- Patients ≥18 years of age with a clinical diagnosis of mild-to-moderate AD (ISGA of 2 or 3) and %BSA ≥0.5 to ≤10 were included
- 2 moderate-to-severe target lesions with identical lesion ISGA scores (≥3 cm × 3 cm, located ≥5 cm apart) were randomly assigned intrapatient (1:1) to receive double-blind crisaborole or vehicle applied only to target lesions, at the investigational site, twice daily at a rate of 3 mg/cm^2 for 14 days
  - Thereafter, patients applied open-label crisaborole twice daily to all AD-affected areas, excluding the scalp, for 28 days

Assessments and Outcomes

- During the double-blind period, pruritus severity was assessed daily by the patient for each target lesion using an 11-point NRS
  - Proportions of target lesions with ≥2-, ≥3-, and ≥4-point improvement from baseline in pruritus NRS score were evaluated in this post hoc analysis
- Punch-biopsy specimens were collected for biomarker analysis at baseline (before dose), day 8 (optional), and day 15
  - Half of each 4.5-mm punch-biopsy specimen was processed for gene expression studies (microarray, qRT-PCR), and half was processed for IHC
  - TaqMan low-density array cards (Applied Biosystems) were used for qRT-PCR; IHC staining was performed on frozen cryostat sections using purified mouse antihuman monoclonal antibodies

Statistical Analysis

- Proportions of target lesions with ≥2-, ≥3-, and ≥4-point improvement in pruritus NRS score were determined
  - Calculations were based on subsets of the full analysis set of lesions (all target lesions that were treated with ≥1 dose of study medication) with pruritus NRS score ≥2, ≥3, and ≥4 at baseline, respectively
  - 95% CIs for proportions of target lesions with pruritus NRS response were calculated by exact method
- Biomarker analyses were performed on the per-protocol set of target lesions (all target lesions that were treated with ≥1 dose of study medication, with day 1 and day 15 biopsies, and without meaningful protocol violations during the double-blind period)
  - Correlations between biomarkers and change from baseline in pruritus NRS at day 15 were evaluated using Spearman correlation

RESULTS

- 40 patients were included in the study, and 38 (95%) completed the study
  - 2 patients discontinued because of the adverse event of worsening AD, which was considered unrelated to treatment: 1 during the double-blind period and 1 during the open-label period
- Biopsy specimens were collected from all 40 patients at baseline and from 22 and 39 patients at days 8 (optional biopsy) and 15, respectively
- Most patients (87.5%) had moderate disease at baseline (per ISGA) with moderate pruritus (mean global pruritus NRS score, 6.3) per published severity strata[10] (**Table 1**)
  - Baseline target lesion characteristics were similar across treatments; most lesions (97.5% for both groups) were moderate (per lesion ISGA) with moderate pruritus (mean target lesion pruritus NRS score 5.9, for both groups) (**Table 2**)

Table 1. Demographics and Baseline Disease Characteristics

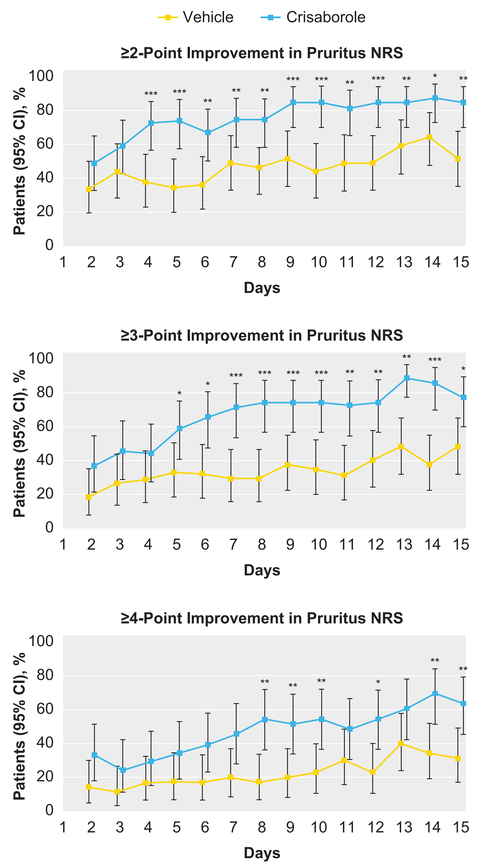
	All Patients N=40
Age, mean (SD), years	32.2 (11.29)
Female, n (%)	27 (67.5)
Race, n (%)	
White	34 (85.0)
Black or African American	3 (7.5)
Asian	3 (7.5)
ISGA, n (%	
Mild (2)	5 (12.5)
Moderate (3)	35 (87.5)
%BSA, mean (SD)	4.3 (2.79)
Pruritus NRS, mean (SD)	6.3 (2.03)

Table 2. Target Lesion Baseline Characteristics

n (%)	Vehicle-Treated Lesions N=40	Crisaborole-Treated Lesions N=40
Lesion ISGA		
Moderate (3)	39 (97.5)	39 (97.5)
Severe (4)	1 (2.5)	1 (2.5)
Lesion pruritus NRS score		
Mean (SD)	5.9 (2.03)	5.9 (2.18)
≥2	40 (100)	40 (100)
≥3	38 (95.0)	36 (90.0)
≥4	36 (90.0)	34 (85.0)

- Improvements in pruritus NRS scores were observed for crisaborole-treated versus vehicle-treated lesions on the first day after treatment initiation (day 2; −1.9 vs −1.0, *P*=0.0188), with continued improvement through day 15 (−3.9 vs −2.0, *P*<0.0001) (**Figure 1**)
  - Global pruritus NRS scores also improved in the open-label portion of the study
- Differences in proportions of target lesions with ≥2-, ≥3-, and ≥4-point improvement in pruritus NRS score for crisaborole-treated compared with vehicle-treated target lesions were observed starting at days 4 (after 3 days of treatment), 5, and 8, respectively (**Figure 2**)

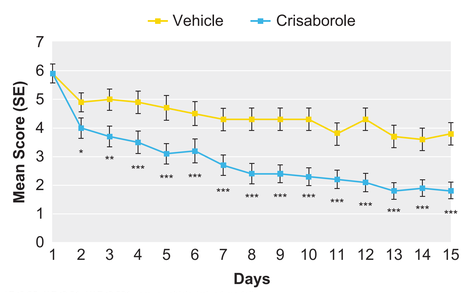
Figure 2. Proportions of Target Lesions With ≥2-, ≥3-, and ≥4-Point Improvement From Baseline in Pruritus NRS Score



*P<0.05, **P<0.01, ***P<0.001 versus vehicle (McNemar's test).

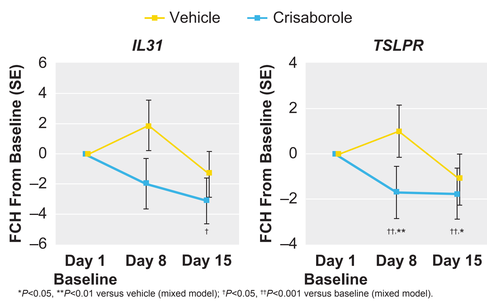
- Compared with vehicle, crisaborole reduced the expression of pruritus-related *IL31* at day 8 (FCH, −1.99 vs 1.92, *P*=0.071) and day 15 (−3.12 vs −1.36, *P*=0.19) and *TSLPR* at day 8 (−1.71 vs 1.01, *P*=0.0086) and day 15 (−1.76 vs −1.14, *P*=0.013) (**Figure 3**)
- Spearman correlation coefficients for change in pruritus biomarkers and change from baseline in target lesion pruritus NRS score across treatments at day 15 were −0.052 for *IL31* and 0.224 for *TSLPR*

Figure 1. Mean Target Lesion Pruritus NRS Scores



*P<0.05, **P<0.01, ***P<0.001 versus vehicle (mixed model).

Figure 3. FCH in Pruritus-Related Biomarkers Measured by qRT-PCR



*P<0.05, **P<0.01 versus vehicle (mixed model); †P<0.05, ††P<0.001 versus baseline (mixed model).

CONCLUSIONS

- **A significant difference between crisaborole and vehicle in improvement in lesion pruritus NRS score was observed starting 1 day after treatment initiation**
- **Numerically greater improvements were observed for crisaborole-treated target lesions compared with vehicle-treated target lesions in patients with mild-to-moderate AD throughout the double-blind period, regardless of the threshold applied for pruritus NRS response; furthermore, significantly greater proportions of crisaborole-treated target lesions showed pruritus NRS improvement starting at days 4-8, depending on the threshold used**
- **Compared with vehicle, crisaborole treatment led to numerically greater reductions in expression of *IL31* and statistically significantly greater reductions in expression of *TSLPR***
- **Despite these patient-reported improvements in pruritus and reduced expression of key pruritus-related biomarkers, no correlations were observed between change from baseline in target lesion pruritus NRS and *IL31* or *TSLPR* expression**
- **Further research is needed to elucidate the mechanism of the effect of crisaborole on pruritus**

Abbreviations **%BSA**, percentage of treatable body surface area; **AD**, atopic dermatitis; **FCH**, fold change; **IHC**, immunohistochemistry; ***IL31***, interleukin 31; **ISGA**, Investigator's Static Global Assessment; **MOA**, mechanism of action; **NRS**, numeric rating scale; **qRT-PCR**, quantitative real-time polymerase chain reaction; **SE**, standard error; ***TSLPR***, thymic stromal lymphopoietin receptor

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