Efficacy Trends With Continuous Long-Term Use of Crisaborole in Patients With Mild-to-Moderate Atopic Dermatitis (AD)

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CrisADe

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BACKGROUND

- AD is a chronic inflammatory skin disease that often requires long-term treatment[1]
- There are safety concerns with the long-term use of commonly recommended topical medications such as topical corticosteroids and topical calcineurin inhibitors[2,3]
- Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD
  - Crisaborole efficacy and safety were demonstrated in identically designed, 28-day, vehicle-controlled, phase 3 studies (AD-301, NCT02118766; AD-302, NCT02118792)[4]
  - The safety of crisaborole was further explored in a 48-week, open-label extension study (AD-303) examining noncontinuous use of crisaborole[5]

OBJECTIVE

- **To assess post hoc the efficacy and safety of continuous long-term use of crisaborole in patients aged ≥2 years with mild-to-moderate AD in the 48-week open-label extension study**

METHODS

Study Design

- Patients aged ≥2 years with mild-to-moderate AD who completed a phase 3 study (AD-301, AD-302) without treatment-related safety issues were eligible to participate in the 48-week, open-label, single-arm, phase 3 safety study (AD-303)
- During the extension study, all patients were treated with open-label crisaborole applied twice daily to all treatable AD-involved areas, excluding the scalp, and were evaluated every 28 days
- At the end of each 28-day treatment cycle, disease severity was assessed using the ISGA (0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe)
  - Patients with ISGA 0/1 at the end of a 28-day cycle did not receive crisaborole for the next 28-day cycle (off treatment)
  - Patients with ISGA ≥2 received crisaborole for the next 28-day cycle (on treatment)

Post Hoc Assessments

- For the purpose of this post hoc analysis, patients were stratified by number of initial consecutive on-treatment cycles (1, 2, 3, or 4 cycles) into cohorts 1-4, respectively
- Efficacy endpoints
  - Proportion of patients achieving ISGA 0/1 at the end of their initial on-treatment period
  - Proportion of patients achieving ISGA 0/1 at end of their first off-treatment cycle who had previously achieved ISGA 0/1 at the end of their initial on-treatment period
  - Proportion of patients who restarted treatment after their first off-treatment period
  - The number of off-treatment cycles before restarting treatment
  - Proportion of patients who recaptured ISGA 0/1 at the end of the first retreatment cycle
- Safety: TEAEs and TRAEs

RESULTS

- 418 patients received crisaborole for 1-4 consecutive initial on-treatment cycles and were included in this analysis
- Baseline characteristics across cohorts were similar except for the distribution of ISGA scores, which represented a numerically higher percentage of patients with moderate and severe disease (higher ISGA score) with the increasing number of initial consecutive on-treatment cycles (**Table 1**)
- In all groups, <6% of patients discontinued the study during the initial set of consecutive on-treatment cycles
  - Only 1 patient discontinued the study during the initial set of consecutive on-treatment cycles because of an AE; other reasons for discontinuation such as "withdrawn consent," "other," and "lost to follow-up" were <4% each across cohorts
- After 1-4 consecutive on-treatment cycles, 77.6%, 76.3%, 59.4%, and 43.1% of patients, respectively, achieved ISGA 0/1 (**Figure 1A**)
  - Of these patients who achieved ISGA 0/1 at the end of the initial on-treatment period, 49.5%, 37.8%, 44.4%, and 45.2% maintained ISGA 0/1 at the end of the next 28-day cycle while off treatment (**Figure 1B**)
- The proportion of patients who reinitiated treatment increased with the number of initial consecutive on-treatment cycles (**Table 2**)

Table 1. Demographics and Baseline Disease Characteristics

	Cohort 1 N=133	Cohort 2 N=106	Cohort 3 N=106	Cohort 4 N=73
Age, mean (SD), y	11.4 (10.1)	13.7 (12.2)	10.9 (9.9)	11.0 (9.8)
White race, n (%)	85 (63.9)	67 (63.2)	66 (62.3)	40 (54.8)
%BSA, mean (SD)	18.3 (18.8)	18.4 (16.4)	20.6 (19.6)	19.6 (17.3)
ISGA, n (%)				
Clear (0)	7 (5.3)	6 (6.7)	3 (2.8)	1 (1.4)
Almost clear (1)	18 (13.5)	10 (9.4)	3 (3.8)	1 (1.4)
Mild (2)	61 (45.9)	47 (44.3)	46 (43.4)	21 (28.8)
Moderate (3)	44 (33.1)	42 (39.6)	50 (47.2)	26 (63.0)
Severe (4)	3 (2.3)	1 (0.9)	3 (2.8)	4 (5.5)
ISGA, mean (SD)	2.1 (0.9)	2.2 (0.9)	2.4 (0.7)	2.7 (0.7)

Figure 1. Patients (A) Who Achieved ISGA 0/1 at the End of Their Initial On-Treatment Period and (B) Who Maintained ISGA 0/1 After 28 Days Off Treatment Among Those Who Previously Achieved ISGA 0/1

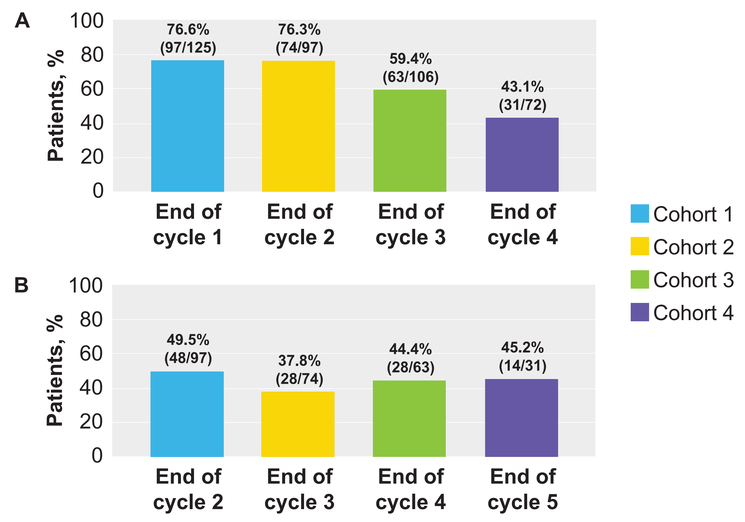

Table 2. Treatment Patterns After Initial On-Treatment Period

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Restarted treatment,[a] n/N (%)	77/97 (79.4)	60/74 (81.1)	55/63 (87.3)	24/31 (77.4)
Consecutive cycles off treatment				
Mean (SD)	2.5 (2.7)	1.9 (2.4)	1.7 (1.8)	2.1 (1.9)
Median (range)	1.0 (0-11)	1.0 (0-10)	1.0 (0-9)	1.0 (0-8)
Reachieved ISGA 0/1 at end of first retreatment cycle,[a] n/N (%)	41/77 (53.3)	26/60 (43.3)	25/55 (45.5)	9/24 (37.5)

[a]Among patients who achieved ISGA 0/1 at the end of their initial on-treatment period.

- No new safety signals were observed with increased duration of use up to 4 cycles (4 months) (**Table 3**)
- The incidence rate (per 100 patient-cycles) of TEAEs during the initial on-treatment period ranged from 12.9 to 23.4 across cohorts
- The incidence rate (per 100 patient-cycles) for any TRAEs was low across all 4 cohorts and decreased with increasing number of initial consecutive on-treatment cycles (5.1 for cohort 1, 2.5 for cohort 2, 1.3 for cohort 3, 0.3 for cohort 4)

Table 3. All-Cause and Treatment-Related Adverse Events by Cohort During On-Treatment Period

	Cohort 1 N=133	Cohort 2 N=106	Cohort 3 N=106	Cohort 4 N=73
TEAEs				
Any TEAE, n (%)	25 (18.8)	33 (31.1)	35 (33.0)	31 (42.5)
Most frequently reported TEAEs (≥5% in any group), n (%)				
Dermatitis atopic	5 (3.8)	5 (4.7)	8 (7.5)	5 (6.8)
Cough	3 (2.3)	1 (0.9)	2 (1.9)	5 (6.8)
Upper respiratory tract infection	4 (3.0)	2 (1.9)	4 (3.8)	5 (6.8)
Viral upper respiratory tract infection	1 (0.8)	3 (2.8)	6 (5.7)	1 (1.4)
TRAEs				
Any TRAE, n (%)	6 (4.5)	5 (4.7)	4 (3.8)	1 (1.4)
Most frequently reported TRAEs (≥2% in any group), n (%)				
Dermatitis atopic	2 (1.5)	4 (3.8)	1 (0.9)	1 (1.4)
Treatment-related application site reactions, n (%)				
Application site dermatitis	0	0	0	0
Application site pain	1 (0.8)	1 (0.9)	2 (1.9)	0
Application site paraesthesia	1 (0.8)	0	0	0
Application site pruritus	0	0	2 (1.9)	0

CONCLUSIONS

- **Continuous long-term treatment with crisaborole beyond 28 days may be necessary to maintain control of AD symptoms in some patients with mild-to-moderate AD, especially for patients with higher ISGA scores**
- **After discontinuing therapy, some patients maintain ISGA 0/1 (clear/almost clear) for ~1-2 months (ie, had 1 or 2 off-treatment cycles before restarting treatment)**
  - **ISGA 0/1 (clear/almost clear) was reachieved after restarting therapy for one-third to one-half of patients**
- **No new safety signals were observed with crisaborole use for multiple consecutive cycles**
- **Use of crisaborole as maintenance or prophylactic therapy for AD should be studied further**

Abbreviations **%BSA**, percentage of treatable body surface area; **AD**, atopic dermatitis; **AE,** adverse event; **ISGA**, Investigator's Static Global Assessment; **TEAE**, treatment-emergent adverse event; **TRAE**, treatment-related adverse event.

References **1.** Weidinger S et al. *Nat Rev Dis Primers.* 2018;4:1. **2.** Hengge UR et al. *J Am Acad Dermatol.* 2006;54:1-15. **3.** Luger T et al. *Pediatr Allergy Immunol.* 2015;26:306-315. **4.** Paller AS et al. *J Am Acad Dermatol.* 2016;75:494-503.e6. **5.** Eichenfield LF et al. *J Am Acad Dermatol.* 2017;77:641-649.e5.