Safety, Effectiveness, and Pharmacokinetics of Crisaborole in Infants Aged 3 to < 24 Months with Mild-to-Moderate Atopic Dermatitis: A Phase IV Open-Label Study (CrisADe CARE 1)

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Abstract

Background Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate atopic dermatitis (AD).

Objectives The aim of this study was to evaluate the safety, effectiveness, and pharmacokinetics (PK) of crisaborole in infants aged 3 to < 24 months with mild-to-moderate AD in an open-label study.

Methods Infants (3 to < 24 months) with Investigator’s Static Global Assessment (ISGA) of mild (2) or moderate (3) and percentage of treatable body surface area (%BSA) ≥ 5 received crisaborole twice daily for 28 days; a cohort with moderate AD per ISGA and %BSA ≥ 35 were included in a PK analysis. Endpoints included safety (primary), efficacy, and PK (exploratory).

Results Included were 137 infants total (mean age [SD], 13.6 months [6.42]), with 21 in the PK cohort (12.7 months [6.58]). Treatment-emergent adverse events (TEAEs) were reported for 88 (64.2%) patients (98.9% rated as mild/moderate). TEAEs were considered treatment-related for 22 patients (16.1%); most frequently reported were application site pain (3.6%), application site discomfort (2.9%), and erythema (2.9%). ISGA clear/almost clear with ≥ 2-grade improvement at day 29 was achieved by 30.2% of patients. From baseline to day 29, mean percentage change in Eczema Area and Severity Index score was − 57.5%, and mean change in Patient-Oriented Eczema Measure total score was − 8.5. Crisaborole systemic exposures in infants were characterized and, based on nonlinear regression analysis, were comparable with that in patients aged ≥ 2 years.

Conclusions In this open-label study, crisaborole was well tolerated and effective in infants (3 to < 24 months) with mild-to-moderate AD with systemic exposures similar to patients aged ≥ 2 years.

Clinical Trial Registration NCT03356977.

Plain Language Summary

Atopic dermatitis (AD) is a skin disease that causes inflamed and itchy skin. Crisaborole is an ointment that is approved to treat patients aged 2 years and older with mild-to-moderate AD. This clinical trial studied crisaborole in infants with mild-to-moderate AD who were 3 to under 24 months old. These infants were treated with crisaborole twice a day for 28 days. The trial studied crisaborole’s safety, effectiveness, and absorption into the bloodstream. In total, 137 infants were treated. Although side effects of some sort occurred in about two-thirds of patients, only 1 in 6 patients experienced side effects
Atopic dermatitis (AD) is a chronic, highly pruritic, inflammatory skin disease that affects an increasing number of patients worldwide, especially in industrialized, temperate countries, such as the United States [1–3]. AD affects patients of all ages and is one of the most common, chronic, relapsing childhood dermatoses, impacting 15–30% of the pediatric population in the United States [1, 3]. Approximately 60% of patients experience first signs and symptoms before 1 year of age, and disease activity for many persists well into adulthood [4]. AD has a profoundly negative effect on the health-related quality of life of pediatric patients—including sleep disturbance, mood changes, and impaired psychosocial functioning—and their caregivers—including psychological distress [2, 5].

There are a limited number of prescription agents approved to treat patients aged < 2 years with AD, some of which have safety concerns that include boxed warnings, resulting in a high unmet need in this patient population. Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD. As of January 2020, it is approved in the United States, Australia, Canada, and Israel for patients aged ≥ 2 years. In two vehicle-controlled phase III clinical studies of 1522 patients aged ≥ 2 years with mild-to-moderate AD (AD-301: NCT02118766; AD-302: NCT02118792), significantly more crisaborole-treated than vehicle-treated patients achieved Investigator’s Static Global Assessment (ISGA) success (defined as clear [0] or almost clear [1] with ≥ 2-grade improvement from baseline); 32.8% versus 25.4% achieved ISGA success in AD-301 (p = 0.038) and 31.4% versus 18.0% achieved ISGA success in AD-302 (p < 0.001) [6]. In addition, ISGA clear or almost clear was achieved in a significantly greater proportion of patients in the crisaborole group than the vehicle group; 51.7% versus 40.6% of patients achieved ISGA clear or almost clear in AD-301 (p = 0.005) and 48.5% versus 29.7% achieved ISGA clear or almost clear in AD-302 (p < 0.001) [6]. ‘Application site pain’ was the most common treatment-related adverse event (AE) in pooled data of the two studies (4.4% vs 1.2%; p = 0.001) [6]. In a long-term (48 weeks), single-arm, open-label safety extension study of the phase III trials (AD-303), the most frequently reported treatment-related AEs were ‘dermatitis atopic’ (3.1%), ‘application site pain’ (2.3%), and ‘application site infection’ (1.2%) [7].

The CrisADe CARE 1 study (NCT03356977), a multicenter, open-label, single-arm, phase IV trial, is the first trial designed to evaluate the safety, effectiveness, and pharmacokinetics (PK) of crisaborole applied twice daily to infants aged 3 to < 24 months with mild-to-moderate AD.

In addition, propylene glycol systemic exposure was assessed. Propylene glycol, an additive in many foods and an excipient in many commonly used medications, cosmetics, and topical products, including infant wipes, is a component of the crisaborole formulation. Propylene glycol is designated by the US Food and Drug Administration as a “generally recognized as safe” substance [8], but exposure to high systemic concentrations from administration or absorption of propylene glycol (especially in infants administered products containing propylene glycol by intravenous route), have resulted in AEs, including central nervous system toxicity, hyperosmolarity, hemolysis, cardiac arrhythmia, and lactic acidosis [9]. The measurement of propylene glycol systemic concentrations during treatment with crisaborole has not previously been studied.

1 Introduction

Atopic dermatitis (AD) is a chronic, highly pruritic, inflammatory skin disease that affects an increasing number of patients worldwide, especially in industrialized, temperate countries, such as the United States [1–3]. AD affects patients of all ages and is one of the most common, chronic, relapsing childhood dermatoses, impacting 15–30% of the pediatric population in the United States [1, 3]. Approximately 60% of patients experience first signs and symptoms before 1 year of age, and disease activity for many persists well into adulthood [4]. AD has a profoundly negative effect on the health-related quality of life of pediatric patients—including sleep disturbance, mood changes, and impaired psychosocial functioning—and their caregivers—including psychological distress [2, 5].

There are a limited number of prescription agents approved to treat patients aged < 2 years with AD, some of which have safety concerns that include boxed warnings, resulting in a high unmet need in this patient population. Crisaborole ointment, 2%, is a nonsteroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD. As of January 2020, it is approved in the United States, Australia, Canada, and Israel for patients aged ≥ 2 years. In two vehicle-controlled phase III clinical studies of 1522 patients aged ≥ 2 years with mild-to-moderate AD (AD-301: NCT02118766; AD-302: NCT02118792), significantly more crisaborole-treated than vehicle-treated patients achieved Investigator’s Static Global Assessment (ISGA) success (defined as clear [0] or almost clear [1] with ≥ 2-grade improvement from baseline); 32.8% versus 25.4% achieved ISGA success in AD-301 (p = 0.038) and 31.4% versus 18.0% achieved ISGA success in AD-302 (p < 0.001) [6]. In addition, ISGA clear or almost clear was achieved in a significantly greater proportion of patients in the crisaborole group than the vehicle group; 51.7% versus 40.6% of patients achieved ISGA clear or almost clear in AD-301 (p = 0.005) and 48.5% versus 29.7% achieved ISGA clear or almost clear in AD-302 (p < 0.001) [6]. ‘Application site pain’ was the most common treatment-related adverse event (AE) in pooled data of the two studies (4.4% vs 1.2%; p = 0.001) [6]. In a long-term (48 weeks), single-arm, open-label safety extension study of the phase III trials (AD-303), the most frequently reported treatment-related AEs were ‘dermatitis atopic’ (3.1%), ‘application site pain’ (2.3%), and ‘application site infection’ (1.2%) [7].

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In addition, propylene glycol systemic exposure was assessed. Propylene glycol, an additive in many foods and an excipient in many commonly used medications, cosmetics, and topical products, including infant wipes, is a component of the crisaborole formulation. Propylene glycol is designated by the US Food and Drug Administration as a “generally recognized as safe” substance [8], but exposure to high systemic concentrations from administration or absorption of propylene glycol (especially in infants administered products containing propylene glycol by intravenous route), have resulted in AEs, including central nervous system toxicity, hyperosmolarity, hemolysis, cardiac arrhythmia, and lactic acidosis [9]. The measurement of propylene glycol systemic concentrations during treatment with crisaborole has not previously been studied.

Key Points

Crisaborole ointment, 2%, was well tolerated in this open-label study of infants aged 3 to < 24 months with mild-to-moderate AD. Application site pain/discomfort was reported at a rate similar to those in crisaborole studies of patients aged ≥ 2 years; no new safety signals were identified.

Improvements from baseline in exploratory efficacy endpoints (including Investigator’s Static Global Assessment, Eczema Area and Severity Index, percentage of treatable body surface area, and Patient-Oriented Eczema Measure outcomes) were observed at the first postbaseline assessment (day 8 or 15, depending on outcome measure) and continued through the end of treatment (day 29).

Based on nonlinear regression analysis accounting for dose and age differences, crisaborole systemic exposure in infants aged 3 to < 24 months was comparable with that observed in crisaborole studies of patients aged ≥ 2 years.
2 Methods

2.1 Study Design

CrisADe CARE 1 was a multicenter, open-label, single-arm, phase IV study designed to evaluate the safety, efficacy, and PK of crisaborole in infants aged 3 to < 24 months with mild-to-moderate AD. The institutional review board at each study site approved the study protocol, and written informed consent was provided by parents or legal guardians. The study was conducted in accordance with the protocol, local legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, International Conference on Harmonisation Guideline for Good Clinical Practice, and the Declaration of Helsinki.

2.2 Patients and Treatment

Patients were recruited from 30 study sites across three countries (United States, Canada, and Australia). Enrolled patients were aged 3 to < 24 months with a diagnosis of AD per Hanifin and Rajka criteria [10], mild (2) or moderate (3) AD per ISGA [6], and a percentage of treatable body surface area (%BSA) ≥ 5, excluding the scalp. Patients were excluded if they had received systemic corticosteroids or immunosuppressive agents within 28 days of the first dose of study drug; used high- or medium-potency topical corticosteroids, topical calcineurin inhibitors (TCIs), topical antibiotics, light therapy, antibacterial soaps (for bathing), bleach baths, or topical sodium hypochlorite-based products on treatable AD lesions; used systemic immunosuppressive agents within 28 days of the first dose of study drug; used emollients, topical antihistamines, or topical hydrocortisone <1% on treatable AD lesions within 8 h of the first dose of study drug; used systemic antihistamines or low-potency topical corticosteroids within 3 days of the first dose of study drug; or used emollients, topical antihistamines, or topical hydrocortisone <1% on treatable AD lesions within 8 h of the first dose of study drug. Patients in the PK cohort (of whom at least three patients were to be aged 3 to < 9 months) were required to have moderate AD per ISGA with a treatable %BSA ≥ 35, excluding the scalp, at baseline and have adequate venous access. Patients were excluded from the PK cohort if they had lesions on the extremities (i.e., below wrists or ankles) or within 2 cm of the mouth to prevent inadvertent ingestion of crisaborole.

Open-label crisaborole was applied twice daily to all AD-involved areas of the body throughout the 28-day duration of the study, even if the AD lesions resolved. Patients in the PK cohort had twice daily visits on days 1 through the morning of day 8 for application of investigational product at the site. Caregivers were instructed to avoid applying crisaborole to mucous membranes and the scalp to avoid potential patient dissatisfaction with ointment application to scalp hair. In the PK cohort, application to the hands, feet, and perioral areas was also avoided to prevent inadvertent ingestion of crisaborole. Crisaborole could also be applied to any new treatable AD-involved areas that appeared outside of these areas following baseline (day 1) after consultation with the investigator at the next visit. Therapies not permitted during the study were systemic corticosteroids, antihistamines, leukotriene receptor antagonists, and immunosuppressants. Additionally, topical agents, such as low-to-high-potency topical corticosteroids, TCIs, topical antihistamines, topical antibiotics, topical sodium hypochlorite-based products, antibacterial soaps, bleach baths, diaper rash creams, lotions, ointments, and powders, and light therapy, were not permitted. Use of bland emollients was permitted to manage dry skin in areas surrounding but not on or overlapping with treatable AD-involved areas or on AD-involved areas where crisaborole was not applied.

For the non-PK cohort, treatment adherence was recorded by site staff for the day 1 morning dose and by parent/guardian at home in a dosing diary for subsequent doses. For the PK cohort, the day 1 morning dose through the day 8 morning dose were recorded by site staff, while all subsequent doses were recorded by parent/guardian at home in the dosing diary. Patients were considered adherent to treatment if 80–120% of the expected number of doses were received.

2.3 Study Outcomes and Assessments

Site visits occurred at screening, baseline (day 1), day 8, day 15, day 22 (telephone visit), and day 29 during the treatment period, and telephone follow-up visits occurred at days 36 and 57.

Primary endpoints were the incidence of treatment-emergent adverse events (TEAEs), which were assessed at all study visits and follow-up visits; clinically significant changes in vital signs, such as temperature, blood pressure, pulse, and respiratory rate (assessed at screening, baseline, day 8, day 15, and day 29); height, weight, and physical examination (assessed at baseline and day 29); electrocardiography (assessed at baseline, day 8, and day 29); and laboratory assessments, including metabolic panels, serum chemistry, and hematology panels (assessed at screening and day 29, and also at day 8 for the PK cohort). Blood pressure, electrocardiography, and cardiovascular and neurologic physical examination were included to monitor for potential cardiovascular and neurologic effects of propylene glycol. The investigator recorded all directly observed TEAEs and all TEAEs spontaneously reported by the patient’s parent/legal guardian. Each patient’s parent/legal guardian was to be questioned about the occurrence of AEs in a non-leading manner. Verbatim AE terms reported by the investigator were coded to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

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Exploratory efficacy endpoints included the proportion of patients who achieved ISGA success (defined as clear [0] or almost clear [1] with ≥ 2-grade improvement from baseline; ISGA was assessed at day 8, day 15, and day 29), proportion of patients who achieved ISGA clear or almost clear, percentage change from baseline in Eczema Area and Severity Index (EASI [11, 12]; assessed at days 15 and 29), change from baseline in %BSA (assessed at days 15 and 29), and change from baseline in Patient-Oriented Eczema Measure (POEM proxy version [13]; assessed at days 8, 15, and 29). Efficacy outcome measures are further described in Supplemental Table 1 (in Electronic Supplementary Material [ESM]).

Exploratory PK endpoints for crisaborole were maximum observed plasma concentration ($C_{\text{max}}$) at day 8, time to reach maximum observed plasma concentration ($T_{\text{max}}$) at day 8, and area under the plasma concentration-time profile for the dosing interval ($\text{AUC}_{\text{tau}}$) at day 8. PK parameters of crisaborole and its metabolites were assessed for the patients in the PK cohort using blood samples collected before the day 8 morning dose, 3 h after the day 8 morning dose, and 12 h after the day 8 morning dose. A 3-h sample time was chosen for $C_{\text{max}}$ based on previous data obtained from patients with AD and healthy volunteers (data on file). In addition, plasma concentrations of propylene glycol were assessed for all patients at screening and day 29 (12 h after the last dose). For patients in the PK cohort, propylene glycol concentrations were also assessed before the day 8 morning dose. Plasma samples were analyzed using validated analytical methods.

2.4 Study Statistical Considerations

All safety, efficacy, PK, and propylene glycol concentration data were summarized using descriptive statistics. The 95% CIs for binary endpoints were obtained by Clopper–Pearson exact method. A target of 125 enrolled patients was chosen to ensure that approximately 100 patients completed the study, assuming a 20% dropout rate. The sample size was determined by clinical judgment based on experience with other clinical studies of the investigational product. Statistical power was not calculated because there was no comparator group within the trial. A sample size of 16 patients was selected for the PK cohort to provide 96.0% overall power for 90% one-sided CIs for $C_{\text{max}}$ and $\text{AUC}_{\text{tau}}$ on day 8 to be less than the previously observed 85th percentiles of 166 ng/mL and 1281 ng h/mL, respectively, under maximum-use conditions in patients aged 2–17 years [14]. For the propylene glycol analysis, unplanned postbaseline visits were excluded.

3 Results

3.1 Patients

A total of 137 patients (non-PK cohort, $n = 116$; PK cohort, $n = 21$) from the United States ($n = 112$; 81.8%), Australia ($n = 15$; 10.9%), and Canada ($n = 10$; 7.3%) were evaluated in the study from January 16, 2018 (first patient first visit), to April 12, 2019 (last patient last visit). In total, nine patients (6.6%) discontinued treatment. Among these, four (2.9%) discontinued treatment because of a TEAE. Other reasons for discontinuing treatment were lack of efficacy ($n = 1$; 0.7%), lost to follow-up ($n = 1$; 0.7%), and withdrawal by parent or guardian ($n = 3$; 2.2%) (Supplemental Fig. 1 in ESM).

Patient demographics and baseline disease characteristics are summarized in Table 1. Overall, the median age was 13 months with median ISGA of 3.0 and mean %BSA of 28.1. One patient with severe AD (ISGA 4) was enrolled in and completed the trial but was considered a protocol deviation due to the severe baseline ISGA. Generally, baseline characteristics were similar between the patients included in the non-PK cohort and the PK cohort; however, %BSA involvement and disease severity (per ISGA and EASI scores) were greater in the PK cohort, consistent with inclusion criteria. A total of 22 patients (16.1%) had a medical history that included at least one other atopic condition, such as asthma, food allergies, and/or allergic/seasonal rhinitis. Approximately half of patients ($n = 72$; 52.6%) had used topical corticosteroids prior to entering the study, and two patients (1.5%) had used TCIs. Overall, 126 patients (92%) were considered adherent to the treatment regimen (received 80–120% of the expected number of doses).

3.2 Safety (Primary Endpoint)

In the overall study population ($N = 137$), all-cause TEAEs were reported for 88 (64.2%) patients; 98.9% of which were rated as mild or moderate. Treatment-related AEs were reported for 22 patients (16.1%). Four (2.9%) patients discontinued treatment because of a TEAE and remained in the study, including one patient who experienced a serious TEAE of ‘febrile convulsion’ (not related to treatment). The other three patients who discontinued treatment because of a TEAE were one patient with ‘dermatitis infected’ (not related to treatment), one patient with ‘application site pain’ (treatment-related), and one patient with ‘application site discomfort’ (treatment-related). The most frequently reported (≥ 5%) all-cause TEAEs were ‘pyrexia’ (9.5%), ‘upper respiratory tract infection’ (7.3%), ‘diabetes’ (7.3%), ‘dermatitis atopica’ (6.6%), ‘dermatitis diaper’ (6.6%), and ‘cough’ (5.1%) (Table 2). The most frequently reported
(≥ 2.5%) treatment-related treatment area AEs were ‘application site pain’ (n = 5; 3.6%), ‘application site discomfort’ (n = 4; 2.9%), and ‘erythema’ (n = 4; 2.9%) (Table 3). Treatment-related ‘application site pain’ or ‘application site discomfort’ (occurring in nine patients with no overlap between each AE term) were reported on the face for four patients, on the leg for four patients, on the arm for three patients, on the chest for two patients, on the back for one patient, on the neck for one patient, and on the abdomen for one patient. (Note: each patient could report more than one body location...
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For ‘application site pain’ or ‘application site discomfort’ AEs. Patients with an ‘application site erythema’ AE did not overlap with any patients with an ‘erythema’ AE. No safety signals were identified in clinical laboratory findings, weight, height, electrocardiograms, or vital signs (data not shown).

### 3.3 Efficacy

In the overall study population, 20.0% of patients achieved ISGA success at day 8 (first postbaseline assessment) and 30.2% achieved ISGA success at day 29 (Fig. 1). In addition, 40.7% of patients achieved ISGA of clear or almost clear at day 8 and 47.3% achieved ISGA of clear or almost clear at day 29 (Fig. 1). Mean (standard error [SE]) EASI score decreased from 11.8 (0.72) at baseline to 5.0 (0.50) for a mean percentage change (SE) from baseline of −57.5% (3.27) at day 29 (Fig. 2). Mean (SE) %BSA was reduced from 28.1 (1.88) at baseline to 12.4 (1.18) for a mean change (SE) from baseline of −15.2 (1.51) at day 29.

### Table 2

Overall all-cause TEAEs by preferred term reported for ≥2.5% of patients and corresponding treatment-related rates

| AD | TEAE | All-cause | Treatment-related |
|----|------|-----------|------------------|
| Pyrexia | 13 (9.5) | 0 |
| Upper respiratory tract infection | 10 (7.3) | 1 (0.7) |
| Diarrhea | 10 (7.3) | 0 |
| Dermatitis atopic | 9 (6.6) | 0 |
| Dermatitis diaper | 9 (6.6) | 0 |
| Cough | 7 (5.1) | 0 |
| Otitis media | 6 (4.4) | 1 (0.7) |
| Eczema | 5 (3.6) | 2 (1.5) |
| Application site pain | 5 (3.6) | 5 (3.6) |
| Conjunctivitis | 5 (3.6) | 0 |
| Rhinorrhea | 5 (3.6) | 0 |
| Dermatitis contact | 4 (2.9) | 1 (0.7) |
| Erythema | 4 (2.9) | 4 (2.9) |
| Rash | 4 (2.9) | 0 |
| Application site discomfort | 4 (2.9) | 4 (2.9) |
| Application site erythema | 4 (2.9) | 3 (2.2) |
| Ear infection | 4 (2.9) | 0 |
| Nasopharyngitis | 4 (2.9) | 0 |
| Teething | 4 (2.9) | 0 |

*AD atopic dermatitis, TEAE treatment-emergent adverse event

*a ‘Dermatitis atopic’ or ‘eczema’ may have been AD worsening/flare or a new AD lesion. A total of 14 patients experienced TEAEs that reflected symptoms of AD (‘dermatitis atopic’ or ‘eczema’) during the study. Of these 14 patients, eight had TEAE onset that occurred on or before day 29, and the other six had TEAE onset that occurred after day 29 (after crisaborole treatment)*

Table 3

Treatment area all-cause and treatment-related AEs by preferred term reported for ≥1 patients

| AD | TEAE | All-cause | Treatment-related |
|----|------|-----------|------------------|
| Pyrexia | 13 (9.5) | 0 |
| Upper respiratory tract infection | 10 (7.3) | 1 (0.7) |
| Diarrhea | 10 (7.3) | 0 |
| Dermatitis atopic | 9 (6.6) | 0 |
| Dermatitis diaper | 9 (6.6) | 0 |
| Cough | 7 (5.1) | 0 |
| Otitis media | 6 (4.4) | 1 (0.7) |
| Eczema | 5 (3.6) | 2 (1.5) |
| Application site pain | 5 (3.6) | 5 (3.6) |
| Conjunctivitis | 5 (3.6) | 0 |
| Rhinorrhea | 5 (3.6) | 0 |
| Dermatitis contact | 4 (2.9) | 1 (0.7) |
| Erythema | 4 (2.9) | 4 (2.9) |
| Rash | 4 (2.9) | 0 |
| Application site discomfort | 4 (2.9) | 4 (2.9) |
| Application site erythema | 4 (2.9) | 3 (2.2) |
| Rash | 4 (2.9) | 0 |
| Application site erythema | 4 (2.9) | 3 (2.2) |
| Dermatitis contact | 4 (2.9) | 1 (0.7) |
| Dermatitis diaper | 4 (2.9) | 0 |
| Rash | 4 (2.9) | 0 |
| Pruritus | 3 (2.2) | 3 (2.2) |
| Application site reaction | 2 (1.5) | 2 (1.5) |
| Rash pustular | 2 (1.5) | 0 |
| Application site irritation | 1 (0.7) | 1 (0.7) |
| Application site pruritus | 1 (0.7) | 1 (0.7) |
| Skin irritation | 1 (0.7) | 1 (0.7) |
| Erythema | 1 (0.7) | 0 |
| Molluscum contagiosum | 1 (0.7) | 0 |
| Dermatitis infected | 1 (0.7) | 0 |
| Impetigo | 1 (0.7) | 0 |
| Dermatitis allergic | 1 (0.7) | 0 |
| Rash papular | 1 (0.7) | 0 |
| Therapeutic procedure | 1 (0.7) | 0 |

*AD atopic dermatitis, AE adverse event

*a ‘Dermatitis atopic’ or ‘eczema’ may have been AD worsening/flare or a new AD lesion. A total of 13 patients experienced treatment area TEAEs that reflected symptoms of AD (‘dermatitis atopic’ or ‘eczema’) during the study. Of these 13 patients, eight had TEAE onset that occurred on or before day 29, and the other five had TEAE onset that occurred after day 29 (after crisaborole treatment)*

Fig. 1 ISGA response with crisaborole. 95% CIs were obtained by Clopper–Pearson exact method. ISGA success was defined as ISGA clear (0) or almost clear (1) with ≥2-grade improvement from baseline. ISGA Investigator’s Static Global Assessment
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29 (Supplemental Fig. 2 in ESM). Mean (SE) POEM total score improved from 14.8 (0.52) at baseline to 6.1 (0.48) for a mean change (SE) from baseline of −8.5 (0.5) at day 29 (Fig. 3). When POEM total score was analyzed by domain, mean changes from baseline ranged from approximately −1 to −2 across subscales at day 29, including improvements in itching and sleep loss (Fig. 4).

3.4 Pharmacokinetics

Eighteen patients were evaluated for PK parameters, and all had quantifiable concentrations of crisaborole (Table 4) and the inactive metabolites (data on file). Based on non-linear regression analysis, which accounts for dose differences (due to differences in %BSA) and age differences (accounting for the difference in clearance of crisaborole), crisaborole exposure was comparable with that in patients aged ≥ 2 years observed in previous studies [14–16].

3.5 Propylene Glycol Concentrations

A majority of the patients had measurable concentrations of propylene glycol at screening covering a wide range.

\[ \Delta \text{Adis} \]
AD is relatively common in patients aged < 2 years, with
tory, or vital sign parameters.
including no changes in electrocardiogram, clinical labora-
section of individual patient profiles, no systematic
following treatment with crisaborole was identified. In addi-
no propylene glycol toxicity effects were identified,
changes in electrocardiogram, clinical laboratory,
or vital sign parameters.

4 Discussion

AD is relatively common in patients aged <2 years, with
an Australian study reporting the cumulative prevalence
for parent-reported atopic eczema as 28.0% in the first
12 months of life [17]. Topical corticosteroids and TCIs are
commonly recommended topical prescription medications
to treat AD; however, most are not approved to treat infants
aged <2 years in most countries, including the United States.
Topical corticosteroids may be used intermittently for flares
but are not recommended for prolonged use because of con-
cerns about local and systemic AEs [18, 19]. Meanwhile,
TCIs have been associated with application site burning and
stinging, and they currently have a boxed warning in the
United States for risk for malignancy [19]. As a result, addi-
tional options to treat AD signs and symptoms and improve
health-related quality of life are needed, specifically for
infants with AD.

This report describes the first clinical study of crisab-
rorole in infants aged <2 years with AD. Crisaborole was
well tolerated with a low incidence of treatment-related AEs.
The most frequently reported TEAEs were similar to those
typically associated with childhood illnesses (e.g., pyrexia,
upper respiratory tract infection, diarrhea, cough). ‘Application
site pain’ and ‘application site discomfort’ were reported
at rates (3.6% and 2.9%, respectively) similar to those of
‘application site pain’ in patients aged ≥2 years treated
with crisaborole in the phase III studies (AD-301/AD-302
pooled: 4.4%) [6]. Although application site discomfort was
not among the most frequently reported TEAEs in the phase
III studies, this comparison is apt because ‘application site
discomfort’ and ‘application site pain’ were often reported
from an observer/parent/caregiver perspective in this study
and not directly from the patient.

In this open-label study, approximately 30% and 47% of
patients achieved ISGA success and/or ISGA clear or almost
clear at day 29, respectively, which is consistent with the
rates reported for crisaborole-treated patients aged ≥2 years
in the pivotal phase III studies for the same endpoints (ISGA
success: 32.8% [AD-301] and 31.4% [AD-302]; ISGA clear/
almost clear: 51.7% [AD-301] and 48.5% [AD-302]) [6].
After 1 week of treatment with crisaborole, up to 20% or
40% of patients had clinical improvements in their AD as
defined by ISGA success and/or ISGA clear or almost clear,
respectively. Additionally, improvements in EASI score and
%BSA involvement were observed as early as the first
postbaseline assessment (day 15). It should be noted that
effectiveness was an exploratory endpoint in this study and
there was no comparator group. However, these results are
consistent with a recently published vehicle-controlled phase
IIa study, which demonstrated improvements in crisaborole-
treated target lesion EASI score by day 15 in adults with
mild-to-moderate AD [20].

Additionally, patient-reported outcomes improved at the
first postbaseline assessment (day 8) and were sustained at
day 29 with mean changes from baseline in POEM total
scores of −6.9 and −8.5, respectively. At both timepoints,
improvements exceeded the minimal clinically important
difference (change of 3.4) [21, 22]. In addition, the POEM
subscales data show an association between crisaborole use
and improvements in sleep and itch, which are important fac-
tors in the quality of life of patients with AD and their car-
egivers. This is the first crisaborole study to include POEM,
which is recommended as a patient/caregiver-reported clini-
cal endpoint in AD trials by several international bodies,
including the Harmonising Outcome Measures for Eczema
(HOME) initiative [23].

Generally, PK parameters were comparable to those seen
in phase I/II studies in patients aged ≥2 years [14–16], indi-
cating that bioavailability (or amount of crisaborole absorbed
per unit dose) does not vary for patients aged >3 months.
With regard to propylene glycol exposure, no systematic
trend for increased propylene glycol concentrations after
above 180,000–250,000 ng/mL [9]).

Furthermore, based on extensive assessments, including
physical examinations, clinical laboratory tests, vital signs,
blood pressure, and electrocardiography, no safety concerns
attributable to propylene glycol exposure (i.e., central nerv-
ous system toxicity, hyperosmolarity, hemolysis, cardiac
arrhythmia, or lactic acidosis) were identified. Although a
wide range of propylene glycol concentrations was observed
at screening (before prior AD treatment washout and before
risaborole treatment), specific sources were not identified
since propylene glycol is found ubiquitously in many prod-
products, including medications, foods, and moisturizers [9].

Limitations of this study include its open-label nature
and lack of a comparator group, as well as the exploratory
nature of the efficacy analyses. In addition, as with any study
in patients of this age range, the study relied on parents/
observational duties to report sensory AEs, such as ‘application site pain.’ Additionally, because propylene glycol is found in numerous products, it was not possible to capture all potential sources of propylene glycol exposure, nor the frequency or quantity of exposure (particularly food/diet sources).

5 Conclusions

Crisaborole was well tolerated in this open-label study of infants aged 3 to < 24 months with mild-to-moderate AD. Safety and efficacy were consistent with that observed in previous studies of crisaborole in patients aged ≥ 2 years. In particular, ‘application site pain’ and ‘application site discomfort’ were reported at rates similar to those seen in crisaborole studies in patients aged ≥ 2 years, and no new safety signals were identified. Improvements from baseline in signs and symptoms of AD and patient-reported outcomes were observed at the first postbaseline assessment (day 8 or 15) and continued to improve through day 29. Overall, the results of this study show that crisaborole may be a safe and efficacious treatment option for infants aged 3 to < 24 months.

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Data Sharing Statement Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Compliance with Ethical Standards

Conflict of interest J. Schlessinger has no conflicts of interest to declare. J. S. Shepard was compensated as a principal investigator for this study and was also compensated to serve on an advisory board for Pfizer Inc. R. Gower has received research grants for Pfizer crisaborole clinical trials, and consulting fees for participating in the Pfizer Crisaborole Advisory Board. J. C. Su has been an investigator, speaker, and/or advisor for Pfizer Inc., Amgen, AbbVie, Ego Pharmaceuticals, Eli Lilly, GlaxoSmithKline, Janssen/Johnson & Johnson, L’Oréal, Meda, Novartis, Pierre Fabre, and Sanofi. C. Lynde has served as a principal investigator, consultant, and/or speaker for Pfizer Inc., AbbVie, Bausch, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, and Valeant. A. Cha, V. Parrott, L. Takuya, J. L. Werth, C. Zang, and B. Vlahos are employees and stockholders of Pfizer Inc. W. C. Ports was an employee of Pfizer Inc. at the time of this study and is a stockholder of Pfizer Inc.

Research involving human participants and/or animals The institutional review board at each study site approved the study protocol, and written informed consent was provided by parents/legal guardians. The study was conducted in accordance with the protocol, local legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, International Conference on Harmonisation Guideline for Good Clinical Practice, and the Declaration of Helsinki.

Informed consent Written informed consent was provided by parents or legal guardians of participants of the study.

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References

1. Bieber T. Atopic dermatitis. N Engl J Med. 2008;358(14):1483–94.
2. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. Int J Clin Pract. 2006;60(8):984–92.
3. Eichenfield LF, Ellis CN, Mancini AJ, Paller AS, Simpson EL. Atopic dermatitis: epidemiology and pathogenesis update. Semin Cutan Med Surg. 2012;31(3 Suppl):S3–5.
4. Eichenfield LF, Tom WL, Chamlin SL, Feldman SR, Hanifin JM, Simpson EL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 2014;70(2):338–51.
5. Kim SH, Hur J, Jang JY, Park HS, Hong CH, Son SJ, et al. Psychological distress in young adult males with atopic dermatitis: a cross-sectional study. Medicine (Baltimore). 2015;94(23):e949.

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6. Paller AS, Tom WL, Lebwohl 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(3):494–503.e6.

7. Eichenfield LF, Call RS, Forsha DW, Fowler J Jr, Hebert AA, Spellman M, et al. Long-term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis. J Am Acad Dermatol. 2017;77(4):641–649.e5.

8. US Food & Drug Administration. GRAS Substances (SCOGS) database. https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database. Accessed 13 Nov 2019.

9. Lim TY, Poole RL, Pageler NM. Propylene glycol toxicity in children. J Pediatr Pharmacol Ther. 2014;19(4):277–82.

10. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol Suppl (Stockh). 1980;92(suppl):44–7.

11. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. Br J Dermatol. 2016;175(5):902–11.

12. Barbier N, Paul C, Luger T, Allen R, De Prost Y, Papp K, et al. Validation of the Eczema Area and Severity Index for atopic dermatitis in a cohort of 1550 patients from the pimecrolimus cream 1% randomized controlled clinical trials programme. Br J Dermatol. 2004;150(1):96–102.

13. Charman CR, Venn AJ, Williams HC. The patient-oriented eczema measure: development and initial validation of a new tool for measuring atopic eczema severity from the patients’ perspective. Arch Dermatol. 2004;140(12):1513–9.

14. Zane LT, Kircik L, Call R, Tschen E, Draelos ZD, Chanda S, et al. Crisaborole topical ointment, 2% in patients 2 to 17 years of age with atopic dermatitis: a phase 1b, open-label, maximal-use systemic exposure (MUSE) study. Pediatr Dermatol. 2016;33(4):380–7.

15. Purohit V, Riley S, Tan H, Ports WC. Patient and disease characteristic predictors of systemic exposure to crisaborole. Presented at: 2019 ACCP Annual Meeting (American College of Clinical Pharmacology); September 15–17, 2019; Chicago, Illinois; Poster 080.

16. Tom WL, Van Syoc M, 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(2):150–9.

17. Martin PE, Koplin JJ, Eckert JK, Lowe AJ, Ponsonby AL, Osborne NJ, et al. The prevalence and socio-demographic risk factors of clinical eczema in infancy: a population-based observational study. Clin Exp Allergy. 2013;43(6):642–51.

18. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol. 2006;54(1):1–15 (quiz 6–8).

19. Lugtert B, Boguniewicz M, Carr W, Cork M, Deleuran M, Eichenfield L, et al. Pimecrolimus in atopic dermatitis: consensus on safety and the need to allow use in infants. Pediatr Allergy Immunol. 2015;26(4):306–15.

20. Bissonnette R, Pavel AB, Diaz A, Werth JL, Zang C, Vranic I, et al. Crisaborole and atopic dermatitis skin biomarkers: an intrapatient randomized trial. J Allergy Clin Immunol. 2019;144(5):1274–89.

21. Schram ME, Spuls PI, Leeflang MM, Lindeboom R, Bos JD, Schmitt J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. Allergy. 2012;67(1):99–106.

22. Gaunt DM, Metcalfe C, Ridd M. The Patient-Oriented Eczema Measure in young children: responsiveness and minimal clinically important difference. Allergy. 2019;144(5):1274–89.

23. Barrett A, Hahn-Pedersen I, Kragh N, Evans E, Gnanasakthy A. Patient-reported outcome measures in atopic dermatitis and chronic hand eczema in adults. Patient. 2019;12(5):445–59.

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