CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc.

Investigational Product: Crisaborole

Clinical Study Report Synopsis: Protocol C3291027

Protocol Title: A Phase 3, Multicenter, Open-Label Study of the Long-Term Safety of Crisaborole Ointment, 2% in Japanese Pediatric and Adult Participants With Mild to Moderate Atopic Dermatitis

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Centers: This study was conducted at 15 centers in Japan. Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None

Study Initiation Date: 14 September 2020

Study Completion Date: 18 December 2020

The study was terminated prematurely due to the Sponsor's business decision and portfolio reprioritization. The decision was not as a result of any safety or efficacy concerns. No participants from Study C3291031 enrolled into this study as Study C3291031 was cancelled due to the Sponsor's business decision before it started.

Report Date: 27 April 2021

Previous Report Date: Not Applicable

Phase of Development: Phase 3

Primary and Secondary Study Objectives and Endpoints:

The study objectives, estimands, and endpoints are summarized in Table S1.

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Table S1. Study Objectives, Estimands, and Endpoints

Type	Objectives	Estimands	Endpoints
Primary:			
Safety	• To study the safety of crisaborole ointment, 2% applied BID in Japanese pediatric and adult participants with mild to moderate AD	• There was no defined estimand for this objective and these endpoints were analyzed descriptively	• The incidence of treatment emergent AEs and SAEs

Abbreviations: AD=atopic dermatitis; AE=adverse event; BID=twice daily; SAE=serious adverse event.

METHODS

Study Design: This study was a Phase 3, multicenter, open-label, long-term safety extension study of Studies C3291032 and C3291031 in Japanese pediatric and adult participants with mild to moderate atopic dermatitis (AD) to support the registration of crisaborole in Japan. After completion of the study intervention period in Studies C3291032 or C3291031 and confirmed Study C3291027 eligibility, participants were offered participation in the study from investigator sites in Japan. The sample size of this study was approximately 150 participants but was determined by the number of participants who completed Studies C3291032 or C3291031 treatment period and met eligibility criteria of this study.

Diagnosis and Main Criteria for Inclusion: Male or female participants who were patients with mild to moderate AD aged 2 years or older and met eligibility criteria for Study C3291032 at the time when entering Study C3291032, and completed treatment period in Study C3291032 without safety issues; or, male or female participants who were patients with mild to moderate AD aged 1 month to <24 months and met eligibility criteria for Study C3291031 at the time when entering study C3291031, and completed treatment period in Study C3291031 without safety issues were included in the study.

Participants who discontinued early from Studies C3291032 or C3291031 treatment, for any reason; or who had a significant active systemic or localized infection, including known actively infected AD were excluded from the study.

Study Treatment: Crisaborole ointment 2% was applied topically as an even layer twice a day (BID) based on a participant's own AD percentage body surface area adjusted by height and weight.

Efficacy Evaluations: Not Applicable.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and/or Other Evaluations: Not Applicable.

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Safety Evaluations: Safety assessments consisted of the collection of adverse events (AEs) and serious adverse events (SAEs).

Statistical Methods: The safety data were summarized descriptively. No statistical hypotheses were tested.

RESULTS

Subject Disposition and Demography: The disposition events summary is presented in Table S2. A total of 40 participants were assigned to study intervention period, and 37 participants received crisaborole ointment 2% BID. Three participants started the study with off-treatment cycle and discontinued without treatment. Of the 40 participants, 30 participants were in <18 years of age group, and 10 participants were in ≥18 years of age group. All 40 participants discontinued the study (39 participants due to study terminated by the Sponsor and 1 participant due to AE) and were included in the safety analysis set (all participants who took at least 1 dose of study intervention, and also who entered the first off-treatment cycle).

Table S2. Disposition Events Summary (Safety Analysis Set) (Protocol C3291027)

	Crisaborole 2%		
Number (%) of Subjects	< 18 years (N=30) n (%)	>= 18 years (N=10) n (%)	Total (N=40) n (%)
Disposition phase: Treatment			
Subjects Entered:	30 (100.0)	10 (100.0)	40 (100.0)
Discontinued	30 (100.0)	10 (100.0)	40 (100.0)
Reason for discontinuation			
Adverse Event	1 (3.3)	0	1 (2.5)
Study Terminated By Sponsor	29 (96.7)	10 (100.0)	39 (97.5)
Completed	0	0	0
Disposition phase: Follow-Up			
Subjects Entered:	30 (100.0)	10 (100.0)	40 (100.0)
Discontinued	0	0	0
Completed	30 (100.0)	10 (100.0)	40 (100.0)
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The median age for all 40 participants in the study was 10.5 years. The median age for <18 years of age group and ≥18 years of age group was 9.0 and 32.0 years, respectively. Out of 40 participants, 21 were male and 19 were female. All the 40 participants were Asian and not-Hispanic or Latino.

Efficacy Results: Not Applicable.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, Immunogenicity and/or Other Results: Not Applicable.

Safety Results: In <18 years of age group, all 30 participants enrolled into the study intervention period. The median duration of crisaborole ointment 2% BID treatment was 29.0 days, with a range of 0 to 51 days. In ≥18 years of age group, all 10 participants enrolled into the study intervention period. The median duration of crisaborole ointment 2% BID treatment was 29.0 days, with a range of 14 to 56 days.

A total of 14 participants (35.0%) experienced a total of 15 all-causality treatment-emergent adverse events (TEAEs). In <18 years of age group, 11 participants (36.7%) experienced 12 all-causality TEAEs. In ≥18 years of age group, 3 participants (30.0%) experienced 3 all-causality TEAEs. One participant (2.5%) in <18 years of age group experienced a TEAE of application site pain which was considered treatment-related. There were no deaths, SAEs or severe AEs reported in either age group in the study. All TEAEs were mild in severity.

Incidence of Adverse Events: The all-causality TEAEs reported in the study are presented by system organ class and preferred term (PT) in Table S3. In <18 years of age group, the most frequently reported all-causality TEAEs by PT were nasopharyngitis (3 participants) and dermatitis atopic (2 participants), all other TEAEs were reported in 1 participant each. In ≥18 years of age group, the all-causality TEAEs by PT were gastroenteritis, wound and joint effusion (1 participant each).

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Table S3. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities) (Safety Analysis Set) (Protocol C3291027)

Number (%) of Subjects: by System Organ Class and Preferred Term	Crisaborole 2% < 18 years (N=30) n (%)	Crisaborole 2% >= 18 years (N=10) n (%)	Crisaborole 2% Total (N=40) n (%)
With Any adverse event	11 (36.7)	3 (30.0)	14 (35.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (3.3)	0	1 (2.5)
Application site pain	1 (3.3)	0	1 (2.5)
INFECTIONS AND INFESTATIONS	7 (23.3)	1 (10.0)	8 (20.0)
Bronchitis	1 (3.3)	0	1 (2.5)
Gastroenteritis	0	1 (10.0)	1 (2.5)
Molluscum contagiosum	1 (3.3)	0	1 (2.5)
Nasopharyngitis	3 (10.0)	0	3 (7.5)
Otitis media acute	1 (3.3)	0	1 (2.5)
Rhinitis	1 (3.3)	0	1 (2.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	1 (10.0)	1 (2.5)
Wound	0	1 (10.0)	1 (2.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (10.0)	1 (2.5)
Joint effusion	0	1 (10.0)	1 (2.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (13.3)	0	4 (10.0)
Acne	1 (3.3)	0	1 (2.5)
Dermatitis atopic	2 (6.7)	0	2 (5.0)
Dermatitis contact	1 (3.3)	0	1 (2.5)

Subjects are only counted once per treatment per event.
Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.
Percentages of gender specific events are calculated using the corresponding gender count as denominator.
Includes data up to lag days after last dose of study drug.
MedDRA v23.1 coding dictionary applied.
CCI [redacted]

TEAEs occurring in the treatment area were application site pain and dermatitis atopic (1 participant each in <18 years of age group), and both the events were mild in severity.

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Most TEAEs were not considered treatment-related, and did not occur in a treatment area. One treatment-related TEAE which did occur in the treatment area was application site pain (1 participant) which was mild in severity.

Permanent Discontinuations Due to Adverse Events: One participant in <18 years of age group discontinued the study due to a TEAE of application site pain on the multiple treatment areas of the face which was mild in severity and considered as treatment-related, and the participant discontinued from the study after 13 days of treatment. This event of application site pain is consistent with the known safety profile of crisaborole.

Dose Reductions or Temporary Discontinuations Due to Adverse Events: One participant in <18 years of age group had a TEAE of dermatitis atopic that led to a drug interruption. It was not related to study treatment.

Conclusions:

This study was planned to assess the 1-year-long-term safety of crisaborole ointment 2% in Japanese pediatric and adult participants with mild to moderate AD but terminated due to the Sponsor's business decision and portfolio reprioritization. Most of the participants (90%) were discontinued early from the study after completion of 1 treatment cycle and the median duration of crisaborole ointment 2% BID treatment was 29.0 days.

There were no deaths, SAEs, or severe AEs reported in the study.

All the TEAEs reported in this study were mild in severity.

The TEAE of application site pain reported in a single participant in <18 years of age group was considered treatment-related.

A dose reduction or temporary/permanent discontinuation due to TEAEs was reported in 1 participant in <18 years of age group in the study.

Crisaborole ointment 2% was well-tolerated in Japanese pediatric and adult participants with mild to moderate AD in BID regimens. No safety issues of concerns were identified in this study. The safety profile observed in this study is consistent with that observed in previous studies.