CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc.

Investigational Product: Crisaborole

Clinical Study Report Synopsis: Protocol C3291028

Protocol Title: A Phase 2b, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled, Intra-Participant Study, to Evaluate Efficacy and Safety of Two Regimens of Crisaborole Ointment 2% in Japanese Pediatric and Adult Participants (2 Years and Older) With Mild to Moderate Atopic Dermatitis

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

Study Centers: This study was conducted at 3 centers in Japan. Refer to CCI for a list of sites involved in this study.

Publications Based on the Study: None.

Study Initiation Date: 15 June 2019

Study Completion Date: 16 December 2019

Report Date: 13 April 2020

Previous Report Date: Not applicable

Phase of Development: Phase 2b.

Primary and Secondary Study Objectives and Endpoints:

The primary and secondary study objectives, endpoints and estimands of this study are presented in Table S1.

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Table S1. Primary and Secondary Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
Primary			
Efficacy	To compare the efficacy of crisaborole ointment 2%, administered QD or BID relative to the corresponding vehicle (QD or BID), on TSS assessment in target lesions, in the treatment of mild to moderate AD in adults (Cohort 1) and pediatrics (Cohort 2)	Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen (Regimen 1: QD, Regimen 2: BID) for each cohort	This estimand was the hypothetical estimand, which estimated the effect as if all participants maintained their randomized treatment. • Population: Participants with mild to moderate AD in adults (Cohort 1) and pediatrics (Cohort 2) as defined by the inclusion and exclusion criteria, and were randomized and received at least 1 of the investigational products • Intercurrent event: All efficacy data after discontinuation of treatment were not considered • Population-level summary: Least-square means of intra-participant difference between crisaborole ointment 2% versus corresponding vehicle in each regimen for each cohort and pooled cohort
Secondary			
Efficacy	To evaluate the efficacy of crisaborole ointment 2% BID relative to crisaborole ointment 2% QD, on TSS assessment in target lesions, in the treatment of mild to moderate AD in adults (Cohort 1) and pediatrics (Cohort 2)	Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen for each cohort	This estimand was the hypothetical estimand, which estimated the effect as if all participants maintained their randomized treatment. • Population: Participants with mild to moderate AD in adults (Cohort 1) and pediatrics (Cohort 2) as defined by the inclusion and exclusion criteria, and were randomized and received at least 1 of the investigational products • Intercurrent event: All efficacy data after discontinuation of treatment were not considered • Population-level summary: Difference in least square means between crisaborole ointment 2% BID and crisaborole ointment 2% QD for each cohort and pooled cohort
	To evaluate the efficacy of crisaborole ointment 2%, administered QD or BID, on TSS, ISGA, and pruritus assessments in target lesions, in the treatment of mild to moderate AD in adults (Cohort 1) and pediatrics	Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 8 in each regimen for each cohort	The other secondary efficacy endpoints were analyzed using the estimands described above
		Change from baseline in ISGA in target lesions treated with crisaborole ointment or vehicle at each visit up to Day 15 in each regimen for each cohort	

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Table S1. Primary and Secondary Study Objectives, Endpoints, and Estimands

Type	Objectives	Endpoints	Estimands
	(Cohort 2)	Change from baseline in pruritus assessments in target lesions treated with crisaborole ointment or vehicle at each day up to Day 15 in each regimen using following scales: Cohort 1: Peak pruritus, NRS (Age ≥12 years), Cohort 2: Itch severity scale (Age 6-11 years) Self-Report, Cohort 2: Caregiver reported itch severity NRS (Age 2-11 years)	
Safety	To assess the safety and local tolerability of crisaborole ointment 2%, administered QD or BID, in the treatment of mild to moderate AD in adults (Cohort 1) and pediatrics (Cohort 2)	Incidence of TEAEs and SAEs in each regimen for each cohort	There was no defined estimand for these endpoints and they were analyzed descriptively

Abbreviations: AD=atopic dermatitis; BID=twice daily; ISGA=Investigator Static Global Assessment; NRS=numerical rating scale; QD=once daily; SAE=serious adverse event; TEAE=treatment-emergent adverse events; TSS=total sign score.

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METHODS

Study Design: This was a Phase 2b, multicenter, randomized, double-blind, vehicle-controlled, intra-participant study to evaluate efficacy and safety of 2 regimens of crisaborole ointment 2% in Japanese pediatric and adult participants (Cohort 1: ≥12 years, Cohort 2: 2 to under 12 years old) with mild to moderate atopic dermatitis (AD). After completing screening activities, including meeting eligibility criteria, 2 target lesions that were moderate in severity were determined by the investigator, participants were randomized to 1 of the 2 regimens, once daily (QD) or twice daily (BID) (randomization ratio; 1:1), and crisaborole ointment 2% or vehicle were randomly assigned to each target lesion at baseline/Day 1. Both target lesions were to be treated at the assigned dosing regimen and dosing regimen was unblinded information to sponsor, investigators/study sites and participants. Participants were treated with investigational products administered for 2 weeks and followed-up 28 days after the end of treatment.

Diagnosis and Main Criteria for Inclusion:

Key inclusion criteria were as follows:

- Male or female participants ages:
  - Cohort 1: ≥12 years at the time of consent;
  - Cohort 2: 2 years to under 12 years old at the time of consent.
- Participants who had confirmed clinical diagnosis of active AD at screening and baseline/Day 1 according to Hanifin and Rajka criteria and who had at least 6 months history prior to screening visit that had been clinically stable for >1 month.
- Participants who had a global Investigator Static Global Assessment (ISGA) of 2 (mild) or 3 (moderate) at baseline/Day 1 visit.
- Participants who had AD lesions on upper limbs, lower limbs or ventral of the body trunk and a body surface area (BSA) covered with AD of at least 1.0% and not >30% at baseline/Day 1, excluding scalp, genitals and groin area. The presence of AD on these areas (scalp, genitals and groin area) was not exclusionary, but was not to be included in the calculation for coverage of BSA with AD.
- Participants who had 2 lesions of AD at least 3 cm × 3 cm with identical lesion ISGA=3 (moderate) for each lesion. These AD lesions were to be at least 10 cm apart. The target lesions were not to be on the face, neck, scalp, axilla, genitals, groin area, palms, dorsal of the hands, dorsal of the body trunk and soles. In addition, 2 AD areas on the same limb were not to be selected as the target lesions. (Note: When possible, AD areas on the bilateral [left/right] area were to be selected as target lesions).

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Key exclusion criteria were as follows:

- Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that could have increased the risk associated with study participation or study drug administration or could have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the participant inappropriate for entry into this study.

- History of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of crisaborole ointment 2%.

- Participants had previous treatment with any topical or systemic phosphodiesterase-4 inhibitor.

- Participants who had undergone treatment for any type of cancer (except squamous cell carcinoma, basal cell carcinoma or carcinoma in situ of the skin, curatively treated with surgical excision only).

Study Treatment:

Crisaborole (PF-06930164) ointment 2% and vehicle ointment were applied topically as a thin layer QD or BID to the affected areas.

At baseline/Day 1, the participants who met the inclusion/exclusion criteria were randomized to 1 of the regimens, QD or BID, and for each of the 2 target lesions (Lesion 1 and Lesion 2) meeting the inclusion criteria identified by the investigator, the study interventions (crisaborole ointment 2% or vehicle) were assigned randomly.

The lesion size and prescribed amount of study interventions were recorded in the source documentation and marked on the dosing instruction document for the parents/caregivers.

The study interventions were applied only to Lesion 1 and Lesion 2, and not applied to other AD affected areas. Only participants enrolled in the study could receive the study intervention and only authorized site staff could supply or administered the study intervention.

The study drug information is provided in Table S2.

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Table S2. Study Drug Information

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
Crisaborole 2% topical ointment in 60 g tube	K072017D	17-004070	20 mg/g	Ointment
Placebo for crisaborole topical ointment in 60 g tube (axomatic)	K121917D	18-000180	0%	Ointment

Efficacy Evaluations: In this study, the lesion is specified when referring to a target lesion assessment.

Severity of AD was characterized at screening and baseline with %BSA and global ISGA, however, %BSA and global ISGA were not included in the efficacy evaluation. In addition, the severity of AD lesion was characterized at baseline and throughout the study with the lesion ISGA, lesion total sign score (TSS), and peak pruritus numerical rating scale (NRS).

Lesion Investigator Static Global Assessment:

The clinical evaluator of AD performed an assessment of each target lesion severity of AD and assigned a lesion ISGA score and category. The assessment was a static evaluation without regard to the score at a previous visit.

For eligibility of assessment, the lesion ISGA at baseline/Day 1 was 3 (moderate) whereas, the global ISGA could be 2 (mild) or 3 (moderate). The assessments were done at Days 1, 8 and 15.

Lesion Total Sign Score:

The lesion TSS was an assessment of the severity of each of the following: erythema, induration/papulation, excoriation, and lichenification. Each of these was rated using the 4-point severity scale. These ratings were then added to create a total score (13-point scale; ranging from 0 to 12 points). The assessments were done at baseline/Day 1, Day 8, and Day 15.

Pruritus Assessments:

The severity of itch (pruritus) due to AD at the target lesion was assessed. The assessments were done from baseline/Day 1 till Day 15. The pruritus assessments for each target lesion were as follows:

- Peak pruritus NRS, Age ≥12 years;
- Itch severity scale Age 6-11 years self-report;

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- Itch severity NRS (caregiver reported) for participants Age 2-11 years.

Percent Body Surface Area With Atopic Dermatitis:

The overall BSA affected by AD was evaluated (from 0% to 100%) to verify each participant's eligibility at the screening and baseline/Day 1 visits. The investigator might have used the "handprint method" by which the area represented by the palmar (ie, outstretched) surface of the participant's hand with all 5 digits adducted together was approximately 1% of the participant's BSA.

The number of handprints of AD skin in a body region could be used to determine the extent (%) to which a body region was involved with AD.

Investigator Static Global Assessment:

The investigator performed an assessment of the overall severity of AD and assigned an ISGA score and category to verify each participant's eligibility at the screening and baseline/Day 1 visits.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and/or Other Evaluations:

The pharmacokinetic, pharmacodynamic, pharmacogenomic and/or other evaluations were not done in the study.

Safety Evaluations: Safety assessments consisted of the collection of adverse events (AEs) and serious adverse events (SAEs), vital signs (only at screening), and conducting physical examination and pregnancy testing.

Statistical Methods:

The details of analysis sets in the study are as follows:

Full Analysis Set (FAS): All participants randomized and who received ≥1 dose of the study drug.

Per-Protocol Analysis Set (PPAS): All participants randomized and who received ≥1 dose of the study drug, with both baseline and Day 15 primary efficacy data, and without protocol violations that were thought to impact the efficacy evaluation during the treatment period.

Safety Analysis Set: All participants who received ≥1 dose of the study drug.

Analysis of Primary Efficacy Endpoint:

The primary endpoint was change from baseline in TSS in target lesions treated with crisaborole ointment 2% or vehicle on Day 15. For the intra-participant comparison of crisaborole ointment 2% versus vehicle in each regimen for each cohort, the intra-participant

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difference of change from baseline in TSS in target lesions between crisaborole ointment 2% and vehicle up to Day 15 was analyzed using a Mixed effect Models for Repeated Measures (MMRM) that included the fixed effect of visit. The main analysis was based on the FAS.

Crisaborole ointment 2% was superior to vehicle for the TSS change at Day 15, if the change for crisaborole ointment 2% was greater than for vehicle and if p-value <0.05 (2-sided).

Analysis of Secondary Efficacy Endpoints:

Change From Baseline in Total Sign Score in Target Lesions at Day 15 (Comparison of Crisaborole Twice Daily Versus Crisaborole Once Daily):

For the inter-participant comparison of crisaborole ointment 2% BID versus crisaborole ointment 2% QD for each cohort, change from baseline in TSS in target lesions between crisaborole ointment 2% BID and crisaborole ointment 2% QD up to Day 15 was analyzed using an MMRM that included the fixed effects of dosing regimen, visit, dosing regimen-by-visit interaction and baseline value. The main analysis was based on the FAS.

Change From Baseline in Total Sign Score in Target Lesions at Day 8:

The Day 8 was a time point in the mixed model for the analysis for TSS change from baseline at Day 15. The analysis for TSS change from baseline at Day 8 was from the same model, and data reporting was same as for Day 15.

Change From Baseline in Investigator Static Global Assessment in Target Lesions at Day 8 and Day 15:

The intra-participant difference of change from baseline in ISGA between crisaborole ointment 2% and vehicle and the inter-participant difference of change from baseline in ISGA between crisaborole ointment 2% BID and crisaborole ointment 2% QD were analyzed. The main analysis was based on the FAS.

Change From Baseline in Pruritus Assessments in Target Lesions at Each Time Point up to Day 15:

The intra-participant difference of change from baseline in pruritus assessment between crisaborole ointment 2% and vehicle and the inter-participant difference of change from baseline in pruritus assessment between crisaborole ointment 2% BID and crisaborole ointment 2% QD were analyzed. The main analysis was based on the FAS.

Safety Analysis: The safety data were summarized descriptively.

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RESULTS

Subject Disposition and Demography:

Participant disposition is summarized in Table S3 for Cohort 1 and Cohort 2.

In Cohort 1, 20 participants were assigned to receive crisaborole ointment 2% QD and vehicle QD (referred to as "QD regimen" hereafter), and 21 participants were assigned to receive crisaborole ointment 2% BID and vehicle BID (referred to as "BID regimen" hereafter). All the participants completed the study.

In Cohort 2, 20 participants each were assigned to receive QD regimen and BID regimen, and all the participants completed the study.

In Cohort 1, 11 (55.0%) male and 9 (45.0%) female participants were enrolled in QD regimen, and 17 (81.0%) male and 4 (19.0%) female participants were enrolled in BID regimen. The mean age (standard deviation [SD]) of participants in QD regimen and BID regimen was 33.3 (10.36) years and 33.9 (10.96) years, respectively. In QD regimen and BID regimen, mean treatable percent BSA (SD) of participants was 18.54 (7.368) and 18.33 (7.217), respectively.

In Cohort 2, 8 (40.0%) male and 12 (60.0%) female participants were enrolled in QD regimen, and 11 (55.0%) male and 9 (45.0%) female participants were enrolled in BID regimen. The mean age (SD) of participants in QD regimen and BID regimen was 7.7 (2.52) years and 7.8 (2.69) years, respectively. In QD regimen and BID regimen, mean treatable percent BSA (SD) of participants was 4.80 (2.263) and 9.19 (7.610), respectively.

In the baseline disease characteristics for each target lesion, TSS was balanced between assigned treatments in each regimen for each cohort. All the participants (100.0%) exhibited moderate lesion severity, based on the ISGA score.

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Table S3. Disposition Events Summary

	Cohort 1		Cohort 2	
	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=21)	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=20)
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Disposition Phase: Treatment				
Subjects Entered:	20 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)
Discontinued	0	0	0	0
Completed	20 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)
Disposition Phase: Follow-Up				
Subjects Entered:	20 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)
Discontinued	0	0	0	0
Completed	20 (100.0)	21 (100.0)	20 (100.0)	20 (100.0)

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Efficacy Results:

All participants were included in the FAS and the PPAS. The efficacy results were the same for both analysis sets.

Primary Endpoint Results:

Change From Baseline in TSS in Target Lesions at Day 15 for Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle – Cohort 1 (Age ≥12 Years):

QD Regimen:

For the QD regimen, the primary efficacy endpoint was achieved. The crisaborole ointment 2% QD treated lesions showed a statistically significant reduction in TSS at Day 15 compared to the vehicle QD treated lesions (Table S4). The least square means (LSM) of intra-participant difference of TSS change from baseline was -1.6 with a p-value of 0.0071 (Table S4).

BID Regimen:

In the BID regimen, the primary efficacy endpoint was also achieved. The crisaborole ointment 2% BID treated lesions showed a statistically significant reduction in TSS at Day 15 compared to the vehicle BID treated lesions (Table S4). The LSM of intra-participant difference of TSS change from baseline was -2.0 with a p-value of 0.0029 (Table S4).

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Table S4. Change From Baseline in Total Sign Score (TSS) on Day 15 for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle in Cohort 1 - Full Analysis Set

Summary Statistics at Day 15	Regimen 1 (QD) (N=20)		Regimen 2 (BID) (N=21)	
	Crisaborole 2% QD (N=20)	Vehicle QD (N=20)	Crisaborole 2% BID (N=21)	Vehicle BID (N=21)
Change from baseline				
n	20	20	21	21
Mean (standard error)	-4.5 (0.60)	-2.9 (0.51)	-4.8 (0.53)	-2.7 (0.47)
Median (range)	-4.5 (-10, -1)	-3.5 (-7, 1)	-5.0 (-11, -1)	-3.0 (-7, 1)
Least squares mean of intra-participant difference of change from baseline (Crisaborole 2% - Vehicle)	-1.6	-	-2.0	-
95% Confidence interval	(-2.7, -0.5)	-	(-3.3, -0.8)	-
p-Value	0.0071	-	0.0029	-

Baseline is defined as the last observation up to and including first dosing date.
Mixed effect Model for Repeated Measures (MMRM) includes the fixed effect of visit, and the covariance structure UN is used.
- = Not applicable.
The Full Analysis Set includes all subjects who are randomized and receive at least one dose of investigational product.
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Change From Baseline in TSS in Target Lesions at Day 15 for Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle – Cohort 2 (Age 2-11 Years):

QD Regimen:

For the QD regimen, the primary efficacy endpoint was achieved. The crisaborole ointment 2% QD treated lesions showed a statistically significant reduction in TSS at Day 15 compared to the vehicle QD treated lesions (Table S5). The LSM of intra-participant difference of TSS change from baseline was -1.5 with a p-value of 0.0250 (Table S5).

BID Regimen:

For the BID regimen, the primary efficacy endpoint was achieved. The crisaborole ointment 2% BID treated lesions showed a statistically significant reduction in TSS at Day 15 compared to the vehicle BID treated lesions (Table S5). The LSM of

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intra-participant difference of TSS change from baseline was -2.1 with a p-value of 0.0014 (Table S5).

Table S5. Change From Baseline in Total Sign Score (TSS) on Day 15 for Intra-Participant Comparison of Crisaborole 2% Versus Vehicle in Cohort 2 - Full Analysis Set

Summary Statistics at Day 15	Regimen 1 (QD) (N=20)		Regimen 2 (BID) (N=20)	
	Crisaborole 2% QD (N=20)	Vehicle QD (N=20)	Crisaborole 2% BID (N=20)	Vehicle BID (N=20)
Change from baseline				
n	20	20	20	20
Mean (standard error)	-3.5 (0.47)	-2.0 (0.50)	-4.7 (0.50)	-2.6 (0.54)
Median (range)	-4.0 (-8, 0)	-1.5 (-7, 1)	-5.0 (-8, 1)	-3.0 (-6, 2)
Least squares mean of intra-participant difference of change from baseline (Crisaborole 2% - Vehicle)	-1.5	-	-2.1	-
95% Confidence interval	(-2.7, -0.2)	-	(-3.3, -0.9)	-
p-Value	0.0250	-	0.0014	-

Baseline is defined as the last observation up to and including first dosing date.
Mixed effect Model for Repeated Measures (MMRM) includes the fixed effect of visit, and the covariance structure UN is used.
- = Not applicable.
The Full Analysis Set includes all subjects who are randomized and receive at least one dose of investigational product.
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Secondary Endpoint Results:

Change From Baseline in TSS in Target Lesions at Day 15 for Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus Crisaborole Ointment 2% QD:

Cohort 1:

BID Regimen Versus QD Regimen:

For the comparison of the BID and QD regimens, the reduction in TSS at Day 15 in the crisaborole ointment 2% BID treated lesions was larger than the reduction observed in the

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crisaborole ointment 2% QD treated lesions. Inter-participant LSM difference of TSS change from baseline was -0.6.

Cohort 2:

BID Regimen Versus QD Regimen:

For the comparison of the BID and QD regimens, the reduction in TSS at Day 15 in the crisaborole ointment 2% BID treated lesions was larger than the reduction observed in the crisaborole ointment 2% QD treated lesions. Inter-participant LSM difference of TSS change from baseline was -0.8.

Change From Baseline in TSS in Target Lesions at Day 8:

Cohort 1:

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

At Day 8, in QD regimen, the LSM of intra-participant difference of TSS change from baseline was -1.9 with a p-value of 0.0029, where as in BID regimen, the LSM of intra-participant difference of TSS change from baseline was -1.4 with a p-value of 0.0282.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus Crisaborole Ointment 2% QD:

At Day 8, inter-participant LSM difference of TSS change from baseline of crisaborole ointment 2% BID and crisaborole ointment 2% QD was -0.1.

Cohort 2:

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

At Day 8, in QD regimen, the LSM of intra-participant difference of TSS change from baseline was -1.2 with a p-value of 0.0237, where as in BID regimen, the LSM of intra-participant difference of TSS change from baseline was -1.7 with a p-value of 0.0077.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus Crisaborole Ointment 2% QD:

At Day 8, inter-participant LSM difference of TSS change from baseline of crisaborole ointment 2% BID and crisaborole ointment 2% QD was -0.1.

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Change From Baseline in ISGA in Target Lesions:

Cohort 1:

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

At Day 15, in QD regimen, the LSM of intra-participant difference of change from baseline was -0.9 with a p-value of 0.0005, and in BID regimen, the LSM of intra-participant difference of change from baseline was -0.7 with a p-value of 0.0098.

At Day 8, in QD regimen, the LSM of intra-participant difference of change from baseline was -0.5 with a p-value of 0.0084 and in BID regimen, the LSM of intra-participant difference of change from baseline was -0.4 with a p-value of 0.0584.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus Crisaborole Ointment 2% QD:

At Day 15, the inter-participant LSM difference of change from baseline between crisaborole ointment 2% BID and crisaborole ointment 2% QD was 0.0.

At Day 8, the inter-participant LSM difference of change from baseline between crisaborole ointment 2% BID and crisaborole ointment 2% QD was 0.1.

Cohort 2:

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

At Day 15, in QD regimen, the LSM of intra-participant difference of change from baseline was -0.7 with a p-value of 0.0093. In BID regimen, the LSM of intra-participant difference of change from baseline was -1.0 with a p-value of 0.0001.

At Day 8, in QD regimen, the LSM of intra-participant difference of change from baseline was -0.3 with a p-value of 0.1435. In BID regimen, the LSM of intra-participant difference of change from baseline was -0.4 with a p-value of 0.0569.

Inter-Participant Comparison of Crisaborole Ointment 2% BID Versus Crisaborole Ointment 2% QD:

At Day 15, the inter-participant LSM difference of change from baseline between crisaborole ointment 2% BID and crisaborole ointment 2% QD was -0.1.

At Day 8, the inter-participant LSM difference of change from baseline between crisaborole ointment 2% BID and crisaborole ointment 2% QD was 0.2.

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Peak Pruitus NRS (Cohort 1, Age ≥12 Years):

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

In QD regimen, a greater improvement in pruritus NRS was observed for the crisaborole treated versus the vehicle treated lesions 1 day after the first application (-1.3 versus -0.7), and the improvement was maintained through Day 15 (-3.5 versus -2.0).

Crisaborole ointment 2% was superior to vehicle at each time point up to Day 15 with p-values <0.05, except at Day 3.

In BID regimen, a slightly greater improvement in pruritus NRS was observed for the crisaborole treated versus the vehicle treated lesions 1 day after the first application (-0.6 versus -0.5), and the improvement was maintained through Day 15 (-3.7 versus -2.9).

Crisaborole ointment 2% was superior to vehicle at several time points but not at all days, with p-values <0.05 up to Day 15.

Inter-Participant Comparison of Crisaborole BID Versus Crisaborole QD:

The LSM was generally greater in crisaborole ointment 2% QD than crisaborole ointment 2% BID from Day 2 to Day 12, but after Day 13, the LSM in crisaborole ointment 2% BID was greater than crisaborole ointment 2% QD.

Itch Severity Scale (Cohort 2, Age 6-11 Years):

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

In QD regimen, the improvement in itch severity scale was observed more in the crisaborole treated lesions than the vehicle treated lesions 1 day after the first application (-0.7 versus -0.3), and was -0.8 versus -0.6 at Day 15.

In BID regimen, the improvement in itch severity scale was observed more in the crisaborole treated lesions than the vehicle treated lesions 1 day after the first application (-0.6 versus -0.4), and was -1.3 versus -0.9 at Day 15.

Inter-Participant Comparison of Crisaborole BID Versus Crisaborole QD:

The LSM of change from baseline of crisaborole ointment 2% BID versus crisaborole ointment 2% QD was generally similar from Day 2 to Day 15.

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Caregiver Reported Itch Severity Numerical Rating Scale (Cohort 2, Age 2-11 Years):

Intra-Participant Comparison of Crisaborole Ointment 2% Versus Vehicle:

A larger reduction was observed in crisaborole compared to the vehicle in both regimens. In QD regimen, improvement in itch severity scale observed for the crisaborole treated was more versus the vehicle treated lesions 1 day after the first application (-0.5 versus -0.4), and the improvement was maintained through Day 15 (-2.5 versus -1.3).

In BID regimen, improvement in itch severity scale observed for the crisaborole treated was less versus the vehicle treated lesions 1 day after the first application (-0.7 versus -0.9), but the improvement was more in crisaborole treated versus the vehicle treated lesions at Day 15 (-4.3 versus -3.0).

Inter-Participant Comparison of Crisaborole BID Versus Crisaborole QD:

The LSM of change from baseline of crisaborole ointment 2% BID was generally more when compared to the crisaborole ointment 2% QD from Day 2 to Day 15.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, Immunogenicity and/or Other Results:

The pharmacokinetic, pharmacodynamic, pharmacogenomic and/or other evaluations were not done in the study.

Safety Results:

Overall Adverse Events:

Cohort 1:

A summary of all-causality treatment-emergent adverse events (TEAEs) by system organ class and preferred term is presented in Table S6.

For the QD regimen, 6 participants (30.0%) experienced a total of 9 all-causality TEAEs, 8 of which were considered as treatment-related. The most frequently reported all-causality TEAEs by preferred term (PT) were application site irritation and application site pruritus (3 participants each), all of which were considered to be treatment-related.

For the BID regimen, 6 participants (28.6%) experienced a total of 12 all-causality TEAEs, 8 of which were considered as treatment-related. The most frequently reported all-causality TEAEs by PT were application site irritation (4 participants) and oropharyngeal pain (3 participants). All of the events of application site irritation were considered to be treatment-related and none of the events of oropharyngeal pain were considered to be treatment-related.

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Cohort 2:

For the QD regimen, 2 participants (10.0%) experienced a total of 2 all-causality TEAEs (arthralgia and hand-foot-and-mouth disease; 1 participant each), neither of which were considered as treatment-related (Table S6).

For the BID regimen, 2 participants (10.0%) experienced a total of 3 all-causality TEAEs (Table S6), of which 2 TEAEs (application site pruritus and application site pain) were considered to be treatment-related.

There were no deaths, SAEs or severe AEs reported in either cohort in the study. There were no cases of dose reduction or temporary/permanent discontinuations due to TEAEs reported in the study. All the TEAEs reported in the study were mild in severity.

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Table S6. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number of Subjects Evaluable for AEs	Cohort 1		Cohort 2	
	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=21)	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=20)
Number (%) of Subjects: by System Organ Class and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With any adverse event	6 (30.0)	6 (28.6)	2 (10.0)	2 (10.0)
Gastrointestinal Disorders	1 (5.0)	0	0	0
Dental caries	1 (5.0)	0	0	0
General Disorders And Administration Site Conditions	5 (25.0)	5 (23.8)	0	1 (5.0)
Application site coldness	0	1 (4.8)	0	0
Application site irritation	3 (15.0)	4 (19.0)	0	0
Application site pain	1 (5.0)	1 (4.8)	0	1 (5.0)
Application site pruritus	3 (15.0)	2 (9.5)	0	1 (5.0)
Infections And Infestations	1 (5.0)	1 (4.8)	1 (5.0)	1 (5.0)
Application site folliculitis	1 (5.0)	1 (4.8)	0	0
Hand-foot-and-mouth disease	0	0	1 (5.0)	1 (5.0)
Musculoskeletal And Connective Tissue Disorders	0	0	1 (5.0)	0
Arthralgia	0	0	1 (5.0)	0
Respiratory, Thoracic And Mediastinal Disorders	0	3 (14.3)	0	0
Oropharyngeal pain	0	3 (14.3)	0	0

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Table S6. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number of Subjects Evaluable for AEs	Cohort 1		Cohort 2	
	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=21)	Crisaborole 2% QD + Vehicle QD (N=20)	Crisaborole 2% BID + Vehicle BID (N=20)
Number (%) of Subjects: by System Organ Class and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**

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 v22.1 coding dictionary applied.
CCI [redacted]

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Adverse Events in the Target Lesions:

Cohort 1:

For the QD regimen, 5 participants (25.0%) experienced a total of 6 TEAEs in crisaborole ointment 2% treated lesion, and 2 participants (10.0%) experienced a total of 3 TEAEs in vehicle treated lesion. In the crisaborole treated lesions, application site irritation and application site pruritus were each reported in 2 participants (10.0%), and application site pain and application site folliculitis were each reported in 1 participant (5.0%). In vehicle treated lesions, application site pruritus was reported in 2 participants (10.0%), and application site irritation was reported in 1 participant (5.0%). All of the TEAEs in both target lesions were considered treatment-related but were mild in severity.

For the BID regimen, 4 participants (19.0%) experienced a total of 7 TEAEs in crisaborole ointment 2% treated lesion, and 2 participants (9.5%) experienced a total of 3 TEAEs in vehicle treated lesion. In the crisaborole treated lesions, application site irritation was reported in 4 participants (19.0%), and application site pain, application site pruritus, and application site folliculitis were each reported in 1 participant (4.8%). In vehicle treated lesions, application site coldness, application site irritation, and application site pruritus were reported in 1 participant (4.8%) each. All of the TEAEs in both target lesions, except for the application site folliculitis in the crisaborole treated lesion, were considered treatment-related but were mild in severity.

Cohort 2:

For the QD regimen, no participant experienced TEAEs in the target lesions.

For the BID regimen, 1 participant (5.0%) experienced 2 TEAEs (application site pain and application site pruritus) in crisaborole ointment 2% treated lesion, both of which were considered to be treatment-related and mild in severity. No participant experienced TEAEs in vehicle treated lesion.

Conclusions:

- The primary efficacy endpoint was achieved in both regimens (QD and BID) and in both cohorts (Cohort 1: ≥12 years, Cohort 2: 2 to under 12 years old) in Japanese participants with mild to moderate AD. The crisaborole treated lesions showed a statistically significant reduction in TSS at Day 15 compared to the vehicle treated lesions. In Cohort 1, in QD regimen, intra-participant difference of TSS change from baseline was -1.6 with a p-value of 0.0071. In BID regimen, intra-participant difference of TSS change from baseline was -2.0 with a p-value of 0.0029. In Cohort 2, in QD regimen, intra-participant difference of TSS change from baseline was -1.5 with a p-value of 0.0250. In BID regimen, intra-participant difference of TSS change from baseline was -2.1 with a p-value of 0.0014.

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- For the comparison of the BID and QD regimens, numerically larger reductions in TSS at Day 15 were observed in crisaborole BID regimen compared to the crisaborole QD regimen in both cohorts.

- The crisaborole treated lesions showed a larger reduction in TSS at Day 8 compared to the vehicle treated lesions in both QD and BID regimens for both cohorts. The reductions in TSS at Day 8 was similar between the crisaborole BID and QD regimens for both cohorts.

- In the ISGA, peak pruritus NRS, itch severity scale and caregiver reported itch severity NRS, for intra-participant comparison, larger reductions were generally observed in crisaborole compared to the vehicle in both regimens for both cohorts.

- In the ISGA and itch severity scale, for inter-participant comparison, similar improvement was observed on Day 8 and Day 15 for ISGA, and from Day 2 to Day 15 for itch severity scale between crisaborole BID regimen and crisaborole QD regimen.

- In the peak pruritus NRS, for inter-participant comparison, similar improvement was observed, generally more in crisaborole QD regimen compared to crisaborole BID regimen from Day 2 to Day 12, but after Day 13, generally more in crisaborole BID regimen compared to crisaborole QD regimen.

- In the caregiver reported itch severity NRS, for inter-participant comparison, a greater improvement was generally observed from Day 2 to Day 15 in crisaborole BID regimen compared to crisaborole QD regimen.

- All the TEAEs reported in this study were mild in severity. Only the TEAEs that occurred in the target lesion were considered treatment-related. There were no deaths, SAEs, severe AEs or discontinuations due to TEAEs reported in the study. Crisaborole ointment 2% was well-tolerated in Japanese pediatric and adult participants with mild to moderate AD in both QD and BID regimens.