

**Protocol C3291028**

**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**

**Statistical Analysis Plan  
(SAP)**

**Version: 2.0**

**Date: 19 Dec 2019**

**TABLE OF CONTENTS**

LIST OF TABLES .....3

APPENDICES .....4

1. VERSION HISTORY .....5

2. INTRODUCTION .....5

    2.1. Study Objectives, Endpoints, and Estimands .....5

    2.2. Study Design .....9

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS .....10

    3.1. Primary Endpoint(s) .....10

    3.2. Secondary Endpoint(s) .....10

**CCI** .....11

**CCI** .....11

    3.4. Baseline Variables .....11

    3.5. Safety Endpoints .....11

        3.5.1. Adverse Events .....11

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS) .....12

5. GENERAL METHODOLOGY AND CONVENTIONS .....12

    5.1. Hypotheses and Decision Rules .....12

    5.2. General Methods .....12

        5.2.1. Analyses for Binary Endpoints .....13

        5.2.2. Analyses for Continuous Endpoints .....13

        5.2.3. Analyses for Categorical Endpoints .....13

    5.3. Methods to Manage Missing Data .....13

6. ANALYSES AND SUMMARIES .....14

    6.1. Primary Endpoint(s) .....14

        6.1.1. Change from Baseline in TSS in Target Lesions at Day 15  
            (Comparison of Crisaborole vs Vehicle in Each Regimen) .....14

            6.1.1.1. Main Analysis .....14

            6.1.1.2. Sensitivity/Supplementary Analyses .....15

    6.2. Secondary Endpoint(s) .....15

        6.2.1. Change from Baseline in TSS in Target Lesions at Day 15  
            (Comparison of Crisaborole BID vs Crisaborole QD) .....15

6.2.1.1. Main Analysis .....	15
6.2.1.2. Sensitivity/Supplementary Analyses.....	16
6.2.2. Change from Baseline in TSS in Target Lesions at Day 8 .....	16
6.2.3. Change from Baseline in ISGA in Target Lesions up to Day 15 .....	16
6.2.3.1. Main Analysis .....	16
6.2.3.2. Sensitivity/Supplementary Analyses.....	17
6.2.4. Change from Baseline in Pruritus Assessments in Target Lesions up to Day 15.....	17
6.2.4.1. Main Analysis .....	17
6.2.5. Incidence of TEAEs and SAEs.....	18
CCI [REDACTED]	19
CCI [REDACTED]	19
CCI [REDACTED]	19
6.4. Subset Analyses.....	19
6.5. Baseline and Other Summaries and Analyses .....	19
6.5.1. Baseline Summaries.....	19
6.5.2. Study Conduct and Participant Disposition.....	20
6.5.3. Study Treatment Exposure .....	20
6.5.4. Concomitant Medications and Nondrug Treatments.....	20
6.6. Safety Summaries and Analyses .....	20
6.6.1. Adverse Events .....	20
7. INTERIM ANALYSES .....	20
7.1. Introduction .....	20
7.2. Interim Analyses and Summaries.....	21
8. REFERENCES .....	21
9. APPENDICES .....	22

**LIST OF TABLES**

Table 1.	Summary of Changes.....	5
----------	-------------------------	---

**APPENDICES**

Appendix 1. SAS Code.....22  
Appendix 2. Definition and Use of Visit Windows in Reporting.....23

## 1. VERSION HISTORY

**Table 1. Summary of Changes**

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 6 Jun 2019	Original 22 Feb 2019	Not Applicable	Not Applicable
2 19 Dec 2019	Original 22 Feb 2019	<u>3.4</u> The baseline data of “Duration of disease (in years)” was not collected.	<u>3.4</u> “Duration of disease (in years)” was deleted.
		<u>Appendix 2</u> The visit windows for analysis were not described.	<u>Appendix 2</u> The visit windows for efficacy variables which were same as study C3291001 were added.

## 2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3291028. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

### 2.1. Study Objectives, Endpoints, and Estimands

Objectives	Endpoints	Estimands
<b>Primary:</b>	<b>Primary:</b>	<b>Primary:</b>
<ul style="list-style-type: none"> <li>To compare the efficacy of crisaborole ointment 2%, administered once daily (QD) or twice daily (BID) relative to the corresponding vehicle (QD or BID), on Total Sign Score (TSS) assessment in target lesions, in the treatment of mild to</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen (regimen 1: QD,</li> </ul>	<ul style="list-style-type: none"> <li>This estimand is the hypothetical estimand, which estimates the effect as if all participants maintain their randomized treatment.</li> <li>Population: Participants with mild to moderate AD in adults (cohort 1) and</li> </ul>

Objectives	Endpoints	Estimands
<p>moderate atopic dermatitis (AD) in adults (cohort 1) and pediatrics (cohort 2).</p>	<p>regimen 2: BID) for each cohort.</p>	<p>pediatrics (cohort 2) as defined by the inclusion and exclusion criteria and are randomized and received at least one of the investigational products.</p> <ul style="list-style-type: none"> <li>• Intercurrent event: All efficacy data after discontinuation of treatment will not be considered.</li> <li>• Population-level summary: Least-square means of intra-participant difference between crisaborole ointment 2% vs corresponding vehicle in each regimen for each cohort and pooled cohort.</li> </ul>
<b>Secondary:</b>	<b>Secondary:</b>	<b>Secondary:</b>
<ul style="list-style-type: none"> <li>• 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).</li> </ul>	<ul style="list-style-type: none"> <li>• Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen for each cohort.</li> </ul>	<ul style="list-style-type: none"> <li>• This estimand is the hypothetical estimand, which estimates the effect as if all participants maintain their randomized treatment.</li> <li>• Population: Participants with mild to moderate AD in adults (cohort 1) and pediatrics (cohort 2) as defined by the inclusion and exclusion criteria and are</li> </ul>

Objectives	Endpoints	Estimands
		<p>randomized and received at least one of the investigational products;</p> <ul style="list-style-type: none"> <li>• Intercurrent event: All efficacy data after discontinuation of treatment will not be considered.</li> <li>• Population-level summary: Difference in least square means between crisaborole ointment 2% BID and crisaborole ointment 2% QD for each cohort and pooled cohort.</li> </ul>
<ul style="list-style-type: none"> <li>• 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 (cohort 2).</li> </ul>	<ul style="list-style-type: none"> <li>• Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 8 in each regimen for each cohort.</li> <li>• 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.</li> <li>• Change from baseline in</li> </ul>	<ul style="list-style-type: none"> <li>• The other secondary efficacy endpoints will be analyzed using the estimands described above.</li> </ul>

Objectives	Endpoints	Estimands
	<p>pruritus assessments in target lesions treated with crisaborole ointment or vehicle at each day up to Day 15 in each regimen using following scales;</p> <p>Cohort 1: Peak Pruritus numerical rating scale (NRS) (age ≥12)</p> <p>Cohort 2: Itch Severity Scale (age 6-11)</p> <p>Cohort 2: Caregiver Reported Itch Severity NRS (age 2-11).</p>	
<ul style="list-style-type: none"> <li>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)</li> </ul>	<ul style="list-style-type: none"> <li>Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) in each regimen for each cohort.</li> </ul>	<ul style="list-style-type: none"> <li>There is no defined estimand for these endpoints and they will be analyzed descriptively.</li> </ul>
<p>CCI [REDACTED]</p>	<p>[REDACTED]</p>	<p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p>	<p>[REDACTED]</p>



Objectives	Endpoints	Estimands
<p>CCI [REDACTED]</p>	<p>[REDACTED]</p>	<p>[REDACTED]</p>

## 2.2. Study Design

This is 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 (cohort 1: 12 years and older, cohort 2: 2 to under 12 years old) with mild to moderate AD. After completing screening activities, including meeting eligibility criteria, two target lesions with same severity will be determined by the investigator, participants will be randomized to one of the regimens, QD or BID (randomization ratio; 1:1), and crisaborole ointment 2% or vehicle will be randomly assigned to each target lesion at Baseline/Day 1. Both target lesions are to be treated at the same assigned dosing regimen and dosing regimen is unblinded information to sponsor, investigators/study sites and participants. Participants will be treated with investigational products administered for 2 weeks and followed-up 28 days after the end of treatment.

Cohort	Regimen	Investigational Products	N	Study Treatment
Cohort 1 <sup>a</sup>	Regimen 1	Crisaborole ointment 2% QD vs Vehicle QD	20	Participants will visit the site <u>once</u> daily to be administered investigational products by site staff.
	Regimen 2	Crisaborole ointment 2% BID vs Vehicle BID	20	Participants will visit the site <u>twice</u> daily to be administered investigational products by site staff.
Cohort 2 <sup>b</sup>	Regimen 1	Crisaborole ointment 2% QD vs Vehicle QD	20	Investigational products will be applied <u>once</u> daily by parent/caregiver (site staff will confirm the compliance directly or via live video chat), or by site staff (site staff will visit the participant's home as needed).
	Regimen 2	Crisaborole ointment 2% BID vs Vehicle BID	20	Investigational products will be applied <u>twice</u> daily by parent/caregiver (site staff will confirm the compliance directly or via live video chat), or by site staff (site staff will visit the participant's home as needed).

BID: twice daily, N: number of participants, QD: once daily

a. ages 12 years and older

b. ages 2 years to under 12 years old

### 3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

#### 3.1. Primary Endpoint(s)

- Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen for each cohort for intra-participant comparison of crisaborole vs vehicle.

#### 3.2. Secondary Endpoint(s)

- Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 15 in each regimen for each cohort for inter-participant comparison of crisaborole BID vs crisaborole QD.
- Change from baseline in TSS in target lesions treated with crisaborole ointment or vehicle on Day 8 in each regimen for each cohort.
- 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.
- 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  $\geq 12$ );
  - Cohort 2: Itch Severity Scale (age 6-11);

- Cohort 2: Caregiver Reported Itch Severity NRS (age 2-11).
- Incidence of TEAEs and SAEs in each regimen for each cohort.

CCI [REDACTED]

### 3.4. Baseline Variables

Demographic and baseline characteristics include:

- Age (in years);
- Sex;
- Race;
- Ethnicity;
- ISGA (global and target lesions);
- %BSA (global);
- TSS (target lesions);
- Peak pruritus NRS (target lesions) for cohort 1;
- Itch severity scale (target lesions) for cohort 2 (6 to 11 years old only);
- Caregiver reported itch severity NRS (target lesions) for cohort 2.

### 3.5. Safety Endpoints

#### 3.5.1. Adverse Events

AEs will be captured and reported in accordance with Pfizer data standards.

An AE is considered a treatment-emergent adverse event (TEAE) if the event started during the effective duration of treatment.

All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date. If an AE starts on the same day as the first dose date, it will be considered treatment emergent unless the case report form (CRF) data indicates otherwise via explicitly recording time for AE onset and treatment dosing.

The effective duration of treatment starts at the date of the first dose of study treatment and ends at the date of the last dose of study treatment plus the lag time. An infinite lag will be used for this study.

**4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)**

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

<b>Population</b>	<b>Description</b>
Full Analysis Set (FAS)	All participants randomized and receiving $\geq 1$ dose of investigational product.
Per-Protocol Analysis Set (PPAS)	All participant randomized and receiving $\geq 1$ dose of investigational product, 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. All protocol deviations will be reviewed and assessed by the study team prior to database release.
Safety Analysis Set	All participants receiving $\geq 1$ dose of investigational product.

**5. GENERAL METHODOLOGY AND CONVENTIONS**

The final analysis will be performed at study participant dataset release after last participant last visit.

**5.1. Hypotheses and Decision Rules**

The primary analysis in each regimen for each cohort will be a superiority test to demonstrate crisaborole ointment 2% is more efficacious than vehicle in the target lesion in participants with mild to moderate AD as measured by change from baseline in TSS between crisaborole treated lesion and vehicle treated lesion. The null hypothesis in each regimen for each cohort is that there is no difference between crisaborole ointment 2% and vehicle, and the alternative hypothesis in each regimen for each cohort is that there is difference between crisaborole ointment 2% and vehicle as measured by change from baseline in TSS at Day 15. In each regimen for each cohort the difference between crisaborole and vehicle in TSS change from baseline at Day 15 is statistically significant if  $p\text{-value} < 0.05$  (two-sided).

**5.2. General Methods**

In general, number and percentage will be presented for categorical variables. Number, mean, standard deviation, minimum, 1st, 2nd and 3rd quartiles and maximum will be presented for continuous variables.

### **5.2.1. Analyses for Binary Endpoints**

The binary endpoints will be descriptively summarized using number, percentage and 95% confidence interval (CI) of percentage at each time point.

For the intra-participant comparison of crisaborole vs vehicle in each regimen at each time point, the binary endpoints will be compared using McNemar's test. For the inter-participant comparison of regimen 1 vs regimen 2 at each time point, the binary endpoints will be compared using Chi-squared test.

### **5.2.2. Analyses for Continuous Endpoints**

The continuous endpoints will be descriptively summarized using number, mean, standard deviation, minimum, 1st, 2nd and 3rd quartiles and maximum.

For the intra-participant comparison of crisaborole vs vehicle in each regimen at each time point, a Mixed effect Models for Repeated Measures (MMRM) will be used to derive least-square mean of intra-participant difference and associated 2-sided 95% CI between crisaborole ointment 2% and corresponding vehicle. A MMRM will include the fixed effect of time point (visit or day) and an unstructured variance and covariance matrix will be used to model the dependence among the same participants across different visits up to Day 15. If there is convergence issue for unstructured variance and covariance matrix, first order autoregressive (AR(1)) variance and covariance matrix will be used.

For the inter-participant comparison of regimen 1 vs regimen 2 at each time point, a MMRM will be used to derive difference in least-square means and associated 2-sided 95% CI between regimen 1 and regimen 2. A MMRM will include the fixed effects of dosing regimen, time point (visit or day), dosing regimen-by-time point (visit or day) interaction, and baseline value of the corresponding endpoint and an unstructured variance and covariance matrix will be used to model the dependence among the same participants across different visits up to Day 15. If there is convergence issue for unstructured variance and covariance matrix, AR(1) variance and covariance matrix will be used.

### **5.2.3. Analyses for Categorical Endpoints**

Categorical endpoints will be descriptively summarized using number and percentage. Shift table from baseline to Day 8 and Day 15 will be provided.

### **5.3. Methods to Manage Missing Data**

Missing data will not be imputed for efficacy descriptive summary.

For the statistical comparison of continuous endpoints, a MMRM analysis will be conducted including only the observed data in the model under the assumption of the missing at random (MAR) for the missing mechanism.

Non responder imputation (NRI) will be used for missing values of lesion ISGA response of clear or almost clear and at least a 2 grade improvement from baseline at Day 8 and Day 15.

In addition, missing values for safety endpoints will not be imputed.

## 6. ANALYSES AND SUMMARIES

### 6.1. Primary Endpoint(s)

#### 6.1.1. Change from Baseline in TSS in Target Lesions at Day 15 (Comparison of Crisaborole vs Vehicle in Each Regimen)

##### 6.1.1.1. Main Analysis

- Estimand strategy: Hypothetical ([Section 2.1](#)).
- Analysis time point: Day 15.
- Analysis set: FAS ([Section 4](#)).
- Analysis methodology: For the intra-participant comparison of crisaborole vs vehicle in each regimen for each cohort, the intra-participant difference of change from baseline in TSS in target lesions between crisaborole and vehicle up to Day 15 will be analyzed using a MMRM that includes the fixed effect of visit specified in [Section 5.2.2](#).
- Intercurrent events and missing data: All efficacy data after discontinuation of treatment will not be considered ([Section 2.1](#)). Observed data will be included in the model, and the missing values will be handled in the model, where the values are assumed to be MAR ([Section 5.3](#)).
- Supporting objective and decision rule: Primary objective, crisaborole is superior to vehicle for the TSS change at Day 15 if the change for crisaborole is greater than for vehicle and if  $p\text{-value} < 0.05$  (two-sided).
- Reporting results:
  - Observed score: The sample size, mean, standard error (SE), standard deviation, median, Q1, Q3, minimum and maximum at baseline and post-baseline visits will be presented for each treatment.
  - Change from baseline: The sample size, mean, SE, standard deviation, median, Q1, Q3, minimum and maximum at post-baseline visits will be presented for each treatment. The least-squares mean of difference and the corresponding SE, 95% CI, p-value will be presented for all post-baseline visits.
  - Figures: 1) Line plots of the mean change ( $\pm$  SE) from baseline to Day 8 and 15 for two treatments (ie, crisaborole vs vehicle) in one figure. Figures will be developed in each regimen for each cohort, separately. In addition, 2) line plots of the mean change ( $\pm$  SE) from baseline to Day 8 and 15 for four treatments (ie, crisaborole BID vs crisaborole QD vs vehicle BID vs vehicle QD) in one figure. Figures will be developed for each cohort, separately.

### **6.1.1.2. Sensitivity/Supplementary Analyses**

To support the interpretation of the main analysis the following analyses will be performed.

#### **6.1.1.2.1. Analysis for PPAS**

Except that analysis set is PPAS, the same estimand strategy, analysis time point, analysis methodology, intercurrent events and missing data, supporting objective and decision rule and reporting results as the main analysis ([Section 6.1.1.1](#)) will be used.

#### **6.1.1.2.2. Analysis for Pooled Cohort**

The same analysis as the main analysis ([Section 6.1.1.1](#)) will be conducted for the pooled cohort of cohort 1 and cohort 2.

## **6.2. Secondary Endpoint(s)**

### **6.2.1. Change from Baseline in TSS in Target Lesions at Day 15 (Comparison of Crisaborole BID vs Crisaborole QD)**

#### **6.2.1.1. Main Analysis**

- Estimand strategy: Hypothetical ([Section 2.1](#)).
- Analysis time point: Day 15.
- Analysis set: FAS ([Section 4](#)).
- Analysis methodology: For the inter-participant comparison of crisaborole BID vs crisaborole QD for each cohort, the change from baseline in TSS in target lesions between crisaborole BID and crisaborole QD up to Day 15 will be analyzed using a MMRM that includes the fixed effects of dosing regimen, visit, dosing regimen-by-visit interaction, and baseline value specified in [Section 5.2.2](#).
- Intercurrent events and missing data: All efficacy data after discontinuation of treatment will not be considered ([Section 2.1](#)). Observed data will be included in the model, and the missing values will be handled in the model, where the values are assumed to be MAR ([Section 5.3](#)).
- Reporting results:
  - Observed score: The sample size, mean, SE, standard deviation, median, Q1, Q3, minimum and maximum at baseline and post-baseline visits will be presented for each treatment.
  - Change from baseline: The sample size, mean, SE, standard deviation, median, Q1, Q3, minimum and maximum at post-baseline visits will be presented for each treatment. The least-squares mean and the corresponding SE, 95% CI for each treatment, the difference between the least-squares means of treatments and the corresponding SE, 95% CI, p-value will be presented for all post-baseline visits.

- Figures: Line plots of the mean change ( $\pm$  SE) from baseline to Day 8 and 15 for two treatments (ie, crisaborole BID vs crisaborole QD) in one figure. Figures will be developed for each cohort, separately.

### **6.2.1.2. Sensitivity/Supplementary Analyses**

To support the interpretation of the main analysis the following analyses will be performed.

#### **6.2.1.2.1. Analysis for PPAS**

Except that analysis set is PPAS, the same estimand strategy, analysis time point, analysis methodology, intercurrent events and missing data and reporting results as the main analysis ([Section 6.2.1.1](#)) will be used.

#### **6.2.1.2.2. Analysis for Pooled Cohort**

The same analysis as the main analysis ([Section 6.2.1.1](#)) will be conducted for the pooled cohort of cohort 1 and cohort 2.

### **6.2.2. Change from Baseline in TSS in Target Lesions at Day 8**

For the intra-participant comparison of crisaborole vs vehicle in each regimen for each cohort, Day 8 is a time point in the mixed model for the primary analysis for TSS change from baseline at Day 15. The analysis for TSS change from baseline at Day 8 is from the same model, and data reporting is same as for Day 15. See [Section 6.1.1](#).

For the inter-participant comparison of crisaborole BID vs crisaborole QD for each cohort, Day 8 is a time point in the mixed model for the secondary analysis for TSS change from baseline at Day 15. The analysis for TSS change from baseline at Day 8 is from the same model, and data reporting is same as for Day 15. See [Section 6.2](#).

### **6.2.3. Change from Baseline in ISGA in Target Lesions up to Day 15**

#### **6.2.3.1. Main Analysis**

- Estimand strategy: Hypothetical ([Section 2.1](#)).
- Analysis time point: Day 8 and Day 15.
- Analysis set: FAS ([Section 4](#)).
- Analysis methodology: For the intra-participant comparison of crisaborole vs vehicle in each regimen for each cohort, the intra-participant difference of change from baseline in ISGA in target lesions between crisaborole and vehicle up to Day 15 will be analyzed using a MMRM that includes the fixed effect of visit specified in [Section 5.2.2](#). For the inter-participant comparison of crisaborole BID vs crisaborole QD for each cohort, the change from baseline in ISGA in target lesions between crisaborole BID and crisaborole QD up to Day 15 will be analyzed using a MMRM that includes the fixed effects of dosing regimen, visit, dosing regimen-by-visit interaction, and baseline value specified in [Section 5.2.2](#).



- Intercurrent events and missing data: All efficacy data after discontinuation of treatment will not be considered ([Section 2.1](#)). Observed data will be included in the model, and the missing values will be handled in the model, where the values are assumed to be MAR ([Section 5.3](#)).
- Reporting results:
  - Observed score: The sample size, number and percentage for each category at baseline and post-baseline visits will be presented for each treatment. The sample size, mean, SE, standard deviation, median, Q1, Q3, minimum and maximum at baseline and post-baseline visits will be presented for each treatment as well.
  - Change from baseline: The sample size, mean, SE, standard deviation, median, Q1, Q3, minimum and maximum at post-baseline visits will be presented for each treatment. For the intra-participant comparison of crisaborole vs vehicle in each regimen for each cohort, the least-squares mean of difference and the corresponding SE, 95% CI, p-value will be presented for all post-baseline visits. For the inter-participant comparison of crisaborole BID vs crisaborole QD for each cohort, the least-squares mean and the corresponding SE, 95% CI for each treatment, the difference between the least-squares means of treatments and the corresponding SE, 95% CI, p-value will be presented for all post-baseline visits.
  - Shift table: Number and percentage from each category at baseline to each category at Day 8 and Day 15 will be presented.

#### **6.2.3.2. Sensitivity/Supplementary Analyses**

To support the interpretation of the main analysis, the same analysis as the main analysis ([Section 6.2.3.1](#)) will be conducted for the pooled cohort of cohort 1 and cohort 2.

#### **6.2.4. Change from Baseline in Pruritus Assessments in Target Lesions up to Day 15**

The following analysis will be conducted for each of the 3 endpoints of peak pruritus NRS (11-point scale), itch severity scale (5-point scale) and caregiver reported itch severity NRS (11-point scale), separately.

##### **6.2.4.1. Main Analysis**

- Estimand strategy: Hypothetical ([Section 2.1](#)).
- Analysis time point: Day 2 to Day 15.
- Analysis set: FAS ([Section 4](#)).

- Analysis methodology: For the intra-participant comparison of crisaborole vs vehicle in each regimen for each cohort, the intra-participant difference of change from baseline in pruritus in target lesions between crisaborole and vehicle up to Day 15 will be analyzed using a MMRM that includes the fixed effect of day specified in [Section 5.2.2](#). For the inter-participant comparison of crisaborole BID vs crisaborole QD for each cohort, the change from baseline in pruritus in target lesions between crisaborole BID and crisaborole QD up to Day 15 will be analyzed using a MMRM that includes the fixed effects of dosing regimen, day, dosing regimen-by-day interaction, and baseline value specified in [Section 5.2.2](#).
- Intercurrent events and missing data: All efficacy data after discontinuation of treatment will not be considered ([Section 2.1](#)). Observed data will be included in the model, and the missing values will be handled in the model, where the values are assumed to be MAR ([Section 5.3](#)).
- Reporting results:
  - Observed score: The sample size, mean, SE, standard deviation, median, Q1, Q3, minimum and maximum at baseline and post-baseline days will be presented for each treatment.
  - Change from baseline: The sample size, mean, SE, standard deviation, median, Q1, Q3, minimum and maximum at post-baseline days will be presented for each treatment. For the intra-participant comparison of crisaborole vs vehicle in each regimen for each cohort, the least-squares mean of difference and the corresponding SE, 95% CI, p-value will be presented for all post-baseline days. For the inter-participant comparison of crisaborole BID vs crisaborole QD for each cohort, the least-squares mean and the corresponding SE, 95% CI for each treatment, the difference between the least-squares means of treatments and the corresponding SE, 95% CI, p-value will be presented for all post-baseline days.
  - Figures: The following figures will be developed for each of the 3 endpoints of NRS assessment, separately. For the intra-participant comparison of crisaborole vs vehicle, 1) line plots of the mean change ( $\pm$  SE) from baseline up to Day 15 for two treatments (ie, crisaborole vs vehicle) in one figure. Figures will be developed in each regimen for each cohort, separately. In addition, 2) line plots of the mean change ( $\pm$  SE) from baseline up to Day 15 for four treatments (ie, crisaborole BID vs crisaborole QD vs vehicle BID vs vehicle QD) in one figure. Figures will be developed for each cohort, separately. For the inter-participant comparison of crisaborole BID vs crisaborole QD, 3) line plots of the mean change ( $\pm$  SE) from baseline up to Day 15 for two treatments (ie, crisaborole BID vs crisaborole QD) in one figure. Figures will be developed for each cohort, separately.

#### 6.2.5. Incidence of TEAEs and SAEs

See [Section 6.6.1](#).

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

- | [Redacted]
- | [Redacted]
- | [Redacted]
- | [Redacted]

[Redacted]

- | [Redacted]
- | [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

**6.4. Subset Analyses**

Not Applicable.

**6.5. Baseline and Other Summaries and Analyses**

**6.5.1. Baseline Summaries**

In each regimen for each cohort, demographic and baseline characteristics will be summarized for safety analysis set according to Pfizer data standards. Lesion baseline data will be summarized by treatment in each regimen for each cohort.

### **6.5.2. Study Conduct and Participant Disposition**

Participants evaluation, disposition, discontinuation will be summarized for safety analysis set according to Pfizer data standards.

### **6.5.3. Study Treatment Exposure**

For participants in regimen 1, a total of 14 doses are expected to be applied. For participants in regimen 2, a total of 28 doses are expected to be applied. A participant will be considered compliant with the dosing regimen if they receive, at least 12 but no more than 16 investigational product doses for regimen 1, at least 23 but no more than 33 investigational product doses for regimen 2 (ie, 80 – 120%, inclusive, of the expected number of doses).

In each regimen for each cohort, the exposure to study drug in each treatment group will be summarized by total number of applications, the total number of days of dosing and number and percentage of participants who are compliant with the dosing regimen.

For cohort 2, total number of applications without confirmation by site staff will be summarized.

### **6.5.4. Concomitant Medications and Nondrug Treatments**

Prior drug and non-drug treatment, concomitant drug and non-drug treatment will be summarized according to Pfizer data standards.

## **6.6. Safety Summaries and Analyses**

### **6.6.1. Adverse Events**

Adverse events will be summarized according to Pfizer data standards.

- TEAEs.
- SAEs.

TEAEs and SAEs occurred in the target lesions will be summarized by treatment in each regimen for each cohort and pooled cohort. General TEAEs and SAEs will be summarized for overall safety analysis set in each regimen for each cohort.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an **CCI** and its purpose is to generate hypotheses for further investigation.

## **7. INTERIM ANALYSES**

### **7.1. Introduction**

No formal interim analysis will be conducted for this study.

**7.2. Interim Analyses and Summaries**

Not Applicable.

**8. REFERENCES**

Not Applicable.

## 9. APPENDICES

### Appendix 1. SAS Code

For the intra-participant comparison of crisaborole vs vehicle for each regimen, the following SAS code can be used for analysis of mixed model repeated measure for lesion TSS change from baseline up to Day 15 and other similar continuous endpoint shown in [Section 3](#).

```
proc mixed data=dataset;
  class subjid visit;
  model difference = visit;

  repeated visit/subject=subjid type=un;/*If there is a convergence issue
for type=un, it can be replaced by type=AR(1)*/
  lsmeans visit/cl;
run;
```

Note: difference is the intra-participant difference of change from baseline at each time point up to Day 15 between crisaborole and vehicle.

For the inter-participant comparison of crisaborole BID vs crisaborole QD, the following SAS code can be used for analysis of mixed model repeated measure for lesion TSS change from baseline up to Day 15 and other similar continuous endpoint shown in [Section 3](#).

```
proc mixed data=dataset;
  class subjid regimen visit;
  model difference = regimen visit regimen*visit baseline;

  repeated visit/subject=subjid type=un;/*If there is a convergence issue
for type=un, it can be replaced by type=AR(1)*/
  lsmeans regimen*visit/cl diff cl;
run;
```

Note: difference is change from baseline at each time point up to Day 15 of each regimen.

**Appendix 2. Definition and Use of Visit Windows in Reporting**

Visit windows will be used for efficacy variables.

If more than one observation from the same participant falls into the same visit window, the value closest to the targeted day will be used as the observation for that time point. All observations will, however, be included in the listings.

<b>TSS and ISGA</b>		
<b>Visit Label</b>	<b>Targeted Day</b>	<b>Analysis window for data sets</b>
Baseline [Screening (Day -35) to up to first dosing date)	Day 1	Last observation up to and including first dosing date
Day 8	Day 8	Day 2 – Day 11
Day 15	Day 15	Day 12 – end of study
<b>Pruritus Assessment</b>		
<b>Visit Label</b>	<b>Targeted Day</b>	<b>Analysis window for data sets</b>
Baseline [Screening (Day -35) to up to first dosing date)	Day 1	Last observation up to and including first dosing date
Day 2	Day 2	Day 2
...	...	...
Day 14	Day 14	Day 14
Day 15	Day 15	Day 15*

\* if the measurement value of pruritus assessment is collected after Day 15, the value will be used as the observation for the day.