

Protocol C3291029

A phase 1, single-center, randomized, vehicle-controlled, parallel-cohort study of crisaborole ointment 2% to evaluate the skin irritation potential in adult Japanese healthy subjects, and to evaluate the safety, tolerability and pharmacokinetics in adult Japanese subjects with mild to moderate atopic dermatitis

Statistical Analysis Plan  
(SAP)

**Version:** 2.0

**Date:** 30-Nov-2017

---

**TABLE OF CONTENTS**

LIST OF TABLES .....3

APPENDICES .....4

1. VERSION HISTORY .....5

2. INTRODUCTION .....5

    2.1. Study Objectives .....5

    2.2. Study Design .....6

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS .....7

    3.1. Primary Endpoints .....7

    3.2. Secondary Endpoints .....7

    3.3. Other Endpoints .....7

        3.3.1. PK Endpoints .....7

        CCI .....8

    3.4. Baseline Variables .....8

    3.5. Safety Endpoints .....8

        3.5.1. Adverse Events .....8

4. ANALYSIS SETS .....8

    4.1. Full Analysis Set .....8

    4.2. Per Protocol Analysis Set .....8

    4.3. Safety Analysis Set .....8

    4.4. Other Analysis Sets .....9

        4.4.1. PK Analysis Sets .....9

    4.5. Protocol Deviations .....9

5. GENERAL METHODOLOGY AND CONVENTIONS .....9

    5.1. Hypotheses and Decision Rules .....9

    5.2. General Methods .....9

        5.2.1. Analyses for Binary Data .....9

        5.2.2. Analyses for Continuous Data .....9

    5.3. Methods to Manage Missing Data .....10

        5.3.1. Safety Data .....10

        5.3.2. Skin Irritation Score .....10

---

5.3.3. Concentrations Below the Limit of Quantification (BLQ).....	10
5.3.4. Deviations, Missing Concentrations and Anomalous Values for PK.....	10
5.3.5. Pharmacokinetic Parameters.....	10
6. ANALYSES AND SUMMARIES .....	11
6.1. Primary Endpoints.....	11
6.1.1. Skin Irritation Index.....	11
6.1.2. Adverse Events .....	11
6.1.3. Laboratory Data .....	11
6.1.4. Vital Signs .....	11
6.1.5. Electrocardiogram.....	12
6.2. Secondary Endpoints.....	12
6.2.1. Adverse Events .....	12
6.2.2. PK Parameters .....	12
6.3. Other Endpoints.....	13
6.3.1. Skin Irritation Score.....	13
CCI [REDACTED] .....	13
6.4. Subset Analyses.....	13
6.5. Baseline and Other Summaries and Analyses.....	14
6.5.1. Baseline Summaries.....	14
6.5.2. Study Conduct and Subject Disposition .....	14
6.5.3. Study Treatment Exposure .....	14
6.5.4. Concomitant Medications and Non-Drug Treatments.....	14
6.6. Safety Summaries and Analyses .....	14
7. INTERIM ANALYSES .....	15
7.1. Introduction .....	15
7.2. Interim Analyses and Summaries.....	15
8. REFERENCES .....	15
9. APPENDICES .....	16

**LIST OF TABLES**

Table 1. Summary of Major Changes in SAP Amendments .....	5
---	---

**APPENDICES**

Appendix 1. DATA DERIVATION DETAILS .....16

## 1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C3291029 is based on the protocol amendment-1 dated 14July2017.

**Table 1. Summary of Major Changes in SAP Amendments**

SAP Version	Change	Rationale
1.0	Not Applicable	Not Applicable
2.0	6.1.4. Vital Signs, 6.1.5. Electrocardiogram, 6.5.1. Baseline Summaries, 6.5.3. Study Treatment Exposure <ul style="list-style-type: none"> <li>• Clarified the analysis plan.</li> </ul> 9. APPENDICES <ul style="list-style-type: none"> <li>• Defined the visit windows for safety parameters.</li> </ul>	Blind table review before the final analysis

## 2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C3291029. 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

#### Cohort 1

The primary objective is to investigate the skin irritation potential of a single topical dose of crisaborole ointment 2% and vehicle in adult Japanese healthy subjects.

The secondary objective is to investigate the safety and tolerability of a single topical dose of crisaborole ointment 2% and vehicle in adult Japanese healthy subjects.

#### Cohort 2

The primary objective is to investigate the safety and tolerability of multiple topical doses of crisaborole ointment 2% twice daily (BID) in adult Japanese subjects with mild to moderate atopic dermatitis (AD).

The secondary objective is to characterize plasma pharmacokinetic (PK) of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) following multiple topical doses of crisaborole ointment 2% BID in adult Japanese subjects with mild to moderate AD.

CCI

## 2.2. Study Design

This is a Phase 1, single-center, randomized, vehicle-controlled, parallel-cohort study of crisaborole ointment 2% to evaluate the skin irritation potential in adult Japanese healthy subjects in Cohort 1, and to evaluate the safety, tolerability and PK in adult Japanese subjects with mild to moderate AD in Cohort 2. Both cohorts will be run in parallel and completion of Cohort 1 is not required to make a decision to proceed with Cohort 2.

Cohort		N	Investigational products
Cohort 1	Skin irritation cohort in healthy subjects	20	Crisaborole ointment 2% and vehicle
Cohort 2	Safety, tolerability and PK cohort in subjects with mild to moderate AD	12	Crisaborole ointment 2% (n=10) Vehicle (n=2)

### Cohort 1

This is a randomized, observer and subject blind, vehicle controlled cohort, of the investigational products (crisaborole ointment 2% and vehicle) under occlusive patch conditions to evaluate the skin irritation potential and safety in Japanese healthy male subjects aged 20 to 55 years, inclusive. Approximately 20 subjects will be enrolled into the cohort. All subjects will have skin area fields designated for the investigational products patches at two randomly assigned, adjacent sites, for the purpose of determining irritation potential. All subjects enrolled in Cohort 1 will receive both products (crisaborole ointment 2%, and vehicle). For Cohort 1, subjects will be randomly assigned in a 1:1 ratio to either Randomization sequence 1 [Application placement 1 (Upper): Crisaborole ointment 2%, Application placement 2 (Lower): Vehicle] or Randomization sequence 2 [Application placement 1 (Upper): Vehicle, Application placement 2 (Lower): Crisaborole ointment 2%].

### Cohort 2

This is a randomized, double blind cohort of crisaborole ointment 2% BID to evaluate the safety, tolerability and PK in adult Japanese subjects with mild to moderate AD. The cohort will enroll male and female subjects with AD aged 20 years to 55 years, inclusive, at the time of screening. Approximately 12 subjects having at least 25% Treatable %BSA, defined as the percent of a subject's total body surface area (BSA) that is AD involved and is not on the scalp or in designated venous access areas, will be enrolled into the study. For Cohort 2, subjects will be randomly assigned in a 5:1 ratio to either crisaborole ointment 2% or vehicle.

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

#### 3.1. Primary Endpoints

##### Cohort 1

- Skin irritation index.

##### Cohort 2

- Adverse events (AEs), clinical laboratory tests, vital signs, and 12 lead electrocardiogram (ECG).

#### 3.2. Secondary Endpoints

##### Cohort 1

- AEs.

##### Cohort 2

- PK parameters:  $C_{max}$ ,  $T_{max}$ ,  $AUC_{last}$ ,  $AUC_{24}$ ,  $AUC_{\tau}$  on Day 1 and Day 8, and  $R_{ac}$  ( $C_{max}$ ) and  $R_{ac}$  ( $AUC_{\tau}$ ) on Day 8.

#### 3.3. Other Endpoints

##### 3.3.1. PK Endpoints

PK parameters are the secondary endpoints for Cohort 2. For each subject, the following PK parameters will be calculated for crisaborole and its identified main oxidative metabolites (AN7602 and AN8323), as data allows using noncompartmental analysis of concentration-time data.

Parameter	Day	Definition	Method of Determination
$AUC_{\tau}$	1, 8	Area under the plasma concentration-time curve from time zero to time tau ( $\tau$ ), the dosing interval, where $\tau = 12$ hours for BID dosing	Linear/Log trapezoidal method
$AUC_{last}$	1, 8	Area under the plasma concentration-time curve from zero time until the last measurable concentration ( $C_{last}$ )	Linear/Log trapezoidal method
$AUC_{24}$	1, 8	Area under the plasma concentration-time curve from time zero to the 24 hours postdose	Linear/Log trapezoidal method
$C_{max}$	1, 8	Maximum observed plasma concentration over the dosing interval (12 hours) and over a 24 hour time period (total daily dose)	Observed directly from data
$T_{max}$	1, 8	Time to reach maximum observed plasma concentration	Observed directly from data as time of first occurrence
$R_{ac}$ ( $C_{max}$ )	8	Accumulation ratio for $C_{max}$	$C_{max, Day 8}/C_{max(first dose)}$
$R_{ac}$ ( $AUC_{\tau}$ )	8	Accumulation ratio for $AUC_{\tau}$	$AUC_{\tau, Day 8}/AUC_{\tau(first dose)}$

CCI



### **3.4. Baseline Variables**

There are no baseline variables used as covariates or stratification factors in analyses.

### **3.5. Safety Endpoints**

#### **3.5.1. Adverse Events**

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

An adverse event is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period), or
- the event was seen prior to the start of treatment but increased in severity during treatment.

The effective duration of treatment is determined by the lag time. Any event occurring within the lag time, whether this occurs during a break in treatment or at the end of treatment, is attributed to the corresponding treatment period. An infinite lag will be used for this study.

## **4. ANALYSIS SETS**

Data for all subjects will be assessed to determine if subjects 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.

### **4.1. Full Analysis Set**

Not Applicable.

### **4.2. Per Protocol Analysis Set**

Not Applicable.

### **4.3. Safety Analysis Set**

The safety analysis population is defined as all subjects who receive at least one dose of study medication. All subjects who receive at least one dose of study medication are classified according actual study treatment received. The safety analysis set is the primary population for treatment administration/compliance and safety. A randomized but not treated

subject will be excluded from the safety analyses. A treated but not randomized subject will be reported under the treatment actually received.

#### **4.4. Other Analysis Sets**

##### **4.4.1. PK Analysis Sets**

- The PK concentration population is defined as all subjects randomized and treated who have at least 1 concentration.
- The PK parameter analysis population is defined as all subjects randomized and treated who have at least 1 of the PK parameters of primary interest.

#### **4.5. Protocol Deviations**

Subjects who experience events that may affect their PK profile may be excluded from the PK analysis. At the discretion of the pharmacokineticist a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviation prior to database closure.

### **5. GENERAL METHODOLOGY AND CONVENTIONS**

- The final analysis will be performed at study subjects' dataset release after last subject last visit.
- All data will be analyzed separately for each cohort.

#### **5.1. Hypotheses and Decision Rules**

There are no statistical hypotheses to be tested.

#### **5.2. General Methods**

##### **5.2.1. Analyses for Binary Data**

Unless otherwise explicitly stated, descriptive statistics for binary variables are the percentage (%), and the numerator (n) and the denominator (N) used in the percentage calculation.

##### **5.2.2. Analyses for Continuous Data**

Unless otherwise explicitly stated, descriptive statistics for continuous variables are n, mean, median, standard deviation, minimum, and maximum.

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

#### **5.3.1. Safety Data**

Handling of missing information related to safety data, such as missing or partially missing data, will be in accordance with Pfizer data standards.

#### **5.3.2. Skin Irritation Score**

Missing values of the skin irritation score will not be imputed in any data analysis.

#### **5.3.3. Concentrations Below the Limit of Quantification (BLQ)**

In all data presentations (except listings), concentrations BLQ will be set to zero (In listings BLQ values will be reported as “<LLQ”, where LLQ will be replaced with value for the lower limit of quantification).

#### **5.3.4. Deviations, Missing Concentrations and Anomalous Values for PK**

In summary tables and plots of mean and median profiles, statistics will be calculated having set concentrations to missing if one of the following cases is true:

- A concentration has been collected as ND (ie, not done) or NS (ie, no sample);
- A deviation in sampling time is of sufficient concern (ie, sampling time outside of 20% of nominal time) or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

#### **5.3.5. Pharmacokinetic Parameters**

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a subject’s concentration data, the parameter will be coded as NC (ie, not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will not be presented for a particular treatment if more than 50% of the data are NC.

If an individual subject has a known biased estimate of a PK parameter (for example, due to an unexpected event before all the drug is absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

## 6. ANALYSES AND SUMMARIES

### 6.1. Primary Endpoints

#### 6.1.1. Skin Irritation Index

Skin irritation index is the primary endpoint for Cohort1. For each investigational product (ie, treatment), the skin irritation index will be calculated as the sum of the individual maximum irritation scores divided by the number of evaluable subjects who have the skin irritation assessment for the safety analysis population and multiplied by 100. The calculated skin irritation index will range from 0 to 400. As show in the following table, for example, when the skin irritation index is equal to or smaller than 5, the investigational product will be categorized as ‘Safe’.<sup>1,2,3</sup>

#### Safety Criteria of Skin Irritation Index

Skin irritation index <sup>a</sup>	Category
0 ≤ - ≤5	Safe
5 < - ≤15	Acceptable
15 < - ≤30	Improvable
30 < - ≤400	Risky

a: Skin irritation index = (Sum of individual maximum irritation scores / number of evaluable subjects) × 100

#### 6.1.2. Adverse Events

AEs are one of the primary endpoints for Cohort 2. The analysis of AEs will be based on the safety analysis population. Descriptive summaries and listing of the AE/SAE data will be provided by treatment. In addition, AEs occurred in the treatment area will be separately summarized by treatment. AEs will be reported in accordance with the Pfizer data standards.

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 exploratory analysis and its purpose is to generate hypotheses for further investigation.

#### 6.1.3. Laboratory Data

Laboratory data are one of the primary endpoints for Cohort 2. The analysis of laboratory data will be based on the safety analysis population. Laboratory data will be descriptively summarized and listed by treatment in accordance with the Pfizer data standards. Baseline will be the last predose measurement.

#### 6.1.4. Vital Signs

Vital signs data are one of the primary endpoints for Cohort 2. The analysis of vital signs data will be based on the safety analysis population. Absolute values and changes from

baseline in blood pressure and pulse rate will be summarized and listed by treatment and visit in accordance with the Pfizer data standards. Baseline will be the last predose measurement.

### 6.1.5. Electrocardiogram

ECG data are one of the primary endpoints for Cohort 2. Absolute values and changes from baseline for the ECG parameters, QT interval, heart rate, QTc (ie, QTcF) interval, PR interval, QRS interval, and RR interval will be summarized descriptively by treatment and visit for the safety analysis population.

The number (%) of subjects with maximum postdose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

#### Safety QTc Assessment

	Borderline (msec)	Prolonged (msec)
Absolute value	≥450 - <480	≥480
Absolute change	30 - <60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

## 6.2. Secondary Endpoints

### 6.2.1. Adverse Events

AEs are the secondary endpoint for Cohort 1. The analysis of AEs will be based on the safety analysis population. Descriptive summaries and listing of the AE/SAE data will be provided. In addition, AEs occurred in the application area will be summarized by treatment separately. AEs will be reported in accordance with the Pfizer data standards.

### 6.2.2. PK Parameters

PK parameters are the secondary endpoints for Cohort 2. PK analysis will be based on the PK analysis set.

PK data will be descriptively summarized by day and analyte for crisaborole and its metabolites respectively. Comparison between days will be performed by descriptive analysis of the within-subject ratio of Day 8/Day 1 PK parameters. The set of summary statistics as specified in the table below:

Day	Parameter	Summary statistics
1, 8	$AUC_{\tau}$ , $AUC_{last}$ , $AUC_{24}$ , $C_{max}$	n, arithmetic mean, median, CV%, standard deviation, minimum, maximum, geometric mean, geometric CV%
1, 8	$T_{max}$	n, median, minimum, maximum
8	$R_{ac}(C_{max})$ , $R_{ac}(AUC_{\tau})$	n, arithmetic mean, median, CV%, standard deviation, minimum, maximum, geometric mean, geometric CV%

A summary of concentrations by day and nominal time point, for crisaborole and its metabolites respectively, where the set of statistics will include n, mean, median, standard deviation, CV(%), minimum, maximum and the number of concentrations above the lower limit of quantification.

Mean and median profiles of the plasma concentration-time data will be plotted through Day 1 to Day 9, for crisaborole and its metabolites respectively. In addition, mean and median profile of trough concentration data on Day 7, Day 8 and Day 9 will be plotted against time for crisaborole and its metabolites respectively. Mean and median profiles against nominal time point will be presented on both linear and semi-log linear scales.

Individual plasma concentration-time data will be plotted through Day 1 to Day 9, for crisaborole and its metabolites respectively. In addition, the individual plasma concentration-time data for all subjects will be plotted through Day 1 to Day 9 on the same graph, for crisaborole and its metabolites respectively. Individual profiles against actual time point will be presented on both linear and semi-log linear scales.

All plasma concentration values and plasma PK parameters will be listed by subject.

### **6.3. Other Endpoints**

#### **6.3.1. Skin Irritation Score**

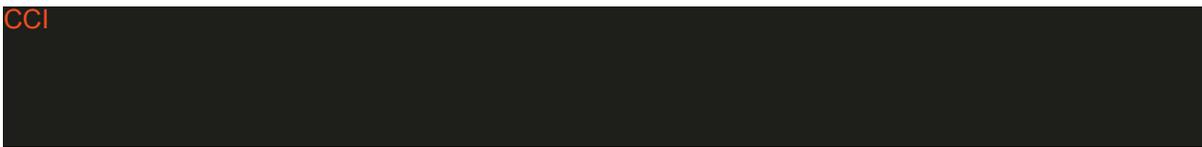
For each subject, the maximum irritation score of the skin irritation assessment through all visits (ie, Day 3 and Day 4) will be calculated.

For the maximum irritation score, the frequency (number and %) of individual maximum irritation scores will be presented for each investigational product. The descriptive statistics (n, number of missing, mean, standard deviation, median, minimum and maximum) of the maximum irritation score will also be calculated for each investigational product.

For the irritation score, the frequency (number and %) of individual irritation scores will be presented for each investigational product at each visit. The descriptive statistics (n, number of missing, mean, standard deviation, median, minimum and maximum) of the irritation score will also be calculated for each investigational product at each visit.

Individual irritation scores will be displayed in a data listing for all subjects.

CCI



### **6.4. Subset Analyses**

Not Applicable

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

### **6.5.1. Baseline Summaries**

For Cohort 1, descriptive summary reports for demographic and baseline characteristics (age, gender, ethnicity, race, weight, height and body mass index) will be provided for the safety analysis population. For cohort 2, descriptive summary reports for demographic and baseline characteristics (age, gender, ethnicity, race, weight, height, body mass index, investigator's static global assessment score and treatable % BSA) will be provided by treatment for the safety analysis population.

Medical history will be summarized for Cohort 1, and by treatment for Cohort 2, for the safety analysis population.

Data will be reported in accordance with the Pfizer data standards.

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

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics (for Cohort 2 only) and safety. Frequency counts will be supplied for subject discontinuation(s) for Cohort 1, and by treatment for Cohort 2.

Data will be reported in accordance with the Pfizer data standards.

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

The administration schedule (duration of treatment, total number of applications) will be summarized descriptively by treatment, separately for each cohort for the safety analysis population.

Data will be reported in accordance with the Pfizer data standards.

### **6.5.4. Concomitant Medications and Non-Drug Treatments**

All prior and concomitant medication(s) as well as non-drug treatment(s) will be summarized for Cohort 1, and by treatment for Cohort 2, and provided in the listings.

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

Physical examination information collected during the course of the study will be considered source data and will not be required to be reported. However, any untoward findings identified on physical examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported.

The statistical analysis for adverse events, laboratory data, vital signs and ECG are described in [Section 6.1](#).

## **7. INTERIM ANALYSES**

### **7.1. Introduction**

No formal interim analysis will be conducted for this study. However, for Cohort 1, as this is a sponsor open study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, skin irritation assessment, and/or supporting clinical development.

### **7.2. Interim Analyses and Summaries**

Not Applicable.

## **8. REFERENCES**

1. Kawamura T, Shoji S, Masuda T et al. Basic studies on the standardization of patch test. *Jpn J Dermatol.* 1970; 80: 301–14 (Japanese).
2. Sugai T. Contact dermatitis and patch test. *Skin Research.* 1977; 19(2): 210–22 (Japanese).
3. Sugai T. Safety Evaluation of Cosmetic Products. *J. Jpn Cosmet Sci Soc.* 1995; 19: 49-56 (Japanese) .

## 9. APPENDICES

### Appendix 1. DATA DERIVATION DETAILS

Definition and use of visit windows in reporting

For cohort 2, the visit windows below will be used for any safety summaries that display by visit.

#### Definition of Visit Windows

Visit Label	Target Day	Definition [Day window]
Day 1	Prior to Day 1, start of study treatment	Day 1
Day 8/ET	Day 8	Day 2 or later

If two or more visits fall into the same window, keep the one closest to the Target Day. If two visits are of equal distance from the Target Day in absolute value, the later visit should be used.