Protocol C3291027

A PHASE 3, MULTICENTER, OPEN-LABEL STUDY OF THE LONG-TERM SAFETY OF CRISABOROLE OINTMENT, 2% IN JAPANESE PEDIATRIC AND ADULT PARTICIPANTS WITH MILD TO MODERATE ATOPIC DERMATITIS

Statistical Analysis Plan
(SAP)

Version: 2

Date: 7 Jan 2021

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 4 Aug 2020	Original 20 May 2020	N/A	N/A
2 7 Jan 2021	Original 20 May 2020	Study termination	Updated the following analyses due to the small sample size and the short exposure period. 6.4. Subset Analyses 6.5.3. Study Treatment Exposure 6.5.4. Concomitant Medications and Nondrug Treatments 6.6.1. Adverse Events

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3291027. 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, Estimands and Endpoints

Objectives	Estimands	Endpoints
Primary:	**Primary:**	**Primary:**
• To study the safety of crisaborole ointment, 2% applied BID in Japanese pediatric and adult participants with mild to moderate AD.	• There is no defined estimand for this objective and these endpoints will be analyzed descriptively.	• The incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs).
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
• To characterize the efficacy of long-term administration of crisaborole ointment, 2%. • To characterize the patient/observer reported outcomes for pruritus of long-term administration of crisaborole ointment, 2%.	• There is no defined estimand for this objective and these endpoints will be analyzed descriptively.	**Efficacy*** • % change from baseline in eczema area and severity index (EASI) over time. • Achievement of EASI50 (≥50% improvement from baseline) over time. • Achievement of EASI75 (≥75% improvement from baseline) over time. • Change from baseline in Treatable % body surface area (BSA) over time. • Achievement of success in investigator's static global assessment

Objectives	Estimands	Endpoints
		(ISGA) [defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline] over time. • Achievement of improvement in ISGA [defined as an ISGA score of Clear (0) or Almost Clear (1)] over time. • Achievement of success in Regional ISGA-face [defined as a Regional ISGA-face score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline] over time. • Achievement of improvement in Regional ISGA-face [defined as a Regional ISGA-face score of Clear (0) or Almost Clear (1)] over time. • Incidence of the use of rescue medication (topical corticosteroids or topical calcineurin inhibitors). **Patient/Observer Reported Outcomes** • Change from baseline in Peak Pruritus NRS over time - for participants ≥12 years. • Changes from baseline in Patient Reported Itch Severity Scale over time - for participants ≥6 years and <12 years. • Change from baseline in Observer Reported Itch Severity Scale over time - for participants <6 years.
• To assess the pharmacokinetic (PK) profile of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) following multiple topical doses of crisaborole ointment, 2% BID from C3291032 on Day 1.	• There is no defined estimand for this objective and these endpoints will be analyzed descriptively.	• Plasma concentrations of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) on Day 1.

* Baseline refers to the baseline data of Study C3291032 or Study C3291031.

2.2. Study Design

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

Study C3291031 treatment period and meet eligibility criteria of this study. Scheduled study visits will occur every 4 weeks (1 cycle) with On-Treatment or Off-Treatment cycles to be decided by the investigator based on the ISGA score. PK blood sampling will be conducted at the selected study sites for the participants aged between 2 years old and 11 years old at the time of signing the ICD in Study C3291032.

When the investigator assessment of ISGA is Almost Clear (1) or greater, an On-Treatment Cycle will be initiated. When the investigator assessment of ISGA is Clear (0), crisaborole ointment, 2% treatment will not be initiated and the participant will enter an Off-Treatment Cycle. Based on the ISGA score throughout the study, a participant may be administered a variable number of cycles of crisaborole ointment, 2% treatment (On-Treatment Cycle) during their up to 52 weeks of study participation.

On Week 56 (End of Study), a follow-up telephone call will be made by site staff to assess for AEs that may have occurred since the last visit.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- The incidence of TEAEs and SAEs.

3.2. Secondary Endpoint(s)

Not applicable.

3.3. Other Endpoint(s)

3.3.1. Tertiary/Exploratory Endpoint(s)

3.3.1.1. Efficacy

- % change from baseline in EASI over time.
- Achievement of EASI50 (≥50% improvement from baseline) over time.
- Achievement of EASI75 (≥75% improvement from baseline) over time.
- Change from baseline in Treatable %BSA over time.
- Achievement of success in ISGA [defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline] over time.
- Achievement of improvement in ISGA [defined as an ISGA score of Clear (0) or Almost Clear (1)] over time.

- Achievement of success in Regional ISGA-face [defined as a Regional ISGA-face score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline] over time.

- Achievement of improvement in Regional ISGA-face [defined as a Regional ISGA-face score of Clear (0) or Almost Clear (1)] over time.

- Incidence of the use of rescue medication (topical corticosteroids or topical calcineurin inhibitors).

3.3.1.2. Patient/Observer Reported Outcomes

- Change from baseline in Peak Pruritus NRS over time - for participants ≥12 years.

- Changes from baseline in Patient Reported Itch Severity Scale over time - for participants ≥6 years and <12 years.

- Change from baseline in Observer Reported Itch Severity Scale over time - for participants <6 years.

3.3.1.3. Pharmacokinetic(s)

- Plasma concentrations of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) on Day 1.

3.4. Baseline Variables

For the purpose of analysis of efficacy and patient/observer reported outcomes endpoints, the baseline values are defined as the baseline values from the participant's parent phase 3 study.

3.5. Safety Endpoints

Safety endpoint is defined above in Section 3.1.

3.5.1. Adverse Events

An adverse event (AE) is considered a 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 of this study, if collected, and before end of study will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date of this study. If an AE starts on the same day as the first dose date of this study, 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 of this study and ends at the date of the last dose of study treatment plus the lag time.

If any AEs are ongoing at the time of the End of Treatment visit within the parent study and the participant is enrolling into this study, such AEs will be transcribed and followed within this study. AE updates following the parent study End of Treatment visit date will only be made within this study for participants who enroll into 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 releasing the database and classifications will be documented per standard operating procedures.

Participant Analysis Set	Description
Full Analysis Set	All participants who take at least one dose of study intervention. The participants who will enter the first Off-Treatment cycle will also be included.
Safety Analysis Set	All participants who take at least one dose of study intervention. The participants who will enter the first Off-Treatment cycle will also be included.
PK Analysis Set	All participants who take at least one dose of study intervention in Study C3291032 and who have at least one concentration value.

5. GENERAL METHODOLOGY AND CONVENTIONS

The final analysis and reporting of results will be performed after the completion of the study and the database is locked. Interim analyses of data may be performed from time to time, see Section 7.

5.1. Hypotheses and Decision Rules

Efficacy analyses will be descriptive in nature; there will be no formal hypothesis testing, though 95% two-sided confidence intervals will be reported. All the safety data will be summarized descriptively.

5.2. General Methods

In general, for descriptive analyses, number and percentage will be presented for binary variables. Number and percentage will be presented for categorical variables. Number, mean, median, standard deviation, minimum and maximum will be presented for continuous variables.

5.3. Methods to Manage Missing Data

In general, for analyses using descriptive statistics, missing values will not be imputed. In addition, for safety endpoints, missing values will not be imputed. Other methods for handling missing values are discussed below.

5.3.1. Patient/Observer Reported Outcomes Endpoints

For the continuous patient/observer reported outcomes variables, rules suggested by the developers of these instruments will be followed in calculating the missing values. If these rules are not enough for imputing a value, then the missing values will be treated as missing.

5.3.2. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (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).

5.3.3. Deviations, Missing Concentrations and Anomalous Values for Pharmacokinetics

In summary tables, 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 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.

6. ANALYSES AND SUMMARIES

The primary endpoint of incidence of AEs will be analyzed using descriptive measures such as percentages along with confidence intervals. No statistical hypotheses will be tested. There is no pre-specified estimand for the safety evaluation and all the safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations.

There is no pre-specified estimand for the efficacy and patient/observer reported outcomes evaluation. Efficacy and patient/observer reported outcomes analyses will be descriptive in nature; there will be no formal hypothesis testing, though 95% two-sided confidence intervals will be reported.

There is no pre-specified estimand for the PK evaluation. Predose (Ctrough) plasma concentrations of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323) will be listed and descriptively summarized, respectively.

6.1. Primary Endpoint(s)

6.1.1. Primary Analysis

- Analysis Set: Safety analysis set (see Section 4).

- Analysis Methodology: Descriptive statistics (see Section 5.2) for incidence of TEAEs and SAEs

6.2. Secondary Endpoint(s)

Not applicable.

6.3. Other Endpoint(s)

6.3.1. Efficacy Endpoints

6.3.1.1. % Change from Baseline in EASI Over Time

- Analysis Set: FAS (see Section 4).
- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for the mean for observed data and % change from baseline in EASI over time

6.3.1.2. Achievement of EASI50 (≥50% improvement from baseline) Over Time

- Analysis Set: FAS (see Section 4).
- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for the proportion of participants with EASI50 (≥50% improvement from baseline) over time.

6.3.1.3. Achievement of EASI75 (≥75% improvement from baseline) Over Time

- Analysis Set: FAS (see Section 4).
- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for the proportion of participants with EASI75 (≥75% improvement from baseline) over time.

6.3.1.4. Change from Baseline in Treatable %BSA Over Time

- Analysis Set: FAS (see Section 4).
- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for the mean for observed data and change from baseline in Treatable %BSA over time.

6.3.1.5. Achievement of Success in ISGA [defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline] Over Time

- Analysis Set: FAS (see Section 4).

- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for the proportion of participants with success in ISGA [defined as an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline] over time. Categorical summary (see Section 5.2) in ISGA will also be reported.

6.3.1.6. Achievement of Improvement in ISGA [defined as an ISGA score of Clear (0) or Almost Clear (1)] Over Time

- Analysis Set: FAS (see Section 4).

- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for the proportion of participants with improvement in ISGA [defined as an ISGA score of Clear (0) or Almost Clear (1)] over time.

6.3.1.7. Achievement of Success in Regional ISGA-face [defined as a Regional ISGA-face score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline] Over Time

- Analysis Set: FAS (see Section 4).

- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for the proportion of participants with success in Regional ISGA-face [defined as a Regional ISGA-face score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline] over time. Categorical summary (see Section 5.2) in Regional ISGA-face will also be reported.

6.3.1.8. Achievement of Improvement in Regional ISGA-face [defined as a Regional ISGA-face score of Clear (0) or Almost Clear (1)] Over Time

- Analysis Set: FAS (see Section 4).

- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for the proportion of participants with improvement in Regional ISGA-face [defined as a Regional ISGA-face score of Clear (0) or Almost Clear (1)] over time.

6.3.1.9. Incidence of the Use of Rescue Medication (topical corticosteroids or topical calcineurin inhibitors)

- Analysis Set: FAS (see Section 4).

- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for incidence of the use of rescue medication (topical corticosteroids or topical calcineurin inhibitors).

6.3.2. Patient/Observer Reported Outcomes Endpoints

6.3.2.1. Change from Baseline in Peak Pruritus NRS Over Time - for Participants ≥12 Years

- Analysis Set: FAS (see Section 4).
- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for the mean for observed data and change from baseline in Peak Pruritus NRS over time - for participants ≥12 years.

6.3.2.2. Changes from Baseline in Patient Reported Itch Severity Scale Over Time - for Participants ≥6 Years and <12 Years

- Analysis Set: FAS (see Section 4).
- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for the mean for observed data and changes from baseline in Patient Reported Itch Severity Scale over time - for participants ≥6 years and <12 years.

6.3.2.3. Change from Baseline in Observer Reported Itch Severity Scale Over Time - for Participants <6 Years

- Analysis Set: FAS (see Section 4).
- Analysis Methodology: Descriptive statistics (see Section 5.2) and 95% two-sided confidence intervals for the mean for observed data and change from baseline in Observer Reported Itch Severity Scale over time - for participants <6 years.

6.3.3. Pharmacokinetics

- Analysis Set: PK analysis set (see Section 4).
- Analysis Methodology: Descriptive statistics including number, mean, median, standard deviation, CV(%), minimum, maximum and the number of concentrations above the lower limit of quantification, for predose (C_{trough}) plasma concentrations of crisaborole and its identified main oxidative metabolites (AN7602 and AN8323).

6.4. Subset Analyses

Summary statistics for % change from baseline in EASI, achievement of improvement in ISGA, achievement of success in ISGA will be presented by subgroup below.

- Age (years) group (2-11, 12-17, <18, ≥18).

Descriptive statistics and 95% confidence intervals will be presented for each defined category of each subgroup.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographics will be summarized according to CaPS (CDISC and Pfizer Standards).

6.5.2. Study Conduct and Participant Disposition

Subjects evaluation, disposition and discontinuation will be summarized according to CaPS.

6.5.3. Study Treatment Exposure

Descriptive statistics (number, mean, standard deviation, median, minimum, maximum) and categorical summary will be reported for duration of treatment (time from the first to the last dosing date of treatment) and total number of applications. Amount of drugs used will be summarized descriptively (number, mean, standard deviation, median, minimum, maximum).

Descriptive statistics (mean, median, minimum, maximum) and categorical summary for number of treatment cycles started per participant will be reported. The same analyses will be conducted for number of Off-Treatment Cycles per participant. In addition, number and percentage of participants with Off-Treatment will be summarized by treatment cycle and all treatment cycles.

The subgroup analysis by age (<18, ≥18) will be conducted.

6.5.4. Concomitant Medications and Nondrug Treatments

Concomitant drug and non-drug treatment will be summarized according to CaPs. Number of days when rescue medication is taken will be descriptively summarized for All-Treatment Period, respectively.

6.6. Safety Summaries and Analyses

Safety analysis will be based on the safety analysis set. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

6.6.1. Adverse Events

The safety data will be summarized in accordance with CaPS. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. The subgroup analysis by age (<18, ≥18) will be conducted, where appropriate. Safety endpoints for the study include:

- Treatment-emergent AEs and SAEs;
- Withdrawals from active treatment due to AEs;

TEAEs and SAEs occurred in the treatment area will be summarized. Location of skin lesions will be listed.

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.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study.

7.2. Interim Analyses and Summaries

As this is an open-label, long-term extension study, the sponsor may conduct reviews of the data during the course of the study for the purpose of internal decision making, due to regulatory requests, or to support regulatory submissions. The data cutoff may occur after 6-month follow-up data across this study and the parent study has been accumulated for approximately 100 participants enrolled in this study.

This study will use a data monitoring committee (DMC). The DMC is independent of the study team and includes only external members. The DMC charter describes the role of the DMC in more detail.

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

8. REFERENCES

Not Applicable.

9. APPENDICES

Appendix 1. Definition and Use of Visit Windows in Reporting

Visit windows will be used for efficacy and patient/observer reported outcomes variables that display or summarize by study visit.

Visit Label	Target Day	Definition [Day window relative to Study C3291027 Day 1]
Screening/Baseline of qualifying parent study		
Week 4	29	Days 16 to 43
Week 8	57	Days 44 to 71
Week 12	85	Days 72 to 99
Week 16	113	Days 100 to 127
Week 20	141	Days 128 to 155
Week 24	169	Days 156 to 183
Week 28	197	Days 184 to 211
Week 32	225	Days 212 to 239
Week 36	253	Days 240 to 267
Week 40	281	Days 268 to 295
Week 44	309	Days 296 to 323
Week 48	337	Days 324 to 351
Week 52	365	Days 352 to

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