Protocol C3291035

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, VEHICLE CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF MAINTENANCE TREATMENT AND FLARE REDUCTION WITH CRISABOROLE OINTMENT, 2%, ONCE DAILY OVER 52 WEEKS IN PEDIATRIC AND ADULT PARTICIPANTS (AGES 3 MONTHS AND OLDER) WITH MILD-TO-MODERATE ATOPIC DERMATITIS, WHO RESPONDED TO TWICE DAILY CRISABOROLE OINTMENT, 2%, TREATMENT

Statistical Analysis Plan
(SAP)

Version: **4**

Date: **20 January 2022**

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1. VERSION HISTORY

This SAP for Study C3291035 is based on the protocol Amendment 1 dated 19MAY2020.

Table 1. Summary of Major Changes in SAP Amendments

Version/Date	Associated Protocol Amendment	Specific Changes	Rationale
1 13Jun2019	Original 04Apr2019	Not Applicable	Not Applicable
2 17July2020	Amendment 1 19May2020	The age of the study participant population was extended to 3 months of age and older. It was clarified that to yield a total of 162 first flares in the double-blind maintenance period of the study, it is estimated that approximately 700 participants will be enrolled in the open-label period for responder identification and that 250 participants will be randomized into the double-blind maintenance period. It is possible that less than 700 or up to 860 participants will be enrolled in the open-label period. Sensitivity/supplementary analyses for the primary analysis were added. "Analysis Set" was changed as Analysis Population; Population definitions were	Per protocol Amendment 1. Per Pfizer's new template and guidance for estimand

		modified; Estimands were updated. Separate listings and/or summaries may be produced for participants who are impacted by COVID-19, have protocol deviations, discontinue from study or study treatment due to the COVID-19 pandemic. Appendix 3 Listing of Abbreviations was added. Some editorial changes.	COVID-19 pandemic.
3 23Sep2021	Amendment 1 19May2020	For POEM and Dermatology Quality of Life Assessments during open-label period: • No change from baseline • Modify to weekly analyses Additional significant changes are: • Removed maintenance IDQoL response • Only participants with ISGA success and EASI50 at randomization be included in the Evaluable-DB population. • Annualized data analysis for total	• Almost all subjects have no baseline data. • Data were collected weekly. • MCID is not available for IDQoL • Based on randomization criteria • Take early

		flare-free days and number of flares as primary analysis • Treat duration of per flare period and duration of per QD period as continuous endpoints, not as time-to-event • Additional summary for overall DB period for efficacy/PRO endpoints • LOCF data will be used for OL period efficacy summary. • Added additional age subgroup analyses for primary and key secondary efficacy endpoints, evaluation and disposition groups, demographic and baseline characteristics, AE data	discontinuation into consideration • May have too many censor data • Provide efficacy/PRO summary for overall DB period • Based on study design (ie, responders at any time during OL period will be randomized into the DB period) • Per Article 46 requirement
4 20Jan2022	Amendment 1 19May2020	• Summary of vital signs (including height and weight) and physical exam was removed • Added safety population for OL	• Team decision • For convenience and consistency among safety tables

		period and overall study. • Removed subgroup analysis by age groups 3 - <24 months, 2 - <12 years, 12 - <18 years, and ≥18 years • Removed subgroup analysis for key secondary endpoint maintenance of pruritus response. • Removed sensitivity analysis for number of flare-free days and number of flares (annualized data) • Prohibited treatment use was removed from intercurrent events	• Article 46 no longer apply • There are already 5 subgroups for maintenance of pruritus response. Sample size will be too small and may not get robust results by further subgroup analysis. • Observed data are more appropriate. • Difficult to identify prohibited medication specifically used for AD.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3291035. 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

Study objectives and corresponding endpoints are provided in the Table 2 below.

Table 2. Study Objectives and Endpoints

Objectives	Endpoints

Primary	
• **Efficacy:** To evaluate the long-term efficacy of crisaborole ointment, 2%, once daily (QD) for maintenance therapy and flare reduction in pediatric and adult participants ≥3 months of age with mild-to-moderate atopic dermatitis (AD) who responded to crisaborole ointment, 2%, twice daily (BID) treatment.	• Flare-free maintenance until onset of first flare during the 52-week double-blind (DB) period.
• **Safety:** To evaluate the safety and local tolerability of crisaborole ointment, 2%, QD for maintenance therapy and flare reduction in pediatric and adult participants ≥3 months of age with mild-to-moderate AD.	• Incidence of treatment emergent adverse events.

Secondary	
• To evaluate other long-term efficacy parameters for maintenance therapy and flare reduction of crisaborole ointment, 2%, QD in pediatric and adult participants ≥3 months of age with mild-to-moderate AD who responded to crisaborole ointment, 2%, BID treatment.	Key secondary endpoints during the 52-week DB period: • Number of flare-free days; • Number of flares; • Maintenance of pruritus response until onset of first flare. Other secondary endpoints during the 52-week DB period: • Maintenance of ≥50% Eczema Area and Severity Index (EASI) response; • Maintenance of dermatology quality of life assessments • Maintenance of Patient Oriented Eczema Measure (POEM). • Most commonly affected AD %BSA collected during the DB period only. The following will be assessed during flare treatment period: • Severity of flare on Investigator's Static Global Assessment (ISGA) and EASI; • Duration of flare periods.
Additional Secondary	
• To evaluate the long-term efficacy of crisaborole ointment, 2%, QD for maintenance therapy and flare reduction in participants ≥3 months of age with mild-to-moderate AD.	The following will be assessed as change from baseline of each respective treatment period (open-label (OL), DB, and flare treatment): • EASI score; • ISGA score; • Treatable AD % Body Surface Area (BSA)
• To evaluate the long-term health impact of crisaborole ointment, 2%, QD for maintenance therapy and flare reduction in participants ≥3 months of age with mild-to-moderate AD.	The following patient reported outcomes (PROs) will be assessed: • Night Time Itch; • AD Skin Pain;

	• Patient/Observer Global Impression of Severity (PGIS/OGIS); • Patient/Observer Global Impression of Change (PGIC/OGIC); • Medical Outcomes Study Sleep (MOS-Sleep) Scale; • EuroQol-5 Dimensions-5 (EQ-5D); • Work and Classroom Productivity; • Hospital Anxiety and Depression Scale (HADS).

2.1.1. Estimand 1 for the Primary Endpoint

Estimand 1: The primary estimand of the main study is a hypothetical estimand, defined according to the primary objective and is in alignment with the primary endpoint. It includes the following 4 attributes:

- Population: Patients who are treated with crisaborole 2% BID up to 8 weeks and achieve response defined by the criteria in the protocol.
- Variable: Duration of flare-free maintenance up until the onset of the first flare during the DB period.
- Intercurrent events: intercurrent events include discontinuation of treatment. If an event (eg, death, dropout, loss to follow up, or end of study) occurs before the first flare, the duration of flare-free maintenance is the time from randomization to the first intercurrent event and is censored. When a flare occurs first, the duration of flare-free maintenance is the time from randomization to the first flare and is not censored.
- Population-level summary: Median duration of flare-free maintenance during the DB period, proportion of participants who are flare-free by time point in each treatment group.

This estimand framework will be used for other time-to-event endpoints as well, such as maintenance of EASI response at randomization, maintenance of dermatology quality of life and maintenance of POEM.

2.1.2. Estimands for Secondary Endpoints

2.1.2.1. Estimand 2

Estimand 2: The second estimand of the study for the secondary endpoint of number of flare-free days during the DB period is a hypothetical estimand. It includes the following 4 attributes:

- Population: Patients who are treated with crisaborole 2% BID up to 8 weeks and achieve response defined by the criteria in the protocol.

- Variable: Flare-free days during the DB period. It is the total days that the participant has no flare during the DB period for each participant.

- Intercurrent events: intercurrent events include discontinuation of treatment. Addressing intercurrent events for the duration of flare-free maintenance at each flare-free period is the same as that for the primary endpoint during the first flare-free period.

- Population-level summary: Difference in least-square means between crisaborole ointment, 2%, QD and vehicle QD for flare-free days over 52 weeks.

2.1.2.2. Estimand 3

Estimand 3: The third estimand of the study for the secondary endpoint of number of flares during the DB period is a hypothetical estimand. It includes the following 4 attributes:

- Population: Patients who are treated with crisaborole 2% BID up to 8 weeks and achieve response defined by the criteria in the protocol.

- Variable: number of flares during the DB period.

- Intercurrent events: intercurrent events include discontinuation of treatment.

- Population-level summary: Median difference between crisaborole ointment, 2%, QD and vehicle QD for number of flares over 52 weeks.

2.1.2.3. Estimand 4

Estimand 4: The fourth estimand of the study for the secondary endpoint of maintenance of pruritus response up until the onset of the first flare (ISGA ≥2) is a hypothetical estimand. It includes the following 4 attributes:

- Population: Patients who are treated with crisaborole 2% BID up to 8 weeks and achieved pruritus response defined as ≥2, 3, or 4 points of improvement from OL baseline in respective pruritus scales (See Section 3.2.1).

- Variable: Duration of maintenance of pruritus response up until the onset of the first flare (ISGA ≥2).

- Intercurrent events: intercurrent events include discontinuation of treatment, first flare [ISGA ≥2]. If an event (eg, death, dropout, first flare [ISGA ≥2], lost to follow up, or end of study) occurs before loss of pruritus response for the first flare-free period, the duration of maintenance of pruritus response is the time from randomization to the first intercurrent event and is censored. When loss of pruritus response occurs first, the duration of pruritus response maintenance is not censored.

- Population-level summary: Median duration of maintenance of pruritus response up until the onset of the first flare during the DB period, proportion of participants who maintain pruritus response by time point in each treatment group.

2.2. Study Design

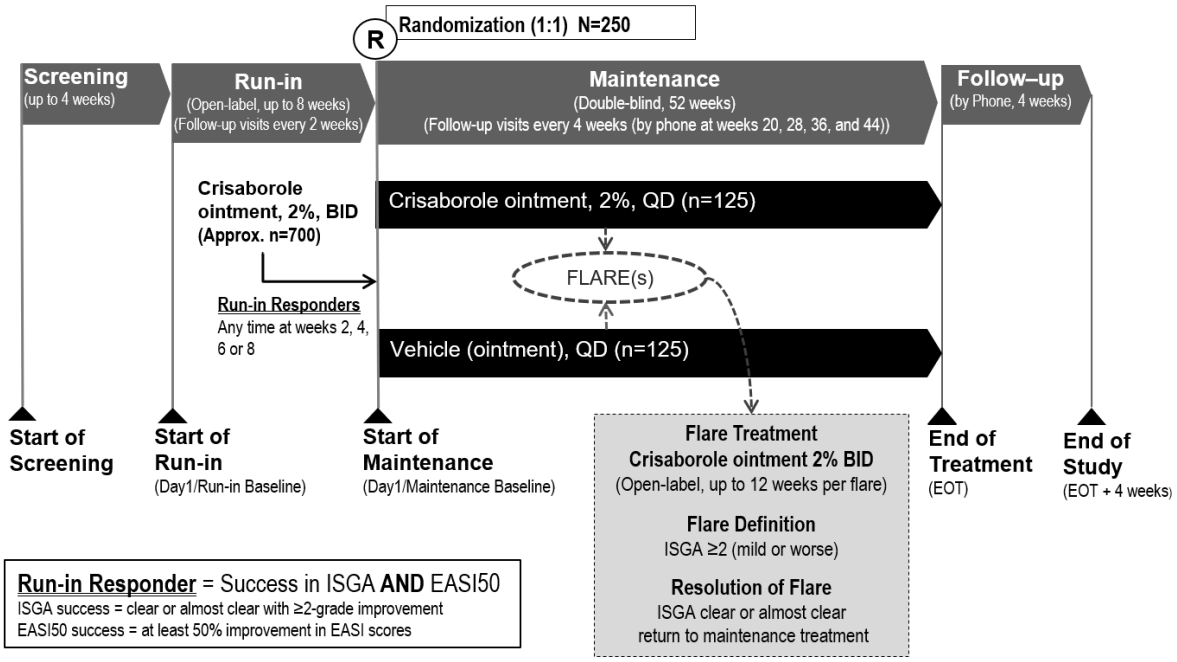
Study C3291035 is a Phase 3, randomized, DB, vehicle-controlled study to assess the efficacy and safety of crisaborole ointment, 2%, QD as maintenance treatment and for the reduction of flare occurrence in participants (3 months of age and older) with mild-to-moderate AD.

Eligible participants will be enrolled to receive crisaborole BID in an OL period of up to a maximum of 8 weeks in duration. Responders to OL treatment at any time during this period will be randomized into the DB period in a 1:1 ratio to receive QD crisaborole or vehicle for 52 weeks.

During the OL period, a responder is defined as a participant who achieves both ISGA success (achieving a score of clear [0] or almost clear [1] with a ≥2 grade improvement from the OL baseline) and EASI50 (at least 50% improvement from the OL baseline in EASI).

Non-responders at the end of the 8-week OL period will be discontinued from the study. To yield a total of 162 first flare events in the DB period of the study, it is estimated that approximately 700 participants will be enrolled in the OL period for responder identification and that approximately 250 participants will be randomized into the DB period. Once adequate participants have been randomized, recruitment will stop; it is possible that less than 700 or up to 860 participants will be enrolled in the OL period.

Figure 1. Study Design Schematic



BID = twice daily; QD = once daily; ISGA = Investigator's Static Global Assessment; EASI = Eczema Area and Severity Index; EOT = End of treatment

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

The primary endpoint is a flare-free maintenance until onset of the first flare during the 52-week DB period.

3.2. Secondary Endpoints

3.2.1. Key Secondary Endpoints

The key secondary endpoints during the 52-week DB period are:

- Number of flare-free days;
- Number of flares;
- Maintenance of pruritus response (defined as the maintenance of the improvement of ≥50% from baseline that was obtained at randomization) until onset of the first flare. Pruritus and itch assessment are age-dependent patient (or observer) reported outcomes. The analysis will be performed separately for 5 age and pruritus response subgroups:

- ≥12 years of age with OL baseline Peak Pruritus Numerical Rating Scale (NRS) ≥3 and ≥3 points reduction from OL baseline to randomization in Peak Pruritus NRS.
- ≥12 years of age with OL baseline Peak Pruritus NRS ≥4 and ≥4 points reduction from OL baseline to randomization in Peak Pruritus NRS.
- 6-<12 years of age with OL baseline Patient Reported Itch Severity (PRIS) Scale ≥2 and ≥2 points reduction from OL baseline to randomization in PRIS Scale.
- 3 months-<6 years of age with OL baseline Observer Reported Itch Severity (ORIS) Scale ≥3 and ≥3 points reduction from OL baseline to randomization in ORIS Scale.
- 3 months-<6 years of age with OL baseline ORIS Scale ≥4 and ≥4 points reduction from OL baseline to randomization in ORIS Scale.

3.2.2. Other Secondary Endpoints

3.2.2.1. The Other Secondary Endpoints during the 52-week Double-blind Period

Maintenance is evaluated for the Other Secondary Endpoints during the 52-week study, up until the time of first flare.

- Maintenance of EASI response, defined as ≥50% of achieved reduction from the Day 1/Baseline OL period to randomization is maintained in EASI;
- Maintenance of dermatology quality of life assessments, defined as no loss in response greater than the Minimal Clinical Important Difference (MCID);
- Maintenance of POEM, defined as no loss in response greater than the MCID.
- Most commonly affected AD %BSA at DB baseline, Day 169, and Day 365 only.

3.2.2.2. Endpoints During Flare Treatment Period

The following endpoints will be assessed during flare treatment period:

- Severity of flare using ISGA and EASI;
- Duration of flare periods.

3.3. Additional Secondary Endpoints

3.3.1. Efficacy Endpoints

The following will be assessed as change from baseline of each respective treatment period: OL, DB, and flare treatment.

- EASI score;
- ISGA score;
- Treatable AD %BSA;

3.3.2. Patient Reported Outcome Endpoints

The following PROs will be assessed:

- Night Time Itch Scale for participants ≥12 years of age.
- AD Skin Pain NRS for participants ≥12 years of age.
- PGIS/OGIS for all participants.
- PGIC/OGIC for all participants.
- MOS-Sleep Scale for participants ≥12 years of age.
- EQ-5D for 2 years and older participants.
- Work and Classroom Productivity for participants ≥12 years of age.
- HADS for participants ≥12 years of age.

For pruritus and itch assessment, night time itch, AD skin pain, and PGIS/OGIS, the data are collected daily. Weekly average will be used for analyses that are analyzed as continuous endpoints. For the key secondary endpoint of maintenance of pruritus response until onset of the first flare, daily data will be used for analysis.

CCI [redacted]

3.5. Baseline Variables

Below demographic and baseline characteristics will be collected at OL baseline and/or at randomization:

	OL Baseline	**DB Baseline**
Demographic	Age, Sex, Race, Ethnicity, Country, Height, Weight, BMI, Duration of disease, prior treatment history	Height, weight, BMI,
Baseline Disease Characteristics	ISGA, EASI, %BSA, pruritus	ISGA, EASI, %BSA, pruritus, most commonly affected AD %BSA

The OL baseline value is defined as the last observation up to and including Day 1 of OL period. The DB baseline value for DB period is defined as the last observation up to and including the randomization day. For daily assessed endpoints (eg, pruritus, itch, pain, etc.), weekly average before randomization will be used.

Age group (3 months-<12 years, ≥12 years), Duration of the BID treatment in OL period (≤ 4, >4 weeks) and ISGA score (clear [0], almost clear [1]) at randomization will be used as covariates or stratification factors in statistical models.

3.6. Safety Endpoints

Safety will be assessed by vital signs, physical examinations, clinical laboratory tests and the spontaneous reporting of adverse events (AEs), in all participants who received at least one dose of study intervention. Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns. Investigators and Pfizer Clinicians will review individual participant data throughout the conduct of the study to ensure participants' well-being. Appendix 5 of the protocol provides liver safety (Suggested Actions and Follow-up Assessments) in details.

3.6.1. Adverse Events

An AE is considered treatment-emergent adverse event (TEAE) to a given treatment (for a participant who received at least one dose) if the event start date is on or after the treatment period start date and before end of study.

Safety endpoints will be assessed by the spontaneous reporting of:

- Incidence of TEAEs;
- Incidence of serious adverse events (SAEs);
- Incidence of AEs leading to discontinuation.

3.6.2. Laboratory Data

Laboratory testing will be performed at screening and post baseline only if clinically indicated. Below are the protocol-required safety laboratory assessments:

Laboratory Assessments	Parameters	
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	White blood cell (WBC) count (% and absolute: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Albumin Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Sodium Glucose (non-fasting)	Blood urea nitrogen (BUN) Alkaline phosphatase Total Protein Creatinine Bicarbonate or total CO_2	Potassium Total bilirubin Calcium Chloride
Urine Pregnancy	For all WOCBP: Test kit (dipsticks) provided by the central laboratory. The results of the urine dipstick test must be recorded in the source document and made available for study review.	
Other Tests	Follicle-stimulating hormone (only for post-menopausal status confirmation at screening). Serum beta human chorionic gonadotropin (β-hCG) pregnancy test (for all WOCBP at screening, and for pregnancy status confirmation if urine dipstick pregnancy test is positive or if a urine dipstick test cannot be confirmed as negative [eg, an ambiguous result]).	

3.6.3. Vital Signs

Temperature and pulse rate will be assessed.

3.6.4. Physical Examinations

A complete physical examination will include, at a minimum, assessments of general appearance, skin, head, ears, eyes, nose, throat, mouth, skin, heart, lung, breast, lymph nodes, extremities, abdomen, external genitalia (optional), and neurological function. In addition, an assessment will be made for skin abnormalities other than AD, including scalp.

A targeted physical examination will include, at a minimum, assessments of the skin, heart, lungs, and abdomen and examination of body systems where there are symptom complaints by the participant.

Height and weight will also be measured and recorded.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the informed consent form.
Evaluable-OL (Eval-OL)	All participants receiving at least 1 dose of study intervention in the OL period
Safety-OL (SAF-OL)	All participants receiving at least 1 dose of study intervention in the OL period. It is same as Evaluable-OL
Evaluable-DB (Eval-DB)	All randomized participants with success in ISGA and EASI50 criteria as responders at randomization and receiving at least 1 dose of study intervention in the DB period. Participants will be analyzed according to the intervention they are randomized to.
Safety-DB (SAF-DB)	All randomized participants receiving at least 1 dose of study intervention in the DB period. Participants will be analyzed according to the intervention they actually received.
Safety (SAF)	All participants receiving at least 1 dose of study intervention during the study.

5. GENERAL METHODOLOGY AND CONVENTIONS

Final analyses will occur after database release.

5.1. Hypotheses and Decision Rules

The primary objective is to establish the superiority of a crisaborole QD to a vehicle QD; detecting a 1.8 ratio of median time of being flare-free (hazard ratio of 0.556) in the first flare-free period at a significance level of 0.05 (2-sided, log-rank test).

5.1.1. Statistical Decision Rules for Multiple Comparisons

A step-down closed testing procedure and Bonferroni's method will be used for Type I error control for testing the primary endpoint and the key secondary endpoints. The order of testing is as follows:

1. Flare-free maintenance up until the onset of the first flare during the DB period.
2. Number of flare-free days over 52 weeks.
3. Number of flares over 52 weeks.

4. Pruritus response maintenance up until the onset of the first flare (ISGA ≥2), defined as the maintenance of improvement ≥50% (ie, if 50% or more of the improvement in pruritus from the baseline to the randomization is maintained). Analysis will be performed for 5 responder subgroups:

    - ≥12 years of age with OL baseline Peak Pruritus NRS ≥3 and ≥3 points reduction OL baseline to randomization in Peak Pruritus NRS.

    - ≥12 years of age with OL baseline Peak Pruritus NRS ≥4 and ≥4 points reduction OL baseline to randomization in Peak Pruritus NRS.

    - 6-<12 years of age with OL baseline PRIS Scale ≥2 and ≥2 points reduction OL baseline to randomization in PRIS Scale.

    - 3 months-<6 years of age with OL baseline ORIS Scale ≥3 and ≥3 points reduction OL baseline to randomization in ORIS Scale.

    - 3 months-<6 years of age with OL baseline ORIS Scale ≥4 and ≥4 points reduction OL baseline to randomization in ORIS Scale.

The statistical significance can be claimed for a given endpoint in the sequence only if the prior endpoint in the sequence is significant. For the endpoints of 1-3, the significance level is 0.05. For pruritus response maintenance, Bonferroni's method is used to adjust the significance level. The significance level is 0.01 for each subgroup, there is no testing order. Only the subgroup with p-value ≤0.01 can claim significance after the primary endpoint and other two secondary endpoints are statistically significant.

5.2. General Methods

In general, number, percent, and 95% CI (Clopper-Pearson method) will be presented for binary endpoints. Descriptive summary statistics (n, Mean, Standard Deviation, Median, Min., Max.) will be presented for continuous endpoints. In addition, graphics may be used to present the data.

5.2.1. Analyses for Binary Data

Descriptive summary will be performed for binary endpoints for this study.

5.2.2. Analyses for Continuous Data

5.2.2.1. Longitudinal Continuous Data

Descriptive summary will be performed for longitudinal continuous endpoints for this study.

5.2.2.2. Non-longitudinal Continuous Data

Analysis of covariance (ANCOVA) will be used to analyze non-longitudinal continuous data, such as number of flare-free days over 52-week DB period. Age group (3 months-<12 years, ≥12 years), duration of the BID treatment in OL period (≤4, >4 weeks), and ISGA score (clear [0], almost clear [1]) at randomization will be included in the model as covariates.

Least square (LS) estimates of mean values and the LS mean differences between crisaborole QD and vehicle QD groups will be derived from the model. The corresponding p-value, standard errors and 95% CI will also be derived from the model.

5.2.3. Analyses for Categorical Data

The frequency and percentage for each category will be presented for category endpoints.

5.2.4. Analyses for Time-to-Event Data

Time-to-event analysis will be used to analyze time-to-event data.

Kaplan-Meier (product limit) method will be used for estimation of proportion of participants with event, time-to-event curve, median (95% CI) time-to-event.

A log-rank test, stratified by age group (3 months-<12 years, ≥12 years), duration of the BID treatment in OL period (≤ 4, >4 weeks), and ISGA score (clear [0], almost clear [1]) at randomization, will be used to test the difference between crisaborole QD versus vehicle QD.

5.3. Methods to Manage Missing Data

For OL period, efficacy and PRO data summary will be based on Last Observation Carried Forward (LOCF) imputation data. For DB period, for descriptive statistics missing values will not be imputed. In addition, for safety endpoints, missing values will not be imputed.

For the continuous patient/observer reported outcomes variables, rules recommended by the developers of these instruments will be followed in the handling of missing data and in the scoring of the questionnaires when data are missing for one or more questionnaire items.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

The primary endpoint is flare-free maintenance until onset of first flare during the 52-week double-blind period.

6.1.1. Main Analysis

- Estimand strategy: Hypothetical (Section 2.1.1).
- Analysis Population: Evaluable-DB.
- Analysis method: Time-to-event analysis, Kaplan-Meier (product limit) method and log-rank test (Section 5.2.4).
- Intercurrent events: intercurrent events include discontinuation of treatment. If an intercurrent event (eg, death, dropout, loss to follow up, or end of study) occurs before the first flare, the duration of flare-free maintenance is the time from randomization to the first intercurrent event and is right censored. When a flare occurs first, the duration of flare-free maintenance is the time from randomization to the first flare and is not censored.

- Reporting results: At each month, the proportion of participants who had maintained flare-free status before the first flare , time-to-event curve, median (95% CI) time of maintaining flare-free, and number (%) of censored participants for each treatment group, and p-value from log-rank test will be presented.

6.1.2. Sensitivity/Supplementary Analysis

For the above main analysis, the definition of flare is based on the investigator assessment of ISGA, time of flare is the assessment time when ISGA≥2. In addition, a sensitivity analysis will be performed where flare definition includes an AD worsening event (preferred term=Dermatitis atopic or Eczema) reported by a participant prior to a confirmatory ISGA ≥2. In this analysis, the time of onset of such event will be used as the onset of the flare. If a participant reported an AD worsening event but the investigator assessment is not a flare at the subsequent visit, this event is not a flare. Estimand strategy, analysis population, analysis method and intercurrent events handling are the same as above for the main analysis.

Another sensitivity analysis is interval censoring survival analysis. Time of flare is between the time of participants reported AD worsening and the time of investigator confirmed ISGA ≥2. Because the exact flare time is not known, the midpoint of the above interval will be used as the flare time. Estimand strategy, analysis population, analysis method and intercurrent events handling are the same as above for the main analysis.

6.2. Key Secondary Endpoints

6.2.1. Number of Flare-Free Days

The first key secondary endpoint is the number of flare-free days during the DB period. It is the total flare-free days during the DB period for each participant regardless censoring or not, ie, the censored number of flare-free days in a flare-free period is truncated at censoring for the calculation of total number of flare-free days.

- Estimand strategy: Hypothetical (Section 2.1.2.1).
- Analysis Population: Evaluable-DB.
- Analysis method: ANCOVA model (Section 5.2.2.2).
- Intercurrent events: intercurrent events include discontinuation of treatment. Addressing intercurrent events for the duration of flare-free maintenance at each flare-free period is the same as that for the primary endpoint during the first flare-free period.
- Reporting results: The LS mean along with the corresponding standard error and 95% CI for each treatment group, LS mean difference along with the corresponding p-value, standard error and 95% CI will be presented.

6.2.2. Total Number of Flares

The second key secondary endpoint is the number of flares during the 52-week DB period.

- Estimand strategy: Hypothetical (Section 2.1.2.2).
- Analysis Population: Evaluable-DB.
- Analysis method: Wilcoxon rank sum test stratified by age group, duration of the BID treatment in OL period, and ISGA score at randomization.
- Intercurrent events: intercurrent events include discontinuation of treatment.
- Reporting results: Median for each treatment group and median difference estimated by the Hodges–Lehmann method[2] along with the 95% CI, p-value from Wilcoxon rank sum test will be reported.

Participants will be ranked in descending order according to the number of flares adjusted for length of time in the DB period, and length of time in flare-free period, ie if participants have same number of observed flares, below conditions will be used as tie-breaker in sequence:

- Participants who prematurely discontinue the study for efficacy reasons (ie, discontinue due to lack of efficacy or AD worsening of AE for treated lesions) will be ranked below others;
- The participant with longer time in the double-blind maintenance period will receive a higher rank;
- The participant with longer time in flare-free period will receive a higher rank.

6.2.3. Maintenance of Pruritus Response until Onset of First Flare (ISGA ≥2)

The third key secondary endpoint is duration of maintenance of pruritus response. It is the time from randomization to the loss of pruritus response or first flare onset (ISGA ≥2) during the 52-week DB period for participants who are pruritus responders at randomization. Pruritus response is maintained if ≥50% of pruritus reduction from OL baseline to randomization is not lost.

- Estimand strategy: Hypothetical (Section 2.1.2.3).
- Analysis Population: Evaluable-DB.
- Analysis method: Time-to-event analysis, Kaplan-Meier (product limit) method and log-rank test (Section 5.2.4).
- Intercurrent events: intercurrent events include discontinuation of treatment, first flare [ISGA ≥2]. If an event (eg, death, first flare [ISGA ≥2], lost to follow up, or end of study) occurs before loss of pruritus response for the first flare-free period, the duration of maintenance of pruritus response is the time from randomization to the first intercurrent event and is censored. When loss of pruritus response occurs first, the duration of maintenance of pruritus response is not censored.

- Reporting results: At each month, the proportion of participants who maintained pruritus response in the first flare-free period, time-to-event curve, median (95% CI) time of maintaining pruritus response, and number (%) of censored participants for each treatment group, and p-value from log-rank test will be presented.

The analysis will be performed separately for each age and pruritus respondse subgroups:

- ≥12 years of age with OL baseline Peak Pruritus NRS ≥3 and ≥3 points reduction from OL baseline to randomization in Peak Pruritus NRS.
- ≥12 years of age with OL baseline Peak Pruritus NRS ≥4 and ≥4 points reduction from OL baseline to randomization in Peak Pruritus NRS.
- 6-<12 years of age with OL baseline PRIS Scale ≥2 and ≥2 points reduction from OL baseline to randomization in PRIS Scale.
- 3 months-<6 years of age with OL baseline ORIS Scale ≥3 and ≥3 points reduction from OL baseline to randomization in ORIS Scale.
- 3 months-<6 years of age with OL baseline ORIS Scale ≥4 and ≥4 points reduction from OL baseline to randomization in ORIS Scale.

6.3. Other Secondary Endpoints

6.3.1. Maintenance of EASI Response

This endpoint is defined as ≥50% of EASI total score reduction from OL baseline to randomization is maintained. Only data up to the first flare onset (ISGA ≥2) during the maintenance period will be used for analysis.

- Estimand strategy: Hypothetical (Section 2.1.1).
- Analysis Population: Evaluable-DB.
- Analysis method: Time-to-event analysis, Kaplan-Meier (product limit) method and log-rank test (Section 5.2.4).
- Intercurrent events: intercurrent events include discontinuation of treatment, first flare. If an intercurrent event (eg, death, dropout, loss to follow up, first flare, or end of study) occurs before loss of EASI response, the duration of maintenance of EASI reduction is the time from randomization to the first intercurrent event and is right censored.
- Reporting results: At each month, the proportion of participants maintaining ≥50% EASI reduction before the first flare, time-to-event curve, median (95% CI) time of maintaining ≥50% EASI reduction, and number (%) of censored participants for each treatment group, and p-value from log-rank test will be presented.

6.3.2. Maintenance of Dermatology Quality of Life Assessments

Maintenance of dermatology quality of life assessments is defined as the response achieved does not lose more than MCID. Only data up to the first flare onset during the DB period will be used for analysis.

- Estimand strategy: Hypothetical (Section 2.1.1).
- Analysis Population: Evaluable-DB.
- Analysis method: Time-to-event analysis, Kaplan-Meier (product limit) method and log-rank test (Section 5.2.4).
- Intercurrent events: intercurrent events include discontinuation of treatment, first flare. If an intercurrent event (eg, death, dropout, loss to follow up, first flare, or end of study) occurs before loss of dermatology quality of life response, the duration of maintenance of dermatology quality of life assessments is the time from randomization to the first intercurrent event and is right censored.
- Reporting results: At each month, the proportion of participants who maintained dermatology quality of life assessments before the first flare, time-to-event curve, median (95% CI) time of maintaining dermatology quality of life assessments, and number (%) of censored participants for each treatment group, and p-value from log-rank test will be presented.

The analysis will be performed separately for two age groups:

- Participants ≥16 years of age, Dermatology Life Quality Index (DLQI).
- Participants 4-<16 years of age, Children's Dermatology Life Quality Index (CDLQI).

MCID is not available for Infant's Dermatitis Quality of Life Index (IDQoL) for participants 3 months – <4 years of age. Maintenance of dermatology quality of life assessments will not be performed for that age group.

6.3.3. Maintenance of Patient Oriented Eczema Measure (POEM)

This endpoint is defined as the response achieved does not lose more than MCID. Only data up to the first flare onset during the DB period will be used for analysis.

- Estimand strategy: Hypothetical (Section 2.1.1).
- Analysis Population: Evaluable-DB.
- Analysis method: Time-to-event analysis, Kaplan-Meier (product limit) method and log-rank test (Section 5.2.4).

- Intercurrent events: intercurrent events include discontinuation of treatment, first flare. If an intercurrent event (eg, death, dropout, loss to follow up, first flare, or end of study) occurs before loss of POEM response, the duration of maintenance of POEM is the time from randomization to the first intercurrent event and is right censored.

- Reporting results: At each month, the proportion of participants who maintained POEM response before the first flare, time-to-event curve, median (95% CI) time of maintaining POEM response, and number (%) of censored participants for each treatment group, and p-value from log-rank test will be presented.

The analysis will be performed separately for two age groups:

- ≥12 years of age (participant reported POEM).

- 3 months-<12 years of age (proxy POEM).

6.3.4. Endpoints during Flare Treatment Period

6.3.4.1. Severity of Flare on Investigator's Static Global Assessment Score

- Analysis Population: Evaluable-DB.

- Method: Descriptive summary for categorical endpoint; Descriptive summary for continuous endpoint.

- Reporting results:

    - ISGA as a categorical endpoint: the number and percent of participants for the first flare period and each time point by ISGA categories and DB treatment assignment group and overall group;

    - ISGA as a continuous endpoint: the number of participants, mean, standard deviation, median, minimum, maximum for the first flare period and each time point by DB treatment assignment group and overall group for observed and change from initiated of the first flare period. The summary is performed by the time point relative to the start of first flare period (ie, Weeks 0, 4, 8, 12 in the first flare period).

6.3.4.2. Severity of Flare on Eczema Area and Severity Index Score

- Analysis Population: Evaluable-DB.

- Method: Descriptive summary for continuous endpoint.

- Reporting results: The number of participants, mean, standard deviation, median, minimum, maximum for the first flare period and each time point by DB treatment assignment group and overall group for observed and change from initiated of the

first flare period. The summary is performed by the time point relative to the start of first flare period (ie, Weeks 0, 4, 8, 12 in the first flare period).

6.3.4.3. Duration of Flare Periods

- Analysis Population: Evaluable-DB.
- Method: Descriptive summary for continuous endpoint. The average duration of flare periods (sum of durations/number of flares) will be calculated for each participant, then summarize the average duration.
- Reporting results: The number of participants, mean, standard deviation, median, minimum, maximum by DB treatment assignment and overall.

6.4. Additional Secondary Endpoints

Analyses of secondary endpoints for OL period will be based on LOCF data.

Analyses of secondary endpoints for DB period will be based on observed data.

6.4.1. EASI

- OL period:
  - Analysis Population: Evaluable-OL.
  - Method: Descriptive summary for continuous endpoint.
  - Reporting results: The number of participants, mean, standard deviation, median, minimum, maximum for observed value and change from OL baseline by time point.
- DB period, First flare-free period, and First flare period:
  - Analysis Population: Evaluable-DB.
  - Method: Descriptive summary for continuous endpoint.
  - Reporting results: The number of participants, mean, standard deviation, median, minimum, maximum for observed value and change from randomization in the DB period (Flare-free/Flare), the first flare-free period, and first flare period. For the first flare period, the change is the change from the start of first flare period, summary is performed by the time point relative to the start of first flare period (ie, Weeks 0, 4, 8, 12 in the first flare period).

6.4.2. ISGA

- OL period:
  - Analysis Population: Evaluable-OL.
  - Method: Descriptive summary for binary endpoint; Descriptive summary for continuous endpoint.
  - Reporting results:

- ISGA success and ISGA clear/almost: the number and percent (95% CI) by time point.
- ISGA as a categorical endpoint: the number and percent of participants.
- ISGA as a continuous endpoint: the number of participants, mean, standard deviation, median, minimum, maximum for observed value and change from OL baseline by time point.

- DB period, First flare-free period, and First flare period:

  - Analysis Population: Evaluable-DB.
  - Method: Descriptive summary for categorical and continuous endpoints.
  - Reporting results:

    - ISGA as a categorical endpoint: the number and percent of participants.
    - ISGA as a continuous endpoint: the number of participants, mean, standard deviation, median, minimum, maximum for observed value and change from randomization in the DB period (Flare-free/Flare), the first flare-free period, and first flare period. For the first flare period, the change is the change from the start of first flare period, summary is performed by the time point relative to the start of first flare period (ie, Weeks 0, 4, 8, 12 in the first flare period).

6.4.3. Treatable AD %BSA

- OL period:

  - Analysis Population: Evaluable-OL.
  - Method: Descriptive summary for continuous endpoint.
  - Reporting results: The number of participants, mean, standard deviation, median, minimum, maximum for observed value and change from OL baseline by time point.

- DB period, First flare-free period, and First flare period:

  - Analysis Population: Evaluable-DB.
  - Method: Descriptive summary for continuous endpoint.
  - Reporting results: The number of participants, mean, standard deviation, median, minimum, maximum for observed value and change from randomization in the DB period (Flare-free/Flare), the first flare-free period, and the first flare period. For the first flare period, the change is the change from the start of first flare period, summary is performed by the time point relative to the start of first flare period (ie, Weeks 0, 4, 8, 12 in the first flare period).

6.4.4. Most Commonly Affected AD %BSA

Most commonly affected AD %BSA is collected at randomization, DB Days 169 and 365.

- Analysis Population: Evaluable-DB.

- Method: Descriptive summary for continuous endpoint.

- Reporting results: The number of participants, mean, standard deviation, median, minimum, maximum by DB treatment assignment for observed value and change from randomization to Days 169 and 365.

6.4.5. Duration of Flare-free periods

- Analysis Population: Evaluable-DB.

- Method: Descriptive summary for continuous endpoint. The average duration of flare-free periods (sum of durations/number of flare-frees) will be calculated for each participant, then summarize the average duration.

- Reporting results: The number of participants, mean, standard deviation, median, minimum, maximum.

6.4.6. Patient Reported Outcome Endpoints

PRO endpoints include:

- Pruritus and Itch Assessments, will be analyzed separately by age group:

  - Peak Pruritus NRS for participants ≥12 years of age;
  - PRIS Scale for participants 6-<12 years of age;
  - ORIS Scale for participants 3 months-<6 years of age.

- Night Time Itch Scale for participants ≥12 years of age.

- AD Skin Pain NRS for participants ≥12 years of age.

- PGIS/OGIS for all participants, will be analyzed separately by age group:

  - PGIS for participants ≥12 years of age;
  - OGIS for participants 3 months-<12 years of age.

- PGIC/OGIC for all participants, will be analyzed separately by age group:

  - PGIC for participants ≥12 years of age;
  - OGIC for participants 3 months-<12 years of age.

- MOS-Sleep Scale for participants ≥12 years of age.

- EQ-5D for all participants, will be analyzed separately by age group:

  - The EQ-5D-5L (5 levels) for participants ≥18 years of age;
  - The EQ-5D-Y (3 levels) for participants 8-<18 years of age;
  - The EQ-5D-Y Proxy (3 levels) for participants 2-<8 years of age.

- Work and Classroom Productivity for participants ≥12 years of age.
- HADS for participants ≥12 years of age.
- Dermatology quality of life assessments, will be analyzed separately by age group:
  - DLQI for participants ≥16 years of age;
  - CDLQI for participants 4-<16 years of age;
  - IDQoL for participants 3 months-<4 years of age.
- POEM: POEM for Proxy Completion (e.g., by parent), participants ages 3 months-<12 years of age, and POEM for Self Completion, participants ≥12 years of age.

All these PRO endpoints will be summarized as below:

- OL period:
  - Analysis Population: Evaluable-OL.
  - Method: Descriptive summary for continuous endpoint.
  - Reporting results: The number of participants, mean, standard deviation, median, minimum, maximum for observed value and change (except dermatology quality of life assessments, POEM and PGIC/OGIC) from OL baseline by time point.
- DB period, First flare-free period, and First flare period:
  - Analysis Population: Evaluable-DB.
  - Method: Descriptive summary for continuous endpoint.
  - Reporting results: The number of participants, mean, standard deviation, median, minimum, maximum for observed value and change (except PGIC/OGIC) from randomization in the DB period (Flare-free/Flare), the first flare-free period, and the first flare period. For the first flare period, the change is the change from the start of first flare period, summary is performed by the time point relative to the start of first flare period (ie, Weeks 0, 4, 8, 12 in the first flare period).

6.5. Subset Analyses

The primary endpoint (main analysis only) and key secondary endpoints number of flare-free days and number of flares will be analyzed by age group (3 months-<12 years, ≥12 years), ISGA score (clear, almost clear) at randomization, race (White, Black, Asian, Other), ethnicity (Hispanic, Non-Hispanic), and number of OL weeks (≤ 4, >4) before randomization.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

Demographics and baseline characteristics listed in Section 3.5 will be summarized for SAF-OL, and SAF-DB by QD treatment group according to Pfizer standards.

For Evaluable-DB, the efficacy and PRO data at randomization will be summarized by QD treatment group according to Pfizer standards. For daily assessed endpoints (eg, pruritus, itch, pain, etc.), weekly average before randomization will be used.

6.6.2. Study Conduct and Participant Disposition

Participants evaluation, disposition, discontinuation will be summarized, separately for OL period and DB period according to Pfizer standards.

6.6.3. Study Intervention Compliance

A participant will be considered compliant with the dosing regimen if they receive 80%-120% of the expected number of doses in accordance with the protocol. The number and percentage of participants who are compliant with the dosing regimen, number of dosing days and number of applications, and amount of intervention used will be summarized by OL period, QD period, and flare treatment period.

6.6.4. Concomitant Medications and Nondrug Treatments

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

6.7. Safety Summaries and Analyses

Safety analyses will be based on the SAF-OL, SAF-DB, according to the period and endpoint.

All clinical AEs, SAEs, TEAEs, withdrawal due to AEs, vital signs and safety laboratory data will be reviewed on an ongoing basis during the study to evaluate the safety of participants.

Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. All safety endpoints will be listed and summarized in accordance with Pfizer Standards. Categorical outcomes (eg, AEs) will be summarized by participant counts and percentage. Continuous outcome will be summarized using N, mean, median, standard deviation, etc. Participant listings will be produced for these safety endpoints accordingly.

Separate listings and/or summaries may be produced for participants who are impacted by COVID-19, have protocol deviations, discontinue from study or study treatment due to the COVID-19 pandemic.

6.7.1. Adverse Events

The safety data will be summarized separately by period: OL period for SAF-OL, DB QD period for SAF-DB, and flare treatment period for SAF-DB in accordance with Pfizer Data Standards. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. The safety data will be summarized for overall events and treatment area events. Safety endpoints for the study include:

- Incidence of TEAEs.
- Incidence of SAEs and AEs leading to discontinuation.

6.7.2. Laboratory Data

Laboratory data will be listed in accordance with the Pfizer reporting standards.

6.7.3. Vital Signs

Vital signs data will be listed.

6.7.4. Physical Examination

Physical examination data will be listed.

7. INTERIM ANALYSES

There is no planned interim analysis.

7.1.1. Data Monitoring Committee

This study uses an External Data Monitoring Committee (E-DMC). The E-DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

8. REFERENCES

1. Pfizer Protocol Amendment 1 C3291035.

2. Hodges. JR, Lehmann EL. Estimates of location based on rank tests. Ann Math Stat 1963; 34:598–611.

9. APPENDICES

Appendix 1: Summary of Efficacy Endpoints

The table below summarizes analyses of primary and secondary efficacy endpoints.

Endpoint	Analysis Population	Statistical Method	Type
Time-to-flare	Evaluable-DB	Time-to-event	Primary
Number of flare-free days	Evaluable-DB	ANCOVA	Key secondary
Total number of flares	Evaluable-DB	Wilcoxon	Key secondary
Time from randomization to loss of ≥50% pruritus response up to first flare by subgroups	Evaluable-DB participants who achieved pruritus response	Time-to-event	Key secondary
Maintenance of dermatology quality of life assessments up to first flare by subgroups	Evaluable-DB participants who achieved dermatology quality of life assessments response	Time-to-event	Secondary
Maintenance of POEM up to first flare	Evaluable-DB participants who achieved POEM response	Time-to-event	Secondary

Appendix 2: Definition and Use of Visit Windows in Reporting

Below visit windows will be used for ISGA, EASI, and %BSAduring OL period.

OL Visit Label	Target Day	Definition [Day window]
Screening		Days -28 to -1
OL Weeks 0-8	**Days of OL Period**	
OL_Day 1/Week 0	Day 1, Baseline	Day 1
OL_Week 2	15	Days 2 to 22
OL_Week 4	29	Days 23 to 36
OL_Week 6	43	Days 37 to 50
OL_Week 8	57	Day 51 to end of OL
End of OL		OL discontinuation or double-blind randomization. IF participants don't enter maintenance period, the follow up period is included in OL.

Below visit windows will be used for Dermatology Quality of Life Assessments and POEM during OL period.

OL Visit Label	Target Day	Definition [Day window]
Screening		Days -28 to -1
OL Weeks 0-8	**Days of OL Period**	
OL_Day 1/Week 0	Day 1, Baseline	Day 1
OL_Week 1	8	Days 2 to 11
OL_Week 2	15	Days 12 to 18
OL_Week 3	22	Days 19 to 25
OL_Week 4	29	Days 26 to 32
OL_Week 5	36	Days 33 to 39
OL_Week 6	43	Days 40 to 46
OL_Week 7	50	Days 47 to 53
OL_Week 8	57	Day 54 to end of OL
End of OL		OL discontinuation or double-blind randomization. IF participants don't enter maintenance period, the follow up period is included in OL.

Below visit windows will be used for efficacy variables during DB period.

	Target Day	Definition [Day window]
DB Weeks 0-52	**Days of DB Period**	
DB Day 1/Week 0	1	Day 1
DB_Week 4	29	Days 2 to 43
DB_Week 8	57	Days 44 to 71
DB_Week 12	85	Days 72 to 99
DB_Week 16	113	Days 100 to 127
DB_Week 20	141	Days 128 to 155
DB_Week 24	169	Days 156 to 183
DB_Week 28	197	Days 184 to 211
DB_Week 32	225	Days 212 to 239
DB_Week 36	253	Days 240 to 267
DB_Week 40	281	Days 268 to 295
DB_Week 44	309	Days 296 to 323
DB_Week 48	337	Days 324 to 351
DB_Week 52	365	Days 352 to last available data

Note: Participants will have an end-of-study (follow-up) by phone at least 28 days after the last study dose of any period.

For the time points just prior and after initiation of a new episode, the initiation date of the episode is the cutoff date for the visit windows.

Below visit windows will be used for efficacy variables during first flare period.

	Target Day	Definition [Day window]
First Flare Weeks	**Days of First Flare Period**	
First Flare Day 1/Week 0	1	First Day of first flare period
First Flare_Week 4	29	Days 2 to 43
First Flare_Week 8	57	Days 44 to 71
First Flare_Week 12	85	Days 72 to end of first flare period or end of DB period

For the lab values, if the calculated study day for the labelled baseline visit is not study Day 1, but falls within 28 days before the start of the study dosing, then that data should be used for the baseline instead of leaving baseline missing.

For the other values, if the calculated study day for the labelled baseline visit is not study Day 1, but falls before the start of the study dosing, then that data should be used for the baseline instead of leaving baseline missing.

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.

Safety analysis will follow Pfizer standards.

Appendix 3: Examples of Summary Table Shells for DB Period

Summary of Endpoint Data in the DB Period (Flare-free/Flare) by Time Point in DB Period

		Maintenance Flare-free Period		Flare Period
Timepoint		Crisaborole QD	Vehicle QD	Crisaborole BID
DB Day 1/Week 0	N	138	137	0
	…			
DB Week 4	N	130	120	20
	…			
DB Week 8	N			
…				
DB Week 52				

Summary of Endpoint Data in the First Flare-free Period by Time Point in DB Period

		First Flare-free Period(1)	
Timepoint		Crisaborole QD	Vehicle QD
DB Day 1/Week 0	N	138	137
	…		
DB Week 4	N	123	112
	…		
DB Week 8	N		
…			
DB Week 52			

(1) Include only the data in the first Flare-free period

Summary of Endpoint Data in the First Flare Period by Time Point in DB Period

		DB Treatment Assignment		
Timepoint		Crisaborole QD	Vehicle QD	Total
First Flare Day 1/Week 0	N	13		
	…			
First Flare Week 4	N	9		
	…			
First Flare Week 8	N			
First Flare Week 12				

(1) Include only the data in the first flare period

Appendix 4: Listing of Abbreviations

Abbreviation	Term
AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CDLQI	children's dermatology life quality index
CI	confidence interval
DB	double-blind
DLQI	dermatology life quality index
DMC	data monitoring committee
EASI	eczema area and severity index
EASI50	≥50% reduction in eczema area and severity index
E-DMC	external data monitoring committee
EQ-5D	EuroQol-5 Dimensions
Eval	evaluable
HADS	hospital anxiety and depression scale
IDQoL	infant's dermatitis quality of life index
ISGA	investigator's static global assessment
LOCF	Last Observation Carried Forward
LS	least squares
MCID	minimal clinical important difference
MOS	medical outcomes study
NRS	numerical rating scale
OGIC	observer global impression of change
OGIS	observer global impression of severity
OL	open label
ORIS	observer reported itch severity
PGIC	patient global impression of change
PGIS	patient global impression of severity
POEM	maintenance of patient oriented eczema measure
PRIS	patient reported itch severity
PRO	patient reported outcome
QD	once daily
SAE	serious adverse event
SAF	safety
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event