Protocol C3291038

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, PROOF-OF-CONCEPT STUDY TO EVALUATE THE EFFICACY, SAFETY, AND LOCAL TOLERABILITY OF CRISABOROLE OINTMENT, 2%, IN ADULT PARTICIPANTS WITH STASIS DERMATITIS WITHOUT ACTIVE SKIN ULCERATION

Statistical Analysis Plan
(SAP)

Version: **4**

Date: **16Sep2021**

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1. VERSION HISTORY

This statistical analysis plan (SAP) for Study C3291038 is based on Protocol Amendment 2 dated 19July2021.

Table 1. Summary of Changes

Version/Date	Associated Protocol Amendment	Rationale	Specific Changes
1 10Mar2020	Amendment 1 10January2020	N/A	N/A
2 11Mar2021	Amendment 1 10January2020	No efficacy data are collected after intercurrent event (ie, discontinuation of study intervention)	Estimand 3 and related analyses were removed
		Only one post-baseline assessment will be performed for these endpoints. All participant with post-baseline assessments can be included in analysis based on new visit windows.	New visit windows are defined for TSS, ISGA, %BSA in-person assessment, CCI [redacted]
		Subset analyses will be performed just for in-person assessment endpoints.	"based on HVP in-person assessment" was added to Section 6.4 Subset Analyses
		Validation analysis will be described in a separate analysis plan	Validation Section was removed.
		Don't need summary and listing for vital signs, height, weight and ECG	Vital signs and ECG were removed from Section 6
3 28Jul2021	Amendment 2 19Jul2021	For non-longitudinal endpoints, the assessments at EOT for early terminated participants are included in the analysis.	Estimand 1 was changed as a while-on-treatment estimand. Estimand 3 was added as a hypothetical estimand for longitudinal continuous endpoints
		Interim analysis may be performed	Details for interim analysis was added.

		To reduce sample size	Sample size was reduced to 70, significance level was changed to 5% one-sided. CI was changed to 90%
		For consistency with protocol	Screened population was added. Enrolled population was changed.
		Subgroup analysis will be performed by type of standard of care/skin type. This supportive analysis is not necessary.	Removed supportive analysis for TSS change from baseline at Week 6/EOT based on in-person assessment (ANCOVA model including type of standard of care/skin type)
4 16Sep2021	Amendment 2 19Jul2021	Sensitivity analyses	Added analyses for % change from baseline in TSS at Week 6 based on in-person assessment for observed cases and multiple imputation for missing data.
		Exclude the assessments far away from last dose	For Week 6 or EOT, the visit window cut at the last dose + 10 days.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C3291038. The summaries and analyses described in this SAP will be reported in the clinical study report (CSR). Validation analysis for comparison between in-person assessment and Central Readers assessments based on images will be described in a separate analysis plan and reported separately from the CSR.

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

2.1.1. Study Objectives and Endpoints

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

Table 2. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of crisaborole ointment, 2%, twice daily (BID) versus vehicle at Week 6 in participants with stasis dermatitis (SD) without active skin ulceration.	• Percent change from baseline in Total Sign Score (TSS) at Week 6/EOT (Home Visit Practitioner [HVP] in-person assessment).
Secondary Efficacy	
• To evaluate the efficacy of crisaborole ointment, 2%, BID versus vehicle over time in participants with SD without active skin ulceration.	• Achievement of an Investigator's Static Global Assessment (ISGA) score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline at all time points (analyze both HVP in-person assessment and Central Readers digital images assessment); • Achievement of an ISGA score of Clear (0) or Almost Clear (1) at all time points (analyze both HVP in-person assessment and Central Readers digital images assessment); • Percent change from baseline in TSS at all time points (Central Readers digital images assessment); • Percent change from baseline in lesional % Body Surface Area (%BSA) at all time points (analyze both HVP in-person assessment and Central Readers digital images assessment).
Secondary Safety	

• To evaluate the safety and local tolerability of crisaborole ointment, 2%, BID versus vehicle in participants with SD without active skin ulceration.	• Incidence and severity of treatment emergent adverse events (AEs), including local tolerability events.
CCI [redacted]	[redacted]

2.1.2. Estimands

Only discontinuation of study intervention will be considered as an intercurrent event.

Estimand 1: The primary estimand of this study is a while-on-treatment estimand, which estimates the treatment effect of crisaborole compared with vehicle at Week 6/EOT. It includes the following 5 attributes:

- Population: participants ≥45 years of age with SD without active skin ulceration;
- Variable: non-longitudinal endpoints at Week 6/EOT;
- Treatment condition: crisaborole 2% BID or vehicle;
- Intercurrent event: all data after an intercurrent event of discontinuation of study intervention will be excluded, data at Week 6 or EOT (within date of last dose + 10 days) will be included;
- Population-level summary: difference in LSM for continuous endpoint and difference in proportion of participants with response for binary endpoints at Week 6/EOT between crisaborole ointment, 2%, BID and vehicle.

Estimand 1 will be used in analyzing the primary endpoint and it will also be used to analyze non-longitudinal continuous secondary endpoints %BSA in-person assessment CCI [redacted]

CCI [redacted] and non-longitudinal binary endpoints ISGA success (ISGA score of clear/almost clear with at least a 2-grade improvement from baseline) and ISGA clear/almost clear based on in-person assessment.

Estimand 2: The second estimand of this study is a composite estimand, which estimates the treatment effect of crisaborole compared with vehicle at each timepoint. It includes the following 4 attributes:

- Population: participants ≥45 years of age with SD without active skin ulceration;
- Variable: binary response endpoint per photography assessment, eg, response defined as a participant with an ISGA score of clear or almost clear with at least a 2-grade improvement from baseline at each time point; a participant after an intercurrent event of discontinuation of study intervention will be considered a non-responder for the visit of interest;
- Treatment condition: crisaborole 2% BID or vehicle;
- Intercurrent event: there will be no intercurrent event since the discontinuation of study intervention is part of the variable definition;
- Population-level summary: difference in proportion of participants with response at each time point between crisaborole ointment, 2%, BID and vehicle.

Estimand 2 will be used in analyzing all applicable longitudinal secondary binary endpoints.

Estimand 3: The third estimand of this study is a hypothetical estimand, which estimates the treatment effect of crisaborole compared with vehicle at each time point under the scenario of no discontinuation of study intervention. It includes the following 5 attributes:

- Population: participants ≥45 years of age with SD without active skin ulceration;
- Variable: percent change from baseline in TSS at each time point;
- Treatment condition: crisaborole 2% BID or vehicle;
- Intercurrent event: all data collected after any intercurrent events will be excluded;
- Population-level summary: difference in mean percent change from baseline in TSS at each time point between crisaborole ointment, 2%, BID and vehicle.

Estimand 3 will be used in analyzing the longitudinal continuous endpoints.

2.2. Study Design

Study C3291038 is a Phase 2a, randomized, double-blind, vehicle-controlled, parallel-group, proof-of-concept study to evaluate the efficacy, safety, and local tolerability of 6 weeks of treatment with crisaborole in adult participants with SD without active skin ulceration.

Approximately 70 eligible participants will be randomized into the double-blind treatment period in a 1:1 ratio to receive crisaborole ointment, 2% or vehicle twice daily for 6 weeks.

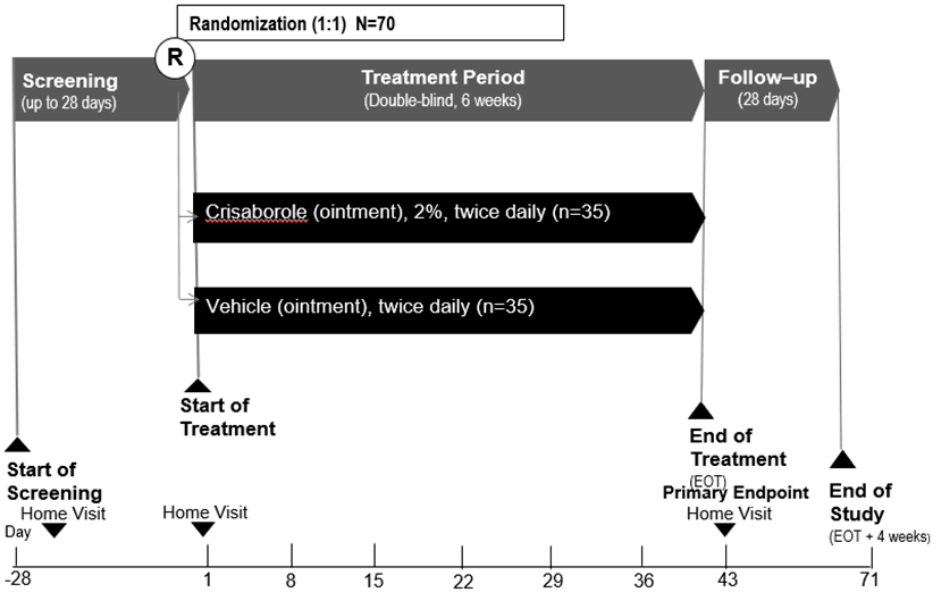
The study will recruit male and female participants aged ≥45 years with a clinical diagnosis of SD. Participants who meet all inclusion but none of the exclusion criteria presented in Section 5 of the protocol will be eligible to participate in the study. If a participant meets any of the exclusion criteria, the participant will be excluded.

The total duration of participation in the study will be up to 14 weeks, including up to 4 weeks for screening, a 6-week double-blind treatment period, and a follow-up period of 4 weeks after treatment completion.

Study enrollment and management will be de-centralized, where participants do not visit an investigator or a clinic for clinical assessment. The participants will participate in the study at home. The sponsor (or designee) will provide home visits by qualified HVP, remote contact by telemedicine (or telephone), and clinical database electronic case report forms (eCRFs), eDiary, and other electronic data entries from 3rd party vendors for study data collection.

Participants who withdraw from further study intervention treatment (but do not withdraw consent for further data gathering) should continue to complete all scheduled assessments at the EOT visit and complete the follow-up phase of the study.

Figure 1. Schema



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

TSS, ISGA and lesional %BSA will be assessed in-person by HVP at the home visits at screening, baseline, and Week 6 (or early termination) and will be used for the primary analyses. Theses efficacy parameters will also be remotely assessed at all scheduled timepoints by an expert dermatologist central reader reviewing digital imaging of the lower extremities acquired by the participant. The data based on Central Readers assessments will be used for supportive analyses. Only initial Central Readers assessments will be used for supportive analyses. Central Readers re-assessments will be used for validation and reliability analyses.

3.1. Primary Endpoint

The primary efficacy endpoint is a percent change from baseline in TSS at Week 6/EOT (HVP in-person assessment).

3.2. Secondary Endpoints

The secondary endpoints are:

- Achievement of an ISGA score of Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline at all time points (analyze both HVP in-person assessment and Central Readers digital images assessment).
- Achievement of an ISGA score of Clear (0) or Almost Clear (1) at all time points (analyze both HVP in-person assessment and Central Readers digital images assessment).
- Percent change from baseline in TSS at all time points (Central Readers digital images assessment).
- Percent change from baseline in lesional %BSA at all time points (analyze both HVP in-person assessment and Central Readers digital images assessment).

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3.4. Baseline Variables

Demographic and baseline characteristics include:

- Age
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (kg/m^2)
- Duration of disease (years)
- Prior TCS/TCI
- Fitzpatrick Skin Type
- Type of standard of care
- TSS
- ISGA
- %BSA

The baseline value is defined as the last observation up to and including Day 1 of intervention period. For daily assessed endpoints, the average of 7-day scores immediately prior to Day 1 (Day -6 to Day 1) will be used as the baseline.

3.5. Safety Endpoints

Safety will be assessed by medical history, physical examinations, vital signs, electrocardiograms (ECG), clinical laboratory tests, and the spontaneous reporting of 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.

3.5.1. Adverse Events

An AE is considered treatment-emergent adverse event (TEAE) to a given treatment 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

3.5.2. Laboratory Data

Laboratory testing will be performed at screening and may be performed at unplanned safety assessment or early termination visit. The tests detailed in the table below will be performed by the central laboratory.

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit		White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Albumin	Bicarbonate or total carbon dioxide (CO_2)	Creatinine	Total Protein
	Alanine Aminotransferase (ALT)	Blood urea nitrogen (BUN)	Glucose (nonfasting)	Sodium
	Alkaline phosphatase	Calcium	Potassium	Hemoglobin A1c
	Aspartate Aminotransferase (AST)	Chloride	Total bilirubin	
Other	Prothrombin time (PT)/ international normalized ratio (INR), follicle stimulating hormone (FSH)[2]			

NOTES:

[1] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 5. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[2] For confirmation of postmenopausal status only.

3.5.3. Vital Signs

Vital signs will be assessed at screening and unplanned safety assessment or early termination visit.

3.5.4. Physical Examinations, Including Height and Weight

A complete physical examination will be assessed at screening and may be performed at unplanned safety assessment or early termination visit.

3.5.5. Electrocardiograms

A single lead ECG will be performed at screening and may be performed at unplanned safety assessment or early termination visit.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

For purposes of analysis, the following analysis sets are defined:

Population	Description
Screened	All participants who sign the informed consent form (ICF).
Enrolled	All participants who sign the ICF and are not screen failure.
Randomly Assigned to Study Intervention	All participants who are randomized.
Full Analysis Set (FAS)	All participants who are randomly assigned to study intervention and apply at least 1 dose of study intervention. Participants will be analyzed according to the intervention they are randomized. For change from baseline or percent change from baseline endpoints it would require that a participant have a baseline value and at least one post-baseline value to be included in the analysis for that endpoint. For the endpoint with a threshold requirement for change from baseline, only participants with a baseline value ≥ the threshold will be included in the analysis.
Safety Analysis Set (SAF)	All participants who are randomly assigned to study intervention and apply at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Full Analysis Set-Interim Analysis (FAS-IA)	All participants who are randomly assigned to study intervention and apply at least 1 dose of study intervention and complete 6 weeks treatment or early discontinue study intervention at the IA cutoff date. Participants will be analyzed according to the intervention they are randomized.
Safety Analysis Set-Interim Analysis (SAF-IA)	All participants who are randomly assigned to study intervention and apply at least 1 dose of study intervention and complete 6 weeks treatment or early discontinue study intervention at the IA cutoff date. Participants will be analyzed according to the intervention they actually received.

5. GENERAL METHODOLOGY AND CONVENTIONS

Final analyses will occur after database lock after Last Participant Last Visit (LPLV).

5.1. Hypotheses and Decision Rules

This protocol is designed to establish the superiority of crisaborole 2% BID to vehicle for the primary endpoint percent change from baseline in the TSS at Week 6/EOT (based on in person assessment by HVP at the home visit). The null hypothesis is that there is no difference between crisaborole arm and vehicle arm, and the alternative hypothesis is that there is a significant difference between crisaborole arm and vehicle arm. Specifically, the alternative hypothesis is that the mean percentage improvement from baseline for crisaborole group is 22% greater than vehicle group. The significance level is 5% one-sided. The interim analysis (if conducted) is an administrative interim analysis; no adjustment of p-values is planned for the analysis of the final study data.

5.2. General Methods

In general, number, percent and 90% confidence interval (CI) will be presented for binary endpoints. Descriptive summary statistics (n, Mean, Standard deviation (Std), Median, Min., Max.) will be presented for continuous endpoints. In addition, graphics may be used to present the data.

Day 1 will be the date when a participant applies the first dose of study intervention. Baseline value will be the last non-missing assessment on or before Day 1 and prior to first dose of study intervention. CCI [redacted]

5.2.1. Analyses for Continuous Data

Analysis of Variance (ANOVA)/Analysis of Covariance (ANCOVA) for Non-longitudinal Continuous Data:

The non-longitudinal continuous data will be analyzed by ANOVA with treatment as the factor. ANCOVA will be used if relevant baseline value and/or other factors are included as covariates. Comparison of crisaborole ointment, 2%, BID to vehicle (providing LSM of the treatments, LSM of the treatment difference, 1-sided p-value and 90% CI) will be generated.

Mixed Effect Model Repeat Measurement (MMRM) for Longitudinal Continuous Data:

The longitudinal continuous endpoints will be analyzed with MMRM that includes fixed effects of treatment group, visit, and treatment-group by visit interaction, without imputation for missing values. If the endpoint is change from baseline, baseline will be included in the model as a covariate. A common unstructured variance-covariance matrix will be used, provided it converges. If this is a convergence issue, other type of covariance matrix such as first order autoregressive (AR[1]), compound symmetry will be used. Comparison of crisaborole ointment, 2%, BID to vehicle (providing least squares means [LSM] of the treatments, LSM of the treatment difference, 1-sided p-value and 90% CI) at each time point during the first 6 weeks will be generated using this model.

5.2.2. Analyses for Binary Data

For binary endpoint at each time point, large sample approximation to the difference in binominal proportions will be used for testing (Normal Z-test) the superiority of crisaborole ointment, 2%, BID to vehicle and for forming 90% CI's and calculating 1-sided p-values.

For non-longitudinal binary endpoints, data at Week 6 or EOT will be included in the analysis.

For analysis of longitudinal binary endpoints, observations after the discontinuation of study intervention or missing values for any reason will be handled by setting the endpoint to nonresponsive. Note that this is a composite endpoint in the sense that a response requires the participant completes a visit of interest eg, Week 6, and achieves a response per the

defined response criteria (otherwise it is considered a nonresponse). This method of handling missing response is known as missing response as non-response (MR-NR). For a single time point (eg, ISGA Clear (0) or Almost Clear (1) with at least a 2-grade improvement from baseline at Week 6), large sample approximation to the difference in binominal proportions will be used for testing (Normal Z-test) the superiority of crisaborole ointment, 2%, BID to vehicle and for forming 90% CI's and calculating p-values. The analysis will be based on Estimand 2 using FAS.

5.2.3. Analyses for Categorical Data

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

5.3. Methods to Manage Missing Data

5.3.1. Binary Endpoints

For non-longitudinal binary endpoints, there is no imputation for missing data, data at Week 6 or EOT will be included in the analysis.

For longitudinal binary endpoints analyzed at each scheduled visit separately, participants with missing data at a time point for any reason will be defined as MR-NR at that time point in the intervention period.

5.3.2. Continuous Endpoints

For non-longitudinal continuous data, primary analysis will be based on the observed cases, there is no imputation for missing data.

For continuous efficacy endpoints measured longitudinally, missing values post-baseline will be handled in a MMRM. For longitudinal continuous endpoints, assuming that the missing data mechanism is missing at random (MAR), the data will be analyzed using a MMRM model for these continuous variables (see Section 5.2.1). Under an assumption that the missing data mechanism is MAR, this model will yield unbiased estimates and valid inferences for treatment effects assuming all participants maintain therapy.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Primary Analysis

The primary endpoint is percent change from baseline in the TSS at Week 6/EOT based on HVP in-person assessment.

- Estimand strategy: while-on-treatment, Estimand 1 (Section 2.1.2)
- Analysis set: FAS (Section 4)
- Variable: Percent change from baseline to Week 6/EOT in TSS
- Analysis method: ANOVA in Section 5.2.1

- Intercurrent event: All data after an intercurrent event (eg, discontinuation of treatment), if collected, will be excluded; data at Week 6 or EOT (within date of last dose + 10 days) will be included.

- The LSM along with the corresponding standard error (SE) for each treatment group, LSM difference along with the corresponding SE, 90% CI, and p-value will be presented. LSM ± SE will also be presented graphically by treatment group.

6.1.2. Sensitivity Analyses

Two sensitivity analyses will be performed for the percent change from baseline in the TSS at Week 6 based on HVP in-person assessment.

1. Observed cases: Principal Stratum estimand will be used. The data after an intercurrent event discontinuation of study intervention, if collected, will be excluded, only no-missing observed cases in-person assessment at Week 6 (based on window definition in Table 3) will be included in the analysis. No imputation for missing data. ANOVA (Section 5.2.1) will be used. The LSM along with the corresponding SE for each treatment group, LSM difference along with the corresponding SE, 90% CI, and 1-sided p-value will be presented. The data after an intercurrent event, if collected, will be excluded, observed cases at Week 6 will be included.

2. Multiple imputations: Hypothetical estimand will be used. The data after an intercurrent event discontinuation of study intervention, if collected, will be excluded, observed cases in-person assessment at Week 6 (based on window definition in Table 3) will be included in the analysis. Missing TSS at Week 6 will be imputed using the method of MCMC multiple imputation under MAR assumption. Multiple imputation and subsequent analysis will involve the following four principal tasks:

1) Calculate the total number of missing values to be imputed by MCMC (nmiss) for Week 6 value.
2) Create a data set, one for each treatment group, of participants with observed values and those needing imputation by MCMC. The missing TSS values in each data set will be filled in using the MCMC method "10 × nmiss" times to generate "10 × nmiss" data sets. The resulting data sets for each treatment group will be combined into one complete data set by imputation. The imputed values will be rounded to the nearest integer of 0 - 12.
3) For each complete data set, derive % change from baseline in TSS at Week 6. The estimated treatment effect and its standard error for each complete data set will be calculated using ANOVA (Section 5.2.1).
4) Combine the estimated treatment effects and standard errors from the above into a single inference using Rubin's formulae as implemented in SAS PROC MIANALYZE.

6.2. Secondary Endpoints

6.2.1. ISGA Success based on Central Readers Assessment

- Estimand strategy: composite, Estimand 2 (Section 2.1.2)
- Analysis set: FAS (Section 4)
- Variable: ISGA success at Weeks 1-6 based on Central Readers digital images assessment
- Analysis method: Normal approximation to binomial
- Intercurrent event: A participant with a missing observation or after an intercurrent event of discontinuation of treatment will be considered a non-responder for the visit of interest.
- P-value from normal approximation test, the estimate of proportion, difference in proportion and the corresponding 90% CI of participants with response at each visit between crisaborole ointment, 2% versus vehicle will be presented. Proportions of response (± SE) will also be presented graphically by treatment group.

6.2.2. ISGA Success at Week 6/EOT based on In-person Assessment

- Estimand strategy: while-on-treatment, Estimand 1 (Section 2.1.2)
- Analysis set: FAS (Section 4)
- Variable: ISGA success at Week 6/EOT based on in-person assessment
- Analysis method: Normal approximation to binomial
- Intercurrent event: all data after an intercurrent event of discontinuation of study intervention will be excluded, data at Week 6 or EOT will be included;
- P-value from normal approximation test, the estimate of proportion, difference in proportion and the corresponding 90% CI of participants with response at Week 6/EOT between crisaborole ointment, 2% versus vehicle will be presented. Proportions of response (± SE) will also be presented graphically by treatment group.

6.2.3. ISGA Score of Clear or Almost Clear based on Central Readers Assessment

- Estimand strategy: composite, Estimand 2 (Section 2.1.2)
- Analysis set: FAS (Section 4)
- Variable: ISGA clear or almost clear at Weeks 1-6 based on Central Readers digital images assessment

- Analysis method: Normal approximation to binomial
- Intercurrent event: A participant with a missing observation or after an intercurrent event of discontinuation of treatment will be considered a non-responder for the visit of interest.
- P-value from normal approximation test, the estimate of proportion, difference in proportion and the corresponding 90% CI of participants with response at each visit between crisaborole ointment, 2% versus vehicle will be presented.

6.2.4. ISGA Score of Clear or Almost Clear based on In-person Assessment

- Estimand strategy: while-on-treatment, Estimand 1 (Section 2.1.2)
- Analysis set: FAS (Section 4)
- Variable: ISGA clear or almost clear at Week 6/EOT based on in-person assessment
- Analysis method: Normal approximation to binomial
- Intercurrent event: all data after an intercurrent event of discontinuation of study intervention will be excluded, data at Week 6 or EOT will be included
- P-value from normal approximation test, the estimate of proportion, difference in proportion and the corresponding 90% CI of participants with response at Week 6/EOT between crisaborole ointment, 2% versus vehicle will be presented.

6.2.5. Percentage Change from Baseline in TSS at Weeks 1-6 based on Central Readers Assessments

- Estimand strategy: hypothetical, Estimand 3 (Section 2.1.2)
- Analysis set: FAS (Section 4)
- Variable: Percent change from baseline to Weeks 1-6 in TSS based on central readers assessment
- Analysis method: MMRM in Section 5.2.1
- Intercurrent event: All data after an intercurrent event (eg, discontinuation of treatment), if collected, will be excluded;
- The LSM along with the corresponding SE for each treatment group, LSM difference along with the corresponding SE, 90% CI, and p-value will be presented. LSM (± SE) will also be presented graphically by treatment group.

6.2.6. Percent Change from Baseline in Lesional %BSA based on In-person Assessment

- Estimand strategy: while-on-treatment, Estimand 1 (Section 2.1.2)
- Analysis set: FAS (Section 4)
- Variable: Percent change from baseline to Week 6/EOT in %BSA based on in-person assessment
- Analysis method: ANOVA in Section 5.2.1
- Intercurrent event: All data after an intercurrent event (eg, discontinuation of treatment), if collected, will be excluded, data at Week 6 or EOT will be included.
- The LSM along with the corresponding SE for each treatment group, LSM difference along with the corresponding SE, 90% CI, and p-value will be presented.

6.2.7. Percent Change from Baseline in Lesional %BSA based on Central Readers Assessment

- Estimand strategy: hypothetical, Estimand 3 (Section 2.1.2)
- Analysis set: FAS (Section 4)
- Variable: Percent change from baseline to Week 1- 6 in %BSA based on Central Readers digital images assessment
- Analysis method: MMRM in Section 5.2.1
- Intercurrent event: All data after an intercurrent event (eg, discontinuation of treatment), if collected, will be excluded.
- The LSM along with the corresponding SE and 90% CI for each treatment group, LSM difference along with the corresponding SE, 90% CI, and p-value will be presented.

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6.4. Subset Analyses

Percentage change from baseline in TSS, ISGA success, ISGA clear/almost based on HVP in-person assessment will be analyzed by subgroups of type of standard of care, skin type, baseline ISGA, disease duration (by median), age (≤ 64 vs ≥ 65), race (White vs Non-white).

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographics and baseline characteristics listed in Section 3.4 will be summarized according to Pfizer standards.

6.5.2. Study Conduct and Participant Disposition

Participants evaluation, disposition, discontinuation will be summarized according to Pfizer standards.

6.5.3. Study Intervention Compliance

Participant compliance with study intervention will be assessed by Investigator (or designee) review of eDiary responses.

A participant will be considered compliant with the dosing regimen if he/she receive 80% to 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 total amount of intervention used will be summarized according to Pfizer standards.

6.5.4. Concomitant Medications and Non-drug Treatments

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), vaccine or non-medication therapies that the participant is receiving at the time of enrollment or receives during the study must be recorded at all study visits/contacts.

All concomitant medications taken during the study must be recorded in study records with indication, reference to any associated adverse event, dose, and start and stop dates of administration.

The Pfizer Medical Monitor should be consulted if there are any questions regarding concomitant or prior therapy for SD prior to determining participant eligibility.

Prior drug and non-drug treatment, concomitant drug and non-drug treatment will be summarized according to Pfizer standards. The summary will be performed by treatment group for overall and separated by SD and non-SD treatments.

6.6. Safety Summaries and Analyses

Safety analyses will be summarized in accordance with Pfizer Data Standards.

All clinical AEs, SAEs, TEAEs, withdrawal due to AEs, will be reviewed and summarized 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 (eg, pulse rate, etc) will be summarized using n, mean, median, standard deviation, etc. Participant listings will be produced for these safety endpoints accordingly.

6.6.1. Adverse Events

The safety data will be summarized in accordance with Pfizer Data Standards. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations. Safety endpoints for the study include:

- Treatment-emergent AEs and SAEs;
- Withdrawals from treatment/study due to AEs.

6.6.2. Laboratory Data

Laboratory data will be listed.

6.6.3. Physical Examination

Physical examination data will be listed.

7. INTERIM ANALYSES

An IA may be performed to assess efficacy after approximately 50 participants complete 6 weeks treatment or early discontinue study intervention. Interim analysis results will be used for decisions regarding stopping for futility and planning for future studies.

All study personnel and sponsor's staff involved with this study will remain blinded to individual subject data for interim analysis.

A third party Pfizer programmer/biostatistician who is unrelated to the study team will conduct the interim analysis. The third party will receive the unblinded treatment codes from clinical pharmacy and make the appropriate changes to the analysis programs prepared by the clinical programmer and study biostatistician in the CCI. After successful execution of

all interim analysis programs, the third party will place the results in CCI . An CCI folder containing summary data will be created and protected such that only designated persons can gain access.

The decision criterion is based on the primary endpoint. The efficacy will not be claimed based on this interim analysis. If the efficacy criterion is met, the study will continue and remain blinded to study personnel until the final database unblinding, and phase 3 studies can start planning. The final analysis will be performed at the final official database release. If futility criterion is met, this study will be terminated.

7.1.1. Data Monitoring Committee

This study will not use a data monitoring committee. However, if an IA is performed, an IRC will be established to review the interim analysis results and make the decision for this study and crisaborole stasis dermatitis project.

8. REFERENCES

None.

9. APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Percent Change from baseline to Week 6/EOT in TSS based on HVP in-person assessment	Summary	FAS	observed data	N/A
	Main analysis	FAS	The data after an intercurrent event, if collected, will be excluded, data at Week 6 or EOT (within date of last dose +10 days) will be included.	ANOVA with term treatment
	Sensitivity analysis	FAS	The data after an intercurrent event, if collected, will be excluded, observed cases at	ANOVA with term treatment

			Week 6 will be included. No imputation for missing data.	
	Sensitivity analysis	FAS	The data after an intercurrent event, if collected, will be excluded, observed cases at Week 6 will be included. Missing data at Week 6 will be derived for the analysis using the method of multiple imputation.	ANOVA with term treatment
Percent Change from baseline to Weeks 1 - 6 in TSS based on central readers assessment	Summary	FAS	observed data	N/A
	Main analysis	FAS	The data after an intercurrent event, if collected, will be excluded. Missing data will not be imputed.	MMRM with terms treatment, visit, and interaction of treatment and visit
ISGA success and ISGA clear/almost clear at Week 6/EOT based on HVP in-person assessment	Main analysis	FAS	The data after an intercurrent event, if collected, will be excluded, data at Week 6 or EOT will be included.	Normal approximation
ISGA success and ISGA clear/almost clear at Weeks	Main analysis	FAS	A participant with a missing observation or after an	Normal approximation

1- 6 based on central readers assessment			intercurrent event of discontinuation of treatment will be considered a non-responder for the visit of interest	
Percent change from baseline in %BSA at Week 6/EOT based on HVP in-person assessment	Summary	FAS	observed data	N/A
	Main analysis	FAS	The data after an intercurrent event, if collected, will be excluded, data at Week 6 or EOT will be included.	ANOVA with term treatment
Percent change from baseline in %BSA at Weeks 1-6 based on central readers assessment	Summary	FAS	observed data	N/A
	Main analysis	FAS	The data after an intercurrent event, if collected, will be excluded. Missing data will not be imputed.	MMRM with terms treatment, visit, and interaction of treatment and visit

Appendix 2. Definition and Use of Visit Windows in Reporting

Visit windows defined in Table 3 will be used for longitudinal efficacy variables. For TSS, ISGA, %BSA in-person assessment, these visit windows will be used for sensitivity analysis.

Table 3. Visit windows for longitudinal efficacy variables

Visit Label	Target Day	Definition [Day window]
Screening		up to -1
Baseline	Day 1, Baseline	Day 1
Week 1	8	Days 2 to 11
Week 2	15	Days 12 to 18
Week 3	22	Days 19 to 25
Week 4	29	Days 26 to 32
Week 5	36	Days 33 to 39
Week 6	43	Days 40 - last dose + 10 days

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

Below visit windows in Table 4 will be used for non-longitudinal efficacy variables.

Table 4. Visit windows for non-longitudinal efficacy variables

Visit Label	Target Day	Definition [Day window]
Screening		up to -1
Baseline	Day 1, Baseline	Day 1
Week 6/EOT	43	Day 2 - last dose + 10 days

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

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. Total Sign Score (TSS)

The TSS is an assessment of the severity of SD skin lesions. Each of the 4 clinical signs (erythema, papulation/elevation [excluding papulation due to lipodermatosclerosis or varicose veins], superficial erosion/denudation, and scaling) across all the treatable SD

lesions will be rated using the 4-point severity scale (ranging from 0 to 3 points). The four sub scores are summed to create the TSS, 13-point scale; ranging from 0 to 12 points, with a higher score representing a higher disease severity. TSS is considered missing if one or more item is missing.

Appendix 4. Investigator's Static Global Assessment (ISGA)

The ISGA, a five-point global assessment of AD severity, will be assessed at times specified in the Study Procedure section of study protocol to characterize subjects' overall disease severity across all treatable AD lesions (excluding the scalp).

The ISGA will be a static evaluation without regard to the score at a previous visit. It must be completed by a clinical assessor blinded for treatment arms. Every effort should be made to ensure that all ISGA assessments for a given subject are done by the same qualified individual throughout the study.

Table 5. ISGA Score

Score	Grade	Definition
0	Clear	Minor residual hypo/hyperpigmentation; no erythema or induration/papulation; no oozing/crusting
1	Almost Clear	Trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting
2	Mild	Faint pink erythema with mild induration/papulation and no oozing/crusting
3	Moderate	Pink-red erythema with moderate induration/papulation with or without oozing/crusting
4	Severe	Deep or bright red erythema with severe induration/papulation and with oozing/crusting

∗ The ISGA will exclude scalp from the assessment/scoring

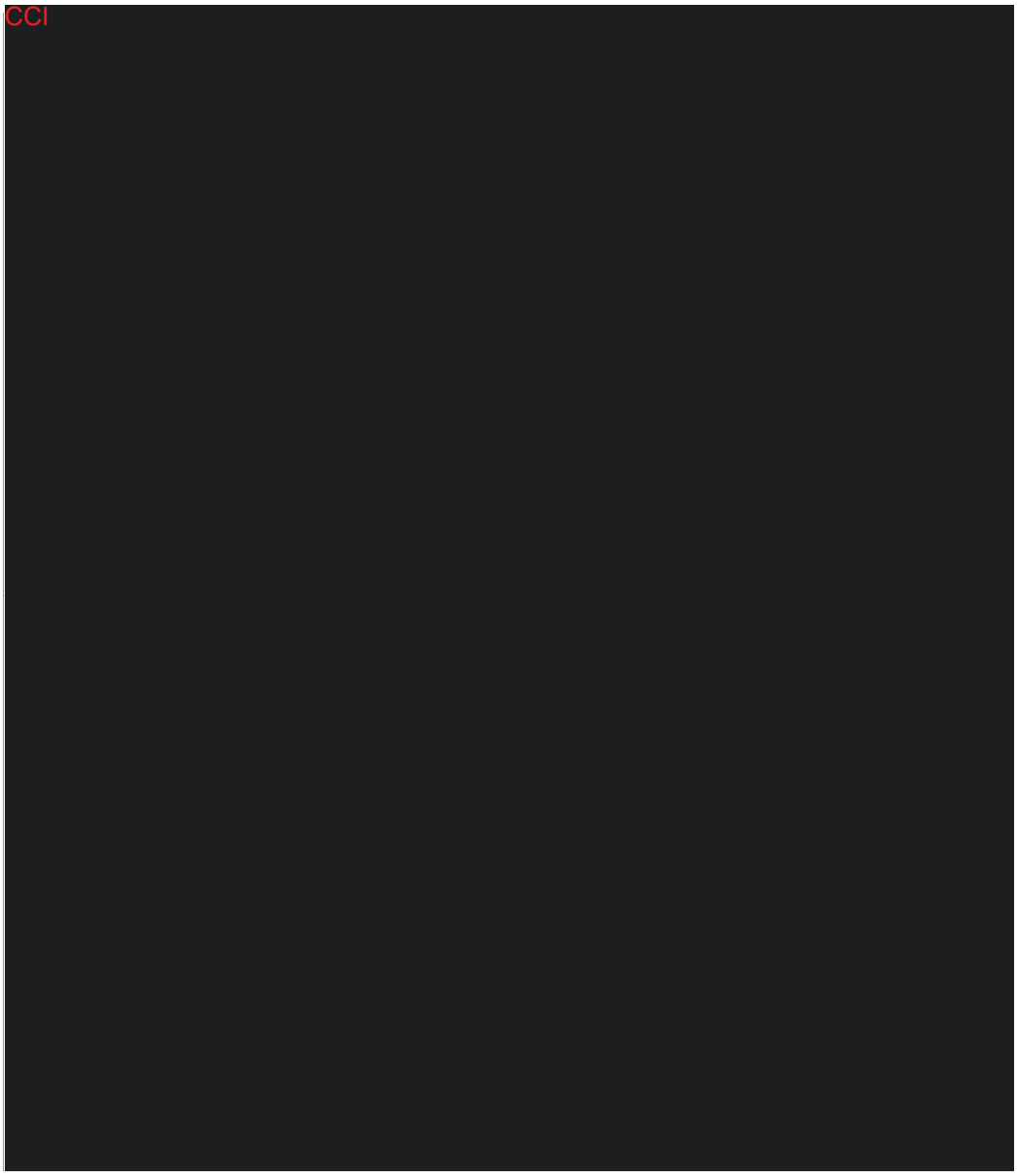
CCI [redacted]

CCI

[redacted]

[redacted]

CCI



CCI

[redacted]

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[redacted]

Detailed analysis of the DLQI

CCI

[redacted]

[redacted]

Appendix 11. List of Abbreviations

Abbreviation	Term
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AR[1]	first order autoregressive
BID	twice daily
BSA	Body surface area
CI	confidence interval
CSR	clinical study report
CCI	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
HVP	home visit practitioner
IA	Interim analysis
ICF	informed consent form
ISGA	investigator's static global assessment
LPLV	last participant last visit
LSM	least-squares mean
MAR	missing at random
MMRM	mixed-effects model with repeated measures
MR-NR	missing response as non-response
N/A	not applicable
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
Std	Standard deviation
SD	stasis dermatitis
CCI	[redacted]
SE	standard error
TCI	Topical Calcineurin Inhibitors
TCS	Topical Corticosteroids
TEAE	treatment emergent adverse event
TSS	total sign score
ULN	upper limit of normal