Protocol C3291002

A PHASE 4, MULTICENTER, OPEN-LABEL SAFETY STUDY OF CRISABOROLE OINTMENT 2% IN CHILDREN AGED 3 MONTHS TO LESS THAN 24 MONTHS WITH MILD TO MODERATE ATOPIC DERMATITIS

Statistical Analysis Plan
(SAP)

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[redacted]

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C3291002 is based on the protocol dated 06Jul2017.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	a. New TEAE definition was added [redacted]	a. Pfizer released new TEAE definition [redacted]

2. INTRODUCTION

Crisaborole, also referred to as PF-06930164 and AN2728, is a low molecular weight benzoxaborole anti-inflammatory phosphodiesterase-4 (PDE-4) inhibitor that penetrates into the skin to the sites of inflammation. PDE-4 inhibition results in increased intracellular cyclic adenosine monophosphate (cAMP) levels. While the specific mechanism(s) by which crisaborole exerts its therapeutic action is not well defined, it is thought that crisaborole reduces the production of several inflammatory cytokines implicated in the pathophysiology of atopic dermatitis (AD).

Across the development program, crisaborole demonstrated an acceptable safety profile, with no crisaborole treatment-related serious adverse events (SAEs) (except 1 case of drug eruption in a Phase 2 study which was classified as possibly related), and the majority of adverse events (AEs) were mild and deemed unlikely or not related to investigational product. Safety and efficacy have not yet been established in patients younger than 2 years of age.

This 4-week study will evaluate the safety, [redacted] *of crisaborole ointment 2%, applied twice daily (BID) in subjects who are 3 months to less than 24 months of age with mild-to-moderate AD. The dose selected for this study has been shown to be safe, well tolerated and efficacious in patients and healthy volunteers 2 years of age and older who participated in previously conducted studies. Based on these results and* [redacted] *satisfactory safety and local tolerability in the pediatric population to be enrolled in this study.*

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C3291002. 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

2.1.1. Primary Objectives

- *To study the safety of crisaborole ointment 2% applied twice daily (BID) in children aged 3 months to less than 24 months with mild to moderate AD.*

2.2. Study Design

This is a Phase 4, multicenter, open label, safety study to evaluate the safety of crisaborole ointment 2% in children aged 3 months to less than 24 months with AD. CCI

Approximately 125 subjects will be enrolled. Subjects will be between 3 months (at the time of the Screening visit) to less than 24 months of age at the time of Baseline/Day 1 with mild-to-moderate AD involving at least *assessed on Baseline/Day 1.*

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3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

- *Incidence of treatment emergent AEs (including application site reactions), SAEs, and clinically significant changes in height, weight, vital signs, ECG and clinical laboratory parameters.*

An adverse event is considered TEAE if the event start date is on or after the treatment period start date and prior to the treatment end date plus lag or within the Active Treatment Phase.

[redacted]

- [redacted]
- [redacted]
- [redacted]
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CCI [redacted]

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- [redacted]
- [redacted]

[redacted]

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- [redacted]
- [redacted]

3.3. Baseline Variables

Demographic and baseline characteristics include:

- Age (in months);
- Sex;
- Race;
- Ethnicity;
- Height (in cms);
- Weight (in kg);
- Body Mass Index;
- Duration of disease (in months);

[redacted]

For endpoints based on scheduled visits, baseline will be defined as the last evaluation taken before the time of the first dose of investigational product.

4. ANALYSIS SETS

4.1. Full Analysis Set

Any subject receiving ≥1 dose of investigational product will be included in full analysis set (FAS).

4.2. Per Protocol Analysis Set

None.

4.3. Safety Analysis Set

Any subject receiving ≥1 dose of investigational product will be included in safety analysis set.

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4.5. Other Analysis Sets

N/A.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

This is an open label safety study. There is no hypotheses and decision rules.

5.2. General Methods

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

5.2.1. Analyses for Binary Data

Binary endpoints will be summarized using number, percentage and 95% CI of percentage.

5.2.2. Analyses for Continuous Efficacy Data

Continuous endpoints will be descriptively summarized using number, mean, standard deviation (standard error of the mean), minimum, 1st, 2nd and 3rd quartiles and maximum.

5.2.3. Analyses for Categorical Data

Categorical endpoints will be summarized using number and percentage.

5.3. Methods to Manage Missing Data

Missing values will not be imputed for safety, CCI [redacted]

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Adverse Events

Adverse events will be summarized according to Pfizer reporting standards for

- TEAEs;
- SAEs.

Overall TEAEs as well as treatment area TEAEs will be summarized by the number of subjects reporting any TEAE, system organ class (SOC), preferred term (PT), severity, relationship to investigational product, and seriousness.

Overall SAEs as well as treatment area SAEs will be summarized by SOC and PT, and individual SAEs will be listed by subject. A list of subjects who prematurely discontinue from the study due to an AE will be provided.

6.1.2. Laboratory Data

Clinical laboratory values and change from screening at Day 29/Early Termination and clinical significant change will be summarized according to Pfizer standards.

6.1.3. Vital Signs

Vital signs and change from baeline and clinical significant change will be summarized according to Pfizer standards.

6.1.4. ECG

ECG and change from baeline and clinical significant change wil be summarized according to Pfizer standards.

6.1.5. Height/Length and Weight

Height/length and weight values and change from baseline at Day 29/Early Termination and clinical significant change will be summarized according to Pfizer standards.

6.1.6. Physical Examination

Descriptive summary tables will be provided in accordance with Pfizer reporting standards.

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CCI [redacted]

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6.3. Subset Analyses

N/A.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

Demographic and baseline characteristics will be summarized according to Pfizer reporting standards [redacted] and overall safety analysis set.

6.4.2. Study Conduct and Subject Disposition

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

6.4.3. Study Treatment Exposure and Compliance

The exposure to study drug will be summarized by total number of applications, the total number of days of dosing, and number and percentage of subjects who are compliant with the dosing regimen will be summarized [redacted]

For [redacted] subjects, a total of 56 doses are expected to be applied. A subject will be considered compliant with the dosing regimen if they receive at least 45 but no more than 67 investigational product doses (ie, 80–120%, inclusive, of the expected number of doses) administered in accordance with the protocol.

6.4.4. Concomitant Medications and Non-Drug Treatments

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

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. However, as this is an open label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment facilitating [redacted] and/or to support clinical development.

This study will use an external data monitoring committee (E-DMC). The E-DMC will be responsible for ongoing monitoring of the safety of subjects 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 a 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 C3291002.

[redacted]

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[redacted]	[redacted]	[redacted]
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