Statistical Analysis Plan

Version 1.0

04 Aug 2020

Hill Dermaceuticals, Inc.

Protocol ID: CP 0418 SS-P2 051

Protocol Title: Open-Label Study of the Pharmacokinetics and Safety Including HPA Axis Suppression Potential of Clobetasol Topical Oil in Pediatric Subjects with Moderate to Severe Atopic Dermatitis

APPROVALS

Author		
Printed Name & Title:	**Signature:**	**Date:**
Suzanne Hackett Biostatistician	Suzanne Hackett	05AUG2020

Reviewer		
Printed Name & Title:	**Signature:**	**Date:**
Hilda Maibach Biostatistician	H L Maibach	05Aug 2020

Sponsor Representative		
Printed Name & Title:	**Signature:**	**Date:**
GERARDO MENDEZ EVP		5 AUG 2020

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1. REVISION HISTORY

Version #	Implemented By	Revision Date	Reason
1.0	Suzanne Hackett	04 Aug 2020	Final version

2. ABBREVIATIONS AND ACRONYMS

Some common abbreviations may not be listed.

AE	Adverse Event
AD	Atopic Dermatitis
BSA	Body surface area
CSR	Clinical Study Report
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
HPA	Hypothalamic-Pituitary-Adrenal
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event

3. PREFACE

Study CP 0418 SS-P2 051 is a phase 2 open-label study to evaluate the HPA axis suppression potential and systemic exposure of 0.05% clobetasol oil under maximal use conditions, in subjects with severe to moderate atopic dermatitis (AD).

Hill Dermaceuticals terminated this study due to the lower than expected enrollment of subjects from the oldest cohort group, which is predictive of the extreme difficulty anticipated with enrollment of the younger cohorts. Additionally, the global COVID-19 pandemic presented overwhelming obstacles to an already difficult recruitment and enrollment process. Therefore, analysis for this study is for an abbreviated safety Clinical Study Report (CSR).

The structure and content of this statistical analysis plan (SAP) provides sufficient detail to meet the requirements for the CSR as identified by the Food and Drug Administration (FDA) and International Conference on Harmonization (ICH). All pharmacokinetic and exploratory endpoints stated in the protocol have been removed and noted as changes to the planned analyses conducted in accordance with this SAP.

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on handling early study termination. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

4. STUDY DESCRIPTION

These following sections detail the prospective design, objectives, and sample size of Study CP 0418 SS-P2 051, Final Version 2.0 incorporating Amendment 1, dated 12-SEP-2019.

4.1 Brief Description of Study Design

Study CP 0418 SS-P2 051 "Open-Label Study of the Pharmacokinetics and Safety Including HPA Axis Suppression Potential of Clobetasol Topical Oil in Pediatric Subjects with Moderate to Severe Atopic Dermatitis" is a multicenter, single-arm, open-label study designed to evaluate the hypothalamic-pituitary-adrenal (HPA) axis suppression potential and systemic exposure to clobetasol, when administered as Clobetasol Topical Oil in pediatric subjects, under conditions consistent with anticipated clinical use and under conditions designed to maximize the potential for drug absorption in subjects with moderate to severe AD.

Up to 12 study centers in the United States will participate in the study. Up to approximately 72 subjects will be enrolled to achieve ≥20 completed subjects per cohort.

The study duration for each subject will be up to 54 days (up to 38 days for Screening assessments, followed by up to 16 days of treatment and follow-up). Additional time will be required for subjects requiring additional hypothalamic-pituitary-adrenal [HPA] axis function testing due to an abnormal result at End of Treatment.

The study will consist of three successively younger pediatric cohorts, as safety data allow:

- Cohort 1: ≥12 to <18 years;
- Cohort 2: ≥6 to <12 years; and
- Cohort 3: ≥2 to <6 years.

Enrollment into each successively younger pediatric cohort will proceed only after the preceding cohort has been completed and safety and exploratory data (including adverse events [AEs], tolerability assessments, clinical laboratory results, and the percentage of subjects with HPA axis suppression) have been reviewed and agreed to be acceptable for progression to the next cohort. Enrollment into Cohorts 2 and 3 will proceed only if the percentage of subjects with HPA axis suppression in Cohorts 1 and 2, respectively, is ≤40%. HPA axis suppression is defined as a cortisol concentration ≤18 µg/100 mL at approximately 30 minutes after stimulation with cosyntropin.

However, the study was terminated during enrollment of Cohort 1, after 8 subjects had been enrolled into the study. No subjects were enrolled into either of Cohorts 2 or 3.

4.2 Study Objectives

The objectives of this study are to assess the following properties of Clobetasol Topical Oil under maximal use conditions in pediatric subjects with moderate to severe AD.

- Safety, including the potential to suppress the HPA axis
- Systemic exposure to clobetasol following repeated application

4.3 Primary Objective

To assess safety, including the potential to suppress the HPA axis.

4.4 Secondary Objective(s)

To assess systemic exposure to clobetasol following repeated application.

4.5 Study Endpoints

The analysis for this study is for an abbreviated safety CSR. With the exception of safety below, all endpoints and analyses stated in the protocol have been removed and noted as changes to the planned analyses.

- Number and percentage of subjects with HPA axis suppression, defined as a post-stimulation serum cortisol concentration ≤18 µg/100 mL.
- Number and percentage of subjects with treatment emergent AEs (TEAEs), with TEAEs defined as those occurring after the start of study drug or increasing in intensity from Baseline to after the start of study drug.
- Clinical laboratory (chemistry and hematology) values at Screening and at the End of Treatment, presented using descriptive statistics.

4.6 Study Sample Size

The sample size for this study (approximately 24 subjects in each of Cohorts 1, 2, and 3) was specified to provide ≥20 evaluable subjects within each cohort. This sample size was not based on statistical considerations and is instead intended to be a reasonable number of subjects upon which to gather both safety (including the potential to suppress the HPA axis) and systemic exposure information under maximal use conditions of Clobetasol Topical Oil in pediatric subjects.

The study was terminated during enrollment of Cohort 1, after 8 subjects had been enrolled into the study. No subjects were enrolled into either of Cohorts 2 or 3.

5. SCOPE

This SAP describes the planned statistical analyses to be performed on safety data from the Study CP 0418 SS-P2 051 "Open-Label Study of the Pharmacokinetics and Safety Including HPA Axis Suppression Potential of Clobetasol Topical Oil in Pediatric Subjects with Moderate to Severe Atopic Dermatitis".

Social & Scientific Systems, Inc. (SSS) is responsible for developing the SAP and carrying out the statistical analyses, including the production of all tables and listings.

6. GENERAL CONSIDERATIONS

All collected data will be presented in listings; no variables will be derived or computed. Data not subject to analyses according to this plan will not appear in any tables or graphics but will be included only in the data listings.

Baseline demographics will be summarized. Baseline for any given variable is defined as the observation immediately prior to application of study drug. The study Screening visit is considered baseline for laboratory and HPA axis suppression tests.

Descriptive statistics for continuous measures will include the number of subjects (n), mean, standard deviation (SD), median, 25th and 75th percentiles, and minimum (min) and maximum (max) values. Categorical and binary variables will be summarized by the frequency count (n) and percentage (%) of subjects with non-missing data per category. No imputation will be made for missing data. All analyses will be completed on the Safety population (see definition below). Additionally, HPA axis data will be summarized on the Evaluable population (see definition below).

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 22.1).

7. ANALYSIS POPULATIONS

7.1 Safety Population

The Safety population will include all enrolled subjects who received at least one application of study drug.

7.2 Evaluable Population

The Evaluable population will be defined as subjects:

1) who met all inclusion/exclusion criteria, and did not report use of a prohibited medication;
2) who during the study period used ≥20% of study drug dispensed, based on the weight effect of the bottles, calculated as [(total (drug dispensed (g) – drug returned (g))) / 120 g dispensed] *100, as recorded on study drug accountability CRF; and
3) who based on data reported on the study drug missed doses CRF were compliant with the last 5 doses (including the final dose administered at the End of Treatment visit).

8. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

8.1 Demographic Characteristics

Subject demographics (including age, sex, race, and ethnicity) will be summarized descriptively for the safety population and will be supported with an individual subject data listing including all enrolled subjects.

8.2 Medical History

At Screening, the investigator or designee interviewed each subject (and parents, guardians, and/or caregivers, as applicable) to obtain a complete medical and medication history, including a history of all surgeries and past medical procedures. This information was reviewed and updated at Baseline, prior to subject enrollment.

Medical history will be presented alphabetically by system organ class and preferred term. Reported terms will be coded using MedDRA version 22.1.

9. SUBJECT DISPOSITION AND PROTOCOL DEVIATIONS

A summary table will be produced detailing the number and percent of subjects enrolled, treated, who completed the study, who were at least 80% compliant with study drug, and who discontinued study participation. The primary reason for discontinuation will also be presented with the number and percentage of subjects in each category.

A listing of all subjects with one or more protocol deviations will be provided. The listing will include the protocol deviation category, visit associated with the deviation (if applicable), and a description of the deviation.

10. EFFICACY

No efficacy analyses will be performed.

11. PHARMACOKINETICS

All analyses are being conducted for an abbreviated safety CSR, and no pharmacokinetic analysis will be included in these analyses. A by-subject listing of plasma concentration levels will be produced.

12. SAFETY

The descriptive summary of safety data will be presented for the Safety population. For the summary of HPA axis function, data will be presented for both the Safety and the Evaluable populations.

12.1 Adverse Events

All AEs occurring during the study will be classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All AEs which start after the start of study drug or which increase from Baseline in severity will be considered treatment emergent adverse events (TEAEs). TEAEs will be summarized by number of events and number and percentage of subjects experiencing TEAEs, across all subjects. When summarizing TEAEs by severity or

relationship to study drug, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category. All reported serious AEs (SAEs) will be summarized by the number of subjects reporting the event, system organ class, preferred term, severity, and relationship to study drug.

12.2 Laboratory Evaluations

Clinical laboratory (chemistry and hematology) values at Screening and at the End of Treatment visits will be presented using descriptive statistics. Data from unscheduled visits will be included in the subject listings.

The number and percentage of subjects with HPA axis suppression, defined as a post-stimulation serum cortisol concentration ≤18 µg/100 mL, will be presented by visit.

13. INTERIM ANALYSES

No interim analysis will be performed in this study.

14. CHANGES IN STUDY CONDUCT OR PLANNED ANALYSIS

Because the study was prematurely terminated as noted in Section 3, pharmacokinetic, exploratory, sensitivity, as well as some safety analyses will not be completed under this SAP.

Additionally, the definition of the Evaluable population (section 7.2) has been revised from the study protocol (section 14.3.2) because "planned doses" were a function of the treatable BSA and the weight of the tubing and caps biased the calculation. So, a simple 80% threshold would have excluded all of the N subjects. Therefore, compliance is computed with consideration of the weight effect of the bottles with the compliance threshold set as greater or equal to 20%.

15. REFERENCES

N/A

16. PRESENTATION OF DATA

16.1 Tables

The Tables are numbered in accordance with the ICH standard numbering conventions.

Number	Description	Analysis Population
Table 14.1.1	Subject Disposition	Safety Population
Table 14.1.3	Demographic Summary	Safety Population
Table 14.3.1.1	AE Summary	Safety Population
Table 14.3.1.2	Summary of All TEAEs by MedDRA System Organ Class: Severity and Relatedness	Safety Population
Table 14.3.6.1	Laboratory Values by Visit	Safety Population

Table 14.3.6.2	HPA Axis Suppression by Visit	Safety Population, Evaluable Population

16.2 Listings

The Listings are numbered in accordance with the ICH standard numbering conventions.

Number	Description	Analysis Population
Listing 16.2.1	Subject Disposition	Safety Population
Listing 16.2.2	Protocol Deviations	Safety Population
Listing 16.2.4.1	Subject Demographics	Safety Population
Listing 16.2.4.2	Inclusion/Exclusion Criteria	Safety Population
Listing 16.2.4.3	Medical History	Safety Population
Listing 16.2.5.1	Study Drug Application	Safety Population
Listing 16.2.5.2	Study Drug Accountability	Safety Population
Listing 16.2.5.3	Study Drug Missed Doses	Safety Population
Listing 16.2.5.4	PK Sampling	Safety Population
Listing 16.2.6	HPA Axis Suppression	Safety Population
Listing 16.2.7	Adverse Events	Safety Population
Listing 16.2.8.1	Safety Lab Testing - Hematology	Safety Population
Listing 16.2.8.2	Safety Lab Testing - Chemistry	Safety Population
Listing 16.2.8.3	Urine Pregnancy Test	Safety Population
Listing 16.2.9.1	Abbreviated Physical Exam	Safety Population
Listing 16.2.9.2	Tolerability Assessments	Safety Population
Listing 16.2.9.3	Atopic Dermatitis Assessment	Safety Population
Listing 16.2.10.1	Prior and Concomitant Medications	Safety Population
Listing 16.2.10.2	Prior and Concomitant Non-Drug Treatment	Safety Population

17. APPENDICES

N/A