CLINICAL TRIAL PROTOCOL

Study 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
Study Number:	CP 0418 SS-P2 051
Study Drug:	Clobetasol Topical Oil
Sponsor:	Hill Dermaceuticals, Inc. 2650 S. Mellonville Ave Sanford, FL 32773
Protocol Date/Version:	28 January 2019 / Version 1.0

1 PROTOCOL APPROVAL

The following individuals approve the 28 January 2019 version of the CP 0418 SS-P2 051 protocol. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

Company:	Hill Dermaceuticals, Inc.
Name:	Linda Payne
Title:	Regulatory Affairs Manager
Address:	2650 South Mellonville Avenue
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Linda Payne

Digitally signed by Linda Payne
DN: c=US, st=FL, l=Sanford, o=Hill Dermaceuticals, Inc, cn=Linda Payne, email=linda.payne@hillderm.com
Reason: I am approving this document
Date: 2019.01.30 13:09:32 -05'00'

Signature Date

2 STUDY ACKNOWLEDGEMENT

Protocol number: CP 0418 SS-P2 051

I have read this protocol and commit to conduct the study as outlined herein, in accordance with current Good Clinical Practices (cGCPs) and all applicable law.

I agree that I or my designee will completely inform all subjects in this study and their legal representative(s) concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with cGCPs and regulatory authority requirements.

I will be responsible for maintaining the assent form signed by each subject (as applicable) and the informed consent form signed by each subject's legal representative(s) and for providing each subject's legal representative with a signed copy of these forms.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____ _____

Investigator's signature Date

_____

Investigator's printed name

3 SYNOPSIS

Name of Sponsor/Company: Hill Dermaceuticals, Inc.

Name of Finished Product: Clobetasol Topical Oil

Name of Active Ingredient: 0.05% clobetasol propionate

Study 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

Study Number: CP 0418 SS-P2 051

Study Center(s): Up to 12 study centers in the United States (US)

Number of Subjects Planned: Up to approximately 72 subjects will be enrolled to achieve ≥20 completed subjects per cohort.

Study Period:

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.

Phase of Development: 1/2

Rationale:

This study is designed to evaluate the safety and HPA axis suppression potential of Clobetasol Topical Oil and systemic exposure to clobetasol when Clobetasol Topical Oil is applied to pediatric subjects with moderate to severe atopic dermatitis (AD) under maximal use conditions.

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

Design and Methodology:

This study is a multicenter, open-label study designed to evaluate the 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. 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%.

Name of Sponsor/Company: Hill Dermaceuticals, Inc.
Name of Finished Product: Clobetasol Topical Oil
Name of Active Ingredient: 0.05% clobetasol propionate
HPA axis suppression is defined as a cortisol concentration ≤18 µg/100 mL at approximately 30 minutes after stimulation with cosyntropin. Starting with Cohort 1 (and continuing with each successively younger pediatric cohort as safety data allow), the study will start with the Screening visit, at which potentially eligible subjects will provide assent and at least one parent and/or guardian will provide informed consent, as applicable. Subjects will then undergo screening evaluations to include an abbreviated physical examination, assessments of their AD (to include an Investigator Static Global Assessment [ISGA] and the percent of total body surface area [BSA] affected by AD as assessed by the investigator), and an evaluation of medical history. Urine will be obtained for pregnancy screening for female subjects of childbearing potential. Prior and concomitant medications will be reported, AEs will be assessed, and blood samples will be taken for clinical laboratory tests (chemistry and hematology). An HPA axis suppression test (cosyntropin stimulation test) will be performed. The Screening visit will start 14 to 38 days (i.e., Day -13 to Day -37) before the start of study drug, to allow for washout of prior medications and due to the requirement that the HPA axis suppression test at Screening be performed ≥28 days before the second HPA axis suppression test which will be performed at the Day 15 (End of Treatment) visit. Subjects with moderate to severe AD and who meet all other eligibility criteria will be scheduled to return to the clinic for the Baseline/Start of Treatment visit on Day 1. At the Baseline/Start of Treatment visit, subjects will undergo assessments of their AD, baseline (pretreatment) assessments of tolerability criteria, a review of eligibility criteria, a urine pregnancy test (for female subjects of childbearing potential) and baseline (pretreatment) assessments of AEs. For subjects who remain eligible for the study, the investigator will designate the areas to be treated with study drug, and subjects and/or their caregivers will apply the first dose of study drug at the site. AEs and tolerability will be assessed. Subjects and/or their caregivers will continue to apply study drug to the affected areas twice daily (morning and evening), at approximately the same times each morning and each evening, up until their next visit. Subjects and/or their caregivers will treat the designated areas for the duration of the dosing period even if the areas begin to improve. Subjects will return to the clinic for a Week 1 visit on Day 8 (with a window of ±1 day). Evaluations performed at the Week 1 visit will include assessments of AD, tolerability, and AEs. Subjects will return all study drug from the previous week, and a new supply of study drug will be dispensed for the upcoming week. Subjects and/or their caregivers will be instructed to continue applying study drug up through the evening immediately preceding their scheduled End of Treatment visit. Subjects will return to the clinic for the End of Treatment visit on Day 15 with a window of +1 day (i.e., as late as Day 16). In advance of this visit, subjects will be instructed to bring their study drug to the site and not to apply any study drug doses on the day of this visit until told to do so at the site; these instructions will be provided so that dosing can be coordinated with the pharmacokinetic (PK) blood sampling that will occur during this visit. At this visit, PK blood samples will be taken predose (this sample will be taken within 12±2 hours of the previous evening's application of study drug and within 1 hour before the application of study drug on the day of this visit) and at the following times following the application of study drug on the day of the visit: 1 h (±10 minutes), 3 h (±15 minutes), and 6 h (±1 hour). Other procedures performed at the End of Treatment visit will include an HPA axis suppression test (which must

Name of Sponsor/Company: Hill Dermaceuticals, Inc.
Name of Finished Product: Clobetasol Topical Oil
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be at least 28 days after the Screening HPA axis suppression test), and assessments of AD, tolerability, and AEs. A urine pregnancy test will be performed for female subjects of childbearing potential. Blood samples will be taken for clinical laboratory (chemistry and hematology) tests. Any subject with a poststimulation cortisol concentration ≤18 µg/100 mL at the End of Treatment visit will be re-tested 4 weeks later and followed clinically until recovery of HPA axis function has been demonstrated or until the lack of recovery can reasonably be explained. If all three cohorts are completed, approximately 72 subjects will be enrolled.
Study Visits: Screening (Day -37 to Day 0); Baseline/Start of Treatment (Day 1); Week 1 (Day 8±1 day); End of Treatment (Day 15+1 day)
Pharmacokinetic Evaluations for Clobetasol: • Maximum observed plasma concentration (C_{max}) • Time of maximum observed plasma concentration (T_{max}) • Area under the curve from time 0 to 6 hours ($AUC_{(0-6)}$)
Safety Evaluations: • HPA axis suppression test • AEs • Clinical laboratory evaluations • Urine pregnancy tests for females of childbearing potential
Exploratory Evaluations: • Percent of total BSA involvement with AD • ISGA • Tolerability assessments
Key Inclusion Criteria: • Male or female subjects in good general health confirmed by medical history. • Subjects with a clinical diagnosis of AD (according to the criteria of Hanifin and Rajka) of moderate to severe intensity (ISGA score of 3 or 4) involving ≥25% to ≤50% of total BSA located within treatable areas (Cohort 1), or ≥35% to ≤50% of total BSA located within treatable areas (Cohorts 2 and 3), with treatable areas including all but the face, axillae, groin, and scalp. • Subjects with a normally functioning HPA axis, defined as a prestimulation serum cortisol level >5 µg/100 mL, and a response to cosyntropin stimulation to >18 µg/100 mL (after approximately 30 minutes); both blood draws for this test should be performed in the morning, if possible. • Female subjects of childbearing potential must have a negative urine pregnancy test, must not be breastfeeding, and must agree to use an acceptable form of birth control for the duration of the study. Female subjects of childbearing potential are defined as all female subjects who have reached menarche and are not two years postmenopausal or who have reached menarche and have not had a hysterectomy, bilateral tubal ligation, and/or complete bilateral oophorectomy.

Name of Sponsor/Company: Hill Dermaceuticals, Inc.

Name of Finished Product: Clobetasol Topical Oil

Name of Active Ingredient: 0.05% clobetasol propionate

Key Exclusion Criteria:

- Subjects who do not have a normally functioning HPA axis (as defined in the inclusion criteria).
- Subjects with an abnormal sleep schedule or who work at night.
- Subjects who have used topical dermal corticosteroids or topical immunomodulators (e.g., tacrolimus or pimecrolimus) within 3 weeks before Day 1, and subjects who are using any systemic medication known to affect cortisol levels or HPA axis integrity, systemic corticosteroids, an acute systemic course of corticosteroids, and/or any biological medication within 30 days before Day 1.
- Subjects with concomitant medical or dermatologic disorders (neurodermatitis, skin atrophy, striae, telangiectasia, etc.) that may interfere with study objectives and/or evaluations.
- Subjects with active skin infection.
- Subjects with any known significant endocrinological disorder that may require prohibited treatment, any known underlying disease that the investigator deems uncontrolled and poses a safety risk for the subject while participating in the study, known sensitivity to any ingredient of the study preparation, or a history of adverse responses to topical or systemic steroid therapy.
- Subjects who are pregnant or nursing.
- Subjects who have used bleach baths, phototherapy, and/or tanning beds, and/or who have had excessive sun exposure within 1 week before Day 1 and/or are planning to use any of these during the study.
- Subjects who have participated in a clinical drug or device research study and/or used any investigational treatment within the last 30 days before Day 1.

Test Product, Dose, and Mode of Administration:

Clobetasol Topical Oil

Active ingredient: 0.05% clobetasol propionate

Other ingredients: refined peanut oil, mineral oil, oleth-2, and isopropyl myristate

Mode of administration: Subjects (and/or their caregivers, as appropriate) will be instructed as following: Blot dry the skin areas to be treated, using a towel, then moisten the skin areas to be treated, using the supplied spritzer according to the supplied instructions. Finally, apply study drug as a thin film to the areas identified by the investigator or designee. Apply study drug twice daily (morning and evening).

Name of Sponsor/Company: Hill Dermaceuticals, Inc.

Name of Finished Product: Clobetasol Topical Oil

Name of Active Ingredient: 0.05% clobetasol propionate

Statistical Analyses:

The safety parameter of HPA axis suppression will be summarized at the completion of each study cohort and at the end of the study. The percentage of subjects (within cohort) who at the End of Treatment visit demonstrated a poststimulation cortisol concentration ≤18 µg/100 mL will be determined and will inform subsequent cohort enrollment.

At the end of the study, cortisol concentrations (both before and after stimulation with cosyntropin) and the percentage of subjects with HPA axis suppression will be summarized both by cohort and across all subjects.

Clobetasol plasma concentrations will be summarized across subjects for each sampling time in aggregate and by cohort. PK parameters (Cmax, Tmax, and AUC(0-6)) will be calculated using non-compartmental analyses.

ISGA results will be summarized at each time point by the number and percentage of subjects in each ISGA category. A combined category for an ISGA score of either 0 or 1 (clear or almost clear) will also be included. In addition, the number and percentage of subjects with an improvement in ISGA score of at least 2 grades from Baseline to each post-Baseline evaluation will be determined, as will the number and percentage of subjects with an ISGA score of either 0 or 1 (clear or almost clear) and an improvement of at least 2 grades from Baseline to each post-Baseline evaluation.

Descriptive statistics for continuous measures will include the number of subjects (N), arithmetic and geometric mean, standard deviation (SD), median, minimum, maximum, and confidence interval (CI), where appropriate. 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 AEs occurring during the study will be recorded and 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 and by cohort.

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.

Sample Size:

The sample size for this study (approximately 24 subjects in each of Cohorts 1, 2, and 3) is in order to achieve ≥20 evaluable subjects within each cohort. Additional subjects may be enrolled if necessary to achieve ≥20 evaluable subjects within each cohort.

4 TABLE OF CONTENTS

4.1 List of Tables

4.2 List of Abbreviations

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AD	Atopic dermatitis
AE	Adverse event
$AUC_{(0-6)}$	Area under the curve from time 0 to 6 hours
β-hCG	Beta-human chorionic gonadotropin
BSA	Body surface area
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CP	Clobetasol propionate
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HPA	Hypothalamic-pituitary-adrenal
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ISGA	Investigator Static Global Assessment
IUD	Intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of subjects
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
TEAE	Treatment emergent adverse event
T_{max}	Time of maximum observed plasma concentration
US	United States
USP	United States Pharmacopeia
WHO-DD	World Health Organization Drug Dictionary

5 INTRODUCTION

5.1 Atopic Dermatitis

Atopic dermatitis (AD) is an inflammatory skin condition characterized by a chronic or relapsing itchy rash, the distribution and characteristics of which change with patient age. In infants and very young children, the pattern of distribution of AD often involves the face, scalp, neck, trunk, and extremities. In older children and some adults, disease often involves skin creases such as in the front of the elbows or ankles or behind the knees, and lichenification is common. In adolescents and adults, disease often manifests as eczematous lesions on the hands or feet.

Present treatments for AD revolve around disease management, rather than cure, with topical corticosteroids being a mainstay of AD management. Clobetasol propionate (CP) is a synthetic fluorinated corticosteroid which has been approved for topical use in the treatment of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, which includes AD. Multiple formulations of CP 0.05% have been approved for use on the body, including cream, gel, ointment, lotion, foam, or spray formulations. Currently available forms of CP 0.05% are classified as superpotent (Class 1, on the 7-point scale generally used in the United States [US]).

While the superpotent topical corticosteroids are associated with greater efficacy than lower-potency topical corticosteroids, they are also associated with greater risks. Risks include the possibility of systemic effects including the potential for hypothalamic-pituitary-adrenal (HPA) axis suppression. Local effects may also occur on the skin and may include skin atrophy, striae, telangiectasia, burning/stinging, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria [Clobex Lotion US full prescribing information 2012; Eichenfield 2017].

5.2 Clobetasol Topical Oil

Clobetasol Topical Oil is a new formulation of CP 0.05% in a proprietary established vehicle containing refined peanut oil, light mineral oil, oleth-2, and isopropyl myristate. The potency of a topical corticosteroid is influenced by the vehicle in which it is formulated. The oil-based vehicle of Clobetasol Topical Oil is substantially similar to that of another product currently marketed by the sponsor, Derma-Smoothe/FS® (fluocinolone acetonide 0.01%). Derma-Smoothe/FS is marketed for adults with AD and for children with moderate to severe AD as young as 3 months. Derma-Smoothe/FS displayed reduced potency in a vasoconstrictor assay compared with another product containing the same concentration of fluocinolone acetonide 0.01%, Synalar® [sponsor data on file]. While results from a vasoconstrictor assay do not necessarily correlate with efficacy or safety in AD, these results highlight the importance of corticosteroid formulation, and not just concentration, for corticosteroid activity.

Clinical experience with Clobetasol Topical Oil exists from a study in 10 adult subjects ≥18 years of age with plaque psoriasis covering ≥20% of the body surface area (BSA). Subjects were treated with Clobetasol Topical Oil twice daily for 14 days. Among the 9 subjects who completed the study, no suppression of the HPA axis was reported, as measured by blood cortisol concentrations before and after stimulation with adrenocorticotropic hormone (ACTH).

Only two adverse events (AEs) were reported in this study, of treatment site erythema in 1 subject on Day 3, for which the subject was withdrawn from the study, and of an abnormal HPA axis suppression test in the same subject approximately 2 weeks later, which was assessed by the investigator as not related to study drug because the subject had only applied study drug for 3 days and had stopped applying study drug approximately 2 weeks before the date of the abnormal HPA axis suppression test. While the study was not designed primarily to assess efficacy, a global assessment of severity of plaque psoriasis demonstrated improvement in all subjects as assessed by both the investigator and the subject. This study is described in more detail in the Investigator's Brochure for Clobetasol Topical Oil [2018].

The lack of HPA axis suppression in the study of Clobetasol Topical Oil in adult subjects with psoriasis, in conjunction with the reduced potency of Derma-Smoothe/FS (which is a fluorinated corticosteroid formulated in an oil vehicle substantially similar to that of Clobetasol Topical Oil) along with the efficacy of Derma-Smoothe/FS in moderate to severe AD in children suggests that Clobetasol Topical Oil may have a favorable efficacy and safety profile in the treatment of pediatric subjects with moderate to severe AD. The use of higher potency topical corticosteroids in pediatric patients is supported under some circumstances, such as for disease control during acute episodes, by current US guidelines of care for the management of AD [Eichenfield 2014].

Children are at a greater risk for systemic adverse reactions such as HPA axis suppression than are adults when treated with topical corticosteroids because of a higher ratio of skin surface area to body mass [Eichenfield 2014]. To minimize the risk to pediatric subjects during this clinical trial, the initial pediatric investigation of Clobetasol Topical Oil will begin with children ≥12 to <18 years (Cohort 1), with enrollment of successively younger pediatric age cohorts (Cohort 2: ≥6 to <12 years; and Cohort 3: ≥2 to <6 years) only after safety results (including evaluations of HPA axis function) are available from the previous (immediately older) cohort and are deemed 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 (defined as a cortisol concentration ≤18 µg/100 mL at approximately 30 minutes after stimulation with cosyntropin) in the previous cohort is ≤40%.

5.3 Study Rationale

The goal of this research is to investigate the safety of Clobetasol Topical Oil and systemic exposure to clobetasol after repeated topical application of Clobetasol Topical Oil in pediatric subjects with moderate to severe AD.

5.4 Rationale for Study Design

In this open-label safety and pharmacokinetic (PK) study, Clobetasol Topical Oil will be applied twice daily for 2 weeks with serial blood sampling on Day 15. Two weeks is considered sufficient to allow for clobetasol concentrations to achieve steady-state. The surface area to be treated and disease severity is consistent with the intended use of Clobetasol Topical Oil for patients with AD.

6 STUDY OBJECTIVES

The objectives of this study are to evaluate 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; and
- Systemic exposure to clobetasol following repeated application.

7 STUDY DESIGN

This study is a multicenter, open-label study designed to evaluate the 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. 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 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.

Starting with Cohort 1 (and continuing with each successively younger pediatric cohort as safety data allow), the study will start with the Screening visit, at which potentially eligible subjects will provide assent and at least one parent and/or guardian will provide informed consent, as applicable. Subjects will then undergo screening evaluations to include an abbreviated physical examination, assessments of their AD (to include an Investigator Static Global Assessment [ISGA] and the percent of total BSA affected by AD as assessed by the investigator), and an evaluation of medical history. Urine will be obtained for pregnancy screening for female subjects of childbearing potential. Prior and concomitant medications will be reported, AEs will be assessed, and blood samples will be taken for clinical laboratory tests (chemistry and hematology). An HPA axis suppression test (cosyntropin stimulation test) will be performed. The Screening visit will start 14 to 38 days (i.e., Day -13 to Day -37) before the start of study drug, to allow for washout of prior medications and due to the requirement that the HPA axis suppression test at Screening be performed ≥28 days before the second HPA axis suppression test which will be performed at the Day 15 (End of Treatment) visit.

Subjects with moderate to severe AD and who meet all other eligibility criteria will be scheduled to return to the clinic for the Baseline/Start of Treatment visit on Day 1.

At the Baseline/Start of Treatment visit, subjects will undergo assessments of their AD, baseline (pretreatment) assessments of tolerability criteria, a review of eligibility criteria, a urine pregnancy test (for female subjects of childbearing potential) and baseline (pretreatment) assessments of AEs. For subjects who remain eligible for the study, the investigator will designate the areas to be treated with study drug, and subjects and/or their caregivers will apply the first dose of study drug at the site. AEs and tolerability will be assessed.

Subjects and/or their caregivers will continue to apply study drug to the affected areas twice daily (morning and evening), at approximately the same times each morning and each evening, up until their next visit. Subjects and/or their caregivers will treat the designated areas for the duration of the dosing period even if the areas begin to improve.

Subjects will return to the clinic for a Week 1 visit on Day 8 (with a window of ±1 day). Evaluations performed at the Week 1 visit will include assessments of AD, tolerability, and AEs. Subjects will return all study drug from the previous week, and a new supply of study drug will be dispensed for the upcoming week.

Subjects and/or their caregivers will be instructed to continue applying study drug up through the evening immediately preceding their scheduled End of Treatment visit.

Subjects will return to the clinic for the End of Treatment visit on Day 15 with a window of +1 day (i.e., as late as Day 16). In advance of this visit, subjects will be instructed to bring their study drug to the site and not to apply any study drug doses on the day of this visit until told to do so at the site; these instructions will be provided so that dosing can be coordinated with the PK blood sampling that will occur during this visit. At this visit, PK blood samples will be taken predose (this sample will be taken within 12±2 hours of the previous evening's application of study drug and within 1 hour before the application of study drug on the day of this visit) and at the following times following the application of study drug on the day of the visit: 1 h (±10 minutes), 3 h (±15 minutes), and 6 h (±1 hour). Other procedures performed at the End of Treatment visit will include an HPA axis suppression test (which must be at least 28 days after the Screening HPA axis suppression test), and assessments of AD, tolerability, and AEs. A urine pregnancy test will be performed for female subjects of childbearing potential. Blood samples will be taken for clinical laboratory (chemistry and hematology) tests.

Any subject with a poststimulation cortisol concentration ≤18 µg/100 mL at the End of Treatment visit will be re-tested 4 weeks later and followed clinically until recovery of HPA axis function has been demonstrated or until the lack of recovery can reasonably be explained.

7.1 Number of Subjects

Approximately 24 eligible subjects are planned to be enrolled into each cohort to achieve ≥20 evaluable subjects within each cohort, with the definition of an evaluable subject provided in Section 14.2. If all three cohorts are completed, approximately 72 subjects will be enrolled. Additional subjects may be enrolled if necessary to achieve ≥20 evaluable subjects within each cohort.

7.2 Investigators

The study will be conducted at up to 12 investigative sites located in the US.

The study will be conducted by investigators who are determined by the sponsor to be suitably qualified by training and experience to conduct this study in compliance with all applicable Good Clinical Practice (GCP) and US Food and Drug Administration (FDA) federal regulations and local regulations. Sub-investigators will be identified on the Form FDA 1572.

7.3 Study Duration

The total duration of the study for a subject from screening until the last visit will be up to 54 days which includes 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 HPA axis function testing due to an abnormal result at End of Treatment.

8 STUDY SUBJECTS

8.1 Inclusion Criteria

In order to be eligible for the study, subjects must meet all of the following criteria:

1. Male or female.
2. Good general health confirmed by medical history.
3. Clinical diagnosis of AD (according to the criteria of Hanifin and Rajka; see Section 17.1) of moderate to severe intensity (ISGA score of 3 or 4; see Section 11.5.1).
4. AD must involve approximately the following percentages of total BSA located within areas eligible for treatment with study drug (i.e., excluding the face, axillae, groin, and scalp), as determined according to the handprint method presented in Section 11.5.2:
   - ≥25% to ≤50% (Cohort 1); or
   - ≥35% to ≤50% (Cohorts 2 and 3).
5. Normally functioning HPA axis, defined as a prestimulation serum cortisol level >5 µg/100 mL, and a response to cosyntropin stimulation to >18 µg/100 mL (after approximately 30 minutes), with both the prestimulation and poststimulation blood draws for this test performed in the morning, if possible.
6. Female subjects of childbearing potential must have a negative urine pregnancy test at both Screening and Baseline and must agree to use an effective method of contraception (as defined in Section 11.3) from Screening up through the End of Treatment visit (see Section 10). Females of childbearing potential include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months). Females who are using oral, implanted, or injectable contraceptive hormones, an intrauterine device (IUD), barrier methods (diaphragm, condoms, spermicide) to prevent pregnancy, practicing abstinence, or whose partner is sterile (e.g., vasectomy), should be considered to be of childbearing potential.
7. Subjects' parent(s) or guardian(s), as applicable, must have full legal capacity to provide consent.
8. Subjects and their parent(s) or guardian(s) must have completed an appropriately administered institutional review board (IRB)-approved assent (as applicable) and informed consent, respectively, prior to performing any study related procedures on the subject.
9. Subjects and their parent(s) or guardian(s), as applicable, must agree to comply with all requirements of the protocol.

8.2 Exclusion Criteria

Subjects meeting any of the following criteria will not be eligible for the study:

1. HPA axis function which does not meet the definition of normally functioning, as defined in Inclusion Criterion 5.
2. Abnormal sleep schedule or work at night.
3. Used topical dermal corticosteroids or topical immunomodulators (e.g., tacrolimus or pimecrolimus) within 3 weeks before Day 1.
4. Used any of the following systemic medications within 30 days before Day 1:
   - Any systemic medication known to affect cortisol levels or HPA axis integrity;
   - An acute systemic course of any corticosteroid, or any use of systemic corticosteroid; and/or
   - Any biological medication.
5. Concomitant medical or dermatologic disorders (such as neurodermatitis, skin atrophy, striae, or telangiectasia) that may interfere with study objectives and/or evaluations.
6. Active skin infection.
7. Known significant endocrinological disorder that may require treatment prohibited by this protocol.
8. Any known underlying disease that the investigator deems uncontrolled and poses a safety concern for the subject while participating in the study.
9. History of adverse responses to topical or systemic steroid therapy.
10. Known sensitivity to any ingredient of the study preparation.
11. Pregnant or nursing (see also Inclusion Criterion 6).
12. Used bleach baths, phototherapy, and/or tanning beds, and/or who have had excessive sun exposure within 1 week before Day 1 and/or are planning to use any of these during the study.
13. Participated in a clinical drug or device research study and/or used any investigational treatment within 30 days before Day 1.
14. Unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.

8.3 Subject Completion

The subject has completed the study when the End of Treatment visit is completed. Subjects who require further follow-up for an AE will be followed according to Section 12.4. Subjects with an abnormal HPA axis suppression test at the End of Treatment visit will be re-tested 4 weeks later and followed clinically until recovery of HPA axis function has been demonstrated or until the lack of recovery can reasonably be explained.

8.4 Subject Discontinuation

A subject MAY be withdrawn from the study (at the discretion of the investigator, sponsor, and/or IRB) prior to study completion for any of the following reasons, including, but not limited to:

- A serious adverse event (SAE) occurring during the course of the study which precludes continued participation
- Intercurrent illness which may, in the investigator's opinion, significantly affect study assessments or the subject's safety
- Failure to follow required study procedures

A subject MUST be discontinued prior to the final study visit for any of the following reasons:

- Whenever the subject or the subject's legal representative decides it is in the subject's best interest to withdraw
- Whenever the investigator decides it is in the subject's best interest to be withdrawn

Prior to discontinuing a subject, every effort should be made to contact the subject's parent, guardian, and/or caregiver, as applicable, to schedule a final study visit and obtain as much follow-up data as possible. If possible, the assessment schedule for the End of Treatment visit should be performed, with the exception of HPA axis suppression testing if the previous HPA axis suppression test was performed <28 days prior. In all cases, an effort should be made to collect all study drug.

Subject discontinuations will be documented clearly on the applicable electronic case report form (eCRF).

8.5 Subjects Lost to Follow-up

An effort must be made to contact a parent, guardian, and/or caregiver of enrolled subjects who do not return for scheduled visits, to schedule the visit and/or obtain as much follow-up data as possible. At least two telephone calls, followed by a certified letter, must be placed to the subject's parent, guardian, and/or caregiver at the first missed visit, to attempt to get the subject to complete the visit and to gather as much follow-up data as possible. At least two telephone calls, followed by a certified letter, must also be placed to the subject's parent, guardian, and/or caregiver for any subsequent missed visits after an attended visit, to attempt to get the subject to complete the visit and to gather as much follow-up data as possible. Subjects who miss a visit may still be scheduled for a subsequent visit. Subjects whose parents, guardians, and/or caregivers cannot be contacted via two telephone calls followed by a certified letter (e.g., the telephone calls and certified letter are unanswered and/or cannot be delivered) may be considered lost to follow-up and discontinued from the study.

All follow-up attempts will be documented and kept with the subject's source documentation, and the applicable eCRFs will be completed. The date a subject will be considered lost to follow-up will be the date when the certified letter was sent.

9 CONCOMITANT THERAPIES

All concomitant therapies including topical moisturizers, sunscreens, and other skin products must be recorded on the eCRF. All therapies within 30 days prior to Day 1 must also be recorded on the eCRF.

Every effort should be made to keep concomitant therapy and dosing constant during the study. Any changes in concomitant therapies during the study must be recorded on the eCRF at each visit. The reason for any change in concomitant therapies should be reported as, or in conjunction with, an AE except as noted below:

- Prophylactic therapies, such as vaccines, must be recorded on the eCRF but should not be reported as AEs.
- Changes in therapy for pre-existing conditions that are not related to a worsening of the condition must be reported on the eCRF but should not be reported as AEs. The condition must be reported on the eCRF as part of the subject's medical history.

9.1 Permitted Medications

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Vitamins and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health.

Non-prohibited chronic therapies being used at Screening and/or Baseline may be continued. Antihistamines and inhalers containing corticosteroids may be continued during the study, in accordance with the subject's normal use of these products. Subjects' normal skin moisturizers, emollients, humectants, sunscreens, and/or makeup may be used during the study, in accordance with the subject's normal use of these products except that topical skin products should not be used within two hours before and one hour after application of study drug. An effort should be made to keep use of these products consistent throughout the study.

9.2 Prohibited Medications

The following medications are prohibited during the study:

- Topical corticosteroids, other than the study drug and corticosteroid-containing inhalers (the use of which is permitted as described in Section 9.1), within 3 weeks before Day 1 and throughout the study.
- Topical immunomodulators, such as tacrolimus or pimecrolimus, within 3 weeks before Day 1 and throughout the study.
- Any systemic medications known to affect cortisol levels or HPA axis integrity, within 30 days before Day 1 and throughout the study.
- An acute systemic course of any corticosteroid, or any use of systemic corticosteroid, within 30 days before Day 1 and throughout the study.

- Any biological medication, within 30 days before Day 1 and throughout the study.
- All topical skin products other than study drug except for the subject's normal skin cleansers, moisturizers, emollients, humectants, sunscreens, and makeup (which may be used in accordance with Section 9.1), and the Clobetasol Topical Oil vehicle, which can be used as a moisturizer if desired.
- Bleach baths, phototherapy, tanning beds, and/or excessive sun exposure.
- Any investigational treatments other than study drug.

10 STUDY SCHEDULE

10.1 Schedule of Assessments

The study schedule of assessments is presented in Table 1.

Table 1 Study Schedule of Assessments

Evaluations and Procedures:	Screening Day -37 to Day 0 [a]	Baseline/ Start of Treatment Day 1 [a]	One Week Day 8 (±1) [b]	End of Treatment Day 15 (+1) [c]
Informed consent/assent	X			
Demographics	X			
Inclusion/exclusion criteria	X	X		
Medical/medication history	X	X		
Abbreviated physical examination	X			
Urine pregnancy test [d]	X	X		X
HPA axis suppression test [e]	X [f]			X [g]
First application of study drug		X		
Assessments of atopic dermatitis [h]	X	X	X	X
Weigh and dispense study drug		X	X	
Dispense subject diary		X	X	
Apply study drug		X [i]	X	X
Collect subject diary			X	X
Collect and weigh study drug			X	X
Tolerability assessments [j]		X [k]	X	X
Adverse events assessments	X	X	X	X
Concomitant medications review	X	X	X	X
Blood sampling for PK				X [l]
Blood sampling for blood chemistry and hematology	X [m]			X

a. Day 0 is defined as the day before first study drug administration, and Day 1 is defined as the day of first study drug administration.
b. This visit may occur up to 1 day sooner or 1 day later than the specified day.
c. This visit may occur up to 1 day later than the specified day.
d. Females of childbearing potential only.
e. Prestimulation cortisol concentrations will be obtained, then subjects will be injected with cosyntropin, then poststimulation cortisol concentrations will be obtained at 30 minutes after cosyntropin injection (with a window of +5 minutes). Both blood draws should be performed in the morning if possible.
f. Screening HPA axis suppression testing must be done 14 to 28 days prior to first application of study drug (i.e., from Day -13 to Day -27), so that the End of Treatment HPA axis suppression test is at least 28 days after the Screening HPA axis suppression test.
g. Any subject with a poststimulation cortisol concentration ≤18 µg/100 mL at the End of Treatment will be re-tested 4 weeks later, and followed clinically until recovery of HPA axis function has been demonstrated, or until the lack of recovery can reasonably be explained.
h. To include the ISGA and percent the BSA affected by AD as assessed by the investigator.
i. The first application of study drug will be performed at the site, after which the subject will apply the remaining doses (including the second dose on Day 1) as instructed by the investigator or designee.
j. To include burning/stinging, atrophy, striae, folliculitis, and telangiectasias.

k. On Day 1, tolerability assessments will be performed before the first application of study drug and will constitute baseline values for each of these parameters; tolerability assessments will be performed again on Day 1 after the first application of study drug.
l. Blood samples for determination of the clobetasol propionate plasma concentration will be collected pre-dose (this sample will be taken within 12±2 hours of the previous evening's application of study drug and within 1 hour before the application of study drug on the day of this visit), and at 1 (±10 minutes), 3 (±15 minutes), and 6 (±1 hour) hours after the application of study drug on the day of this visit.
m. To be performed no earlier than 28 days prior to Baseline/Start of Treatment (i.e., no earlier than Day -27).

Details about study procedures and how they are to be performed are presented in Section 11.

10.1.1 Screening (Day -37 to Day 0)

Prior to the signing of informed consent and assent (as applicable), the investigator or designee will explain the purpose of the study, procedures, and subject responsibilities to the potential study subject and the subject's parent(s) and/or guardian(s), as applicable. The willingness and ability of the subject and all applicable parents and/or guardians to meet the follow-up requirements of the study will be determined.

The Screening period will start 14 to 38 days before the start of study drug (i.e., no earlier than Day -37 and no later than Day -13). This time period is to allow for washout of any prohibited medications prior to the start of study treatment, and also to allow for a separation of ≥28 days between the two HPA axis suppression tests planned for this study. The last day of the Screening period is designated as Day 0.

Screening procedures will include:

- Verbal and written informed consent and assent (as applicable), to be obtained prior to the performance of any study-related procedures.
- Assessments of AD, to be performed anytime during the Screening period (from Day -37 to Day 0).
- Medical history, to be obtained anytime during the Screening period (from Day -37 to Day 0).
- Prior and concomitant medications, to be evaluated anytime during the Screening period (from Day -37 to Day 0).
- Abbreviated physical examination, to be performed anytime during the Screening period (from Day -37 to Day 0).
- Urine pregnancy test (for female subjects of childbearing potential only), to be performed anytime during the Screening period (from Day -37 to Day 0).
- HPA axis suppression test, to be performed no sooner than Day -27 and no later than Day -13 of the Screening period.
- Blood sampling for clinical laboratory evaluations (blood chemistry and hematology), to be performed no sooner than Day -27 of the Screening period.
- AE assessments, to occur throughout the Screening period.
- Preliminary determination of subject eligibility for the study, to be evaluated throughout the Screening period.

Subjects who are potentially eligible for the study will be scheduled to return to the study site for a final determination of eligibility and possible start of study treatment on Day 1.

10.1.2 Baseline/Start of Treatment (Day 1)

Baseline procedures to be performed before a subject is enrolled into the study will include:

- Assessments of AD.
- Urine pregnancy test (for female subjects of childbearing potential only).
- AE assessments.
- Tolerability assessments.
- Review of medical and medication history, including all current medications and all medications taken since the prior visit that have since been discontinued.
- Review of all clinical laboratory results.
- Review of all inclusion and exclusion criteria to determine subject eligibility for the study.

Following completion of these procedures, subjects meeting all inclusion and exclusion criteria will be enrolled into the study.

For subjects who are enrolled into the study, the following procedures and evaluations will be performed on Day 1:

- Definition by the investigator of body areas to be treated with study drug.
- Weighing and dispensation of study drug to the subject, along with instructions on how to apply the study drug.
- Dispensation of a subject diary to the subject.
- First application of study drug. The first application of study drug will be performed by the subject (or the subject's parent, guardian, or caregiver, as applicable) at the site under the instruction and supervision of study staff.
- AE assessments.
- Tolerability assessments.
- Review of concomitant medications.

Subjects will be scheduled for the next study visit and (along with their parent, guardian, or caregiver, as applicable) will be instructed to continue applying study drug twice daily (morning and evening) to all areas designated by the investigator, even if those areas have cleared, and to complete the subject diary after each application of study drug, up through the next study visit at One Week.

Subjects (and the subject's parent, guardian, or caregiver, as applicable) will be instructed to bring all study drug and their completed subject diary to the next study visit at One Week.

Depending on the scheduled time of the One Week visit, the investigator may request that the subject (or the subject's parent, guardian, or caregiver, as applicable) wait until the visit to apply any doses of study drug on the day of the One Week visit. Alternatively, the investigator at his/her discretion may allow the subject (or the subject's parent, guardian, or caregiver, as applicable) to apply study drug before the visit on this day.

10.2 One Week (Day 8)

This visit may occur up to 1 day sooner or up to 1 day later than the specified day (i.e., this visit may occur between Day 7 and Day 9).

The following procedures and evaluations will occur at this visit:

- Assessments of AD.
- AE assessments.
- Tolerability assessments.
- Review of concomitant medications.
- Collection and review of the completed subject diary from the previous week and dispensation of a new subject diary for the following week.
- Collection and weighing of study drug from the previous week and weighing and dispensation of a new supply of study drug for the following week.

Subjects will be scheduled for the next study visit and (along with their parent, guardian, or caregiver, as applicable) will be instructed to continue applying study drug twice daily (morning and evening) to all areas designated by the investigator, even if those areas have cleared, and to complete the subject diary after each application of study drug, up through the evening before the next study visit at End of Treatment.

For the evening before the scheduled End of Treatment visit, subjects (along with their parent, guardian, or caregiver, as applicable) will be instructed to apply that evening's dose of study drug 12 hours before the scheduled time of their End of Treatment visit. Subjects (along with their parent, guardian, or caregiver, as applicable) will also be instructed not to apply any study drug on the day of their scheduled End of Treatment visit and to bring all study drug and their completed subject diary to the next study visit at End of Treatment.

10.3 End of Treatment (Day 15)

This visit may occur up to 1 day later than the specified day (i.e., this visit may occur on either Day 15 or Day 16).

The following procedures and evaluations will occur at this visit:

- Collection of predose PK blood sample, to be performed 12±2 hours after the dose of study drug on the previous evening, and within 1 hour before the dose of study drug that will be applied at the study site on this day.
- Collection and review of the completed subject diary from the previous week.
- Collection of study drug from the previous week.
- Study drug application, to be performed by the subject (or the subject's parent, guardian, or caregiver, as applicable) at the site under the supervision of study staff.
- Weighing of study drug (to be completed after the final study drug application that is performed at the site).
- HPA axis suppression test.
- Assessments of AD.
- AE assessments.
- Tolerability assessments.
- Urine pregnancy test (for female subjects of childbearing potential only).
- Review of concomitant medications.
- Collection of postdose PK blood samples, to be performed at 1 (±10 minutes), 3 (±15 minutes), and 6 (±1 hour) hours after study drug application.
- Blood sampling for clinical laboratory evaluations (blood chemistry and hematology).

For subjects who discontinue prematurely from study treatment, the procedures planned for the End of Treatment visit should be performed if possible, with the exception of HPA axis suppression testing if the previous HPA axis suppression test was performed <28 days prior.

10.4 Unscheduled

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional examinations should be fully documented in the source files and eCRFs, as appropriate. Data from visits that fall outside the designated scheduled visit window but that are intended to fulfill scheduled visit requirements will be collected and transcribed to the appropriate scheduled visit eCRF.

If a subject is seen for multiple visits during a given visit time frame, the data from the visit(s) that are intended to meet the protocol requirements for the scheduled visit should be captured on

the visit eCRF. Any other data from any additional visits within a scheduled visit interval will be captured elsewhere on the eCRF.

10.5 Post-study Follow-up

If a subject requires further follow-up of AEs or of an abnormal HPA suppression axis test upon discontinuation or completion of the study, the investigator should schedule post-study follow-up contact(s) and/or visit(s), as necessary.

10.6 Missed Visits

If a subject misses the One Week visit and cannot be seen prior to the start of the visit range for the End of Treatment visit, the One Week visit will be considered missed.

10.7 Subject Completion

The subject has completed the study when the End of Treatment visit is completed. Subjects who require further follow-up for an AE and/or an abnormal HPA axis suppression test will be followed according to Section 10.5.

10.8 Early Study Termination

The sponsor reserves the right to terminate this study prematurely. If during the study it becomes evident to the sponsor that the study should be stopped prematurely, the study will be terminated and appropriate notification will be given to the investigator, IRB, and FDA, as applicable. The sponsor or designee will instruct the investigator to stop enrolling subjects and will arrange for study closeout at the site.

11 STUDY PROCEDURES

The required study procedures are detailed in this section. The timeline for these procedures is presented in Section 10.

11.1 Medical/Medication History

At Screening, the investigator or designee will interview each subject (and parents, guardians, and/or caregivers, as applicable) and obtain a complete medical and medication history, including a history of all surgeries and past medical procedures. This information will be reviewed and updated at Baseline, prior to subject enrollment. The subject must not require any treatment or medication for concurrent illnesses as specified by the inclusion and exclusion criteria or anticipate the need for any excluded concomitant medications.

11.2 Abbreviated Physical Examination

At Screening, the investigator or designee will perform an abbreviated physical examination to include the following: general appearance; head, eyes, ears, nose, throat; neck; cardiovascular; lungs; lymph nodes; extremities; and skin.

11.3 Urine Pregnancy Test

The urine pregnancy test (performed for females of childbearing potential only) must have a minimum sensitivity of 25 mIU of beta-human chorionic gonadotropin (β-hCG)/mL of urine.

11.4 HPA Axis Suppression Test

HPA axis suppression testing will be done in accordance with the package insert for Cortrosyn® (cosyntropin) 0.25 mg Injection, as shown in Section 17.2, and as follows. For each test, a baseline (prestimulation) blood sample will be taken, and the sample will be processed for the measurement of cortisol concentrations according to instructions provided in a separate laboratory manual. Within approximately 5 minutes after collection of the prestimulation blood sample, the subject will be injected either intramuscularly or intravenously with 0.25 mg Cortrosyn, in accordance with the Cortrosyn package insert. At ≥30 minutes after the Cortrosyn injection (with a window of +5 minutes, i.e., up to 35 minutes), a second (poststimulation) blood sample will be drawn. This blood sample will again be processed for the measurement of cortisol concentrations according to instructions provided in a separate laboratory manual.

Blood draws for the HPA axis suppression test should be done at in the morning, if possible, preferably starting around 8 AM and with both the prestimulation and poststimulation blood draws completed preferably by no later than 10 AM.

11.5 Assessments of AD

Assessments of AD will include the ISGA as described in Section 11.5.1, and the percentage of total BSA affected by AD contained within areas eligible for treatment with study drug as described in Section 11.5.2. The same evaluator should assess the subject throughout the subject's participation in the study, if possible.

Additionally, at Screening, the investigator will determine the subject's eligibility for the study in accordance with the diagnostic criteria for AD as described in Appendix 17.1.

11.5.1 ISGA

The investigator or designee will assess each subject's AD according to the scale shown in Table 2. If the ISGA evaluation encompasses multiple areas affected by AD, the score should reflect the investigator's overall impression, based on predominance and taking into consideration all of the areas affected by AD that are eligible for treatment with study drug (i.e., excluding the face, axillae, groin, and scalp).

Table 2 Scale for ISGA

Score	Definition
0	Clear, minor residual discoloration; 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

11.5.2 Percentage of Total BSA Affected by AD

The investigator or designee will use the handprint method to assess the percentage of total BSA affected by AD, as well as the percentage of total BSA affected by AD that is eligible for study treatment (i.e., excluding the face, axillae, groin, and scalp). The investigator or designee will estimate the percentages of BSA affected by AD in relation to the surface area of the subject's palm, including all the digits. For the purpose of this estimation, the subject's palm, including all the digits, will be assumed to cover ~1% of the subject's total BSA.

11.6 Tolerability Assessments

For the tolerability assessment of burning/stinging, the investigator or designee will ask the subject (or the subject's parent, guardian, or caregiver, as appropriate) to rate the subject's sensation of burning/stinging within the past 24 hours according to the scale shown in Table 3.

Table 3 Scale for Assessment of Burning/Stinging

Score	Definition
0	None; no burning or stinging
1	Mild; slight burning/stinging sensation that is not really bothersome
2	Moderate; warm, burning/stinging that is somewhat bothersome
3	Severe; hot burning/stinging sensation that causes definite discomfort and may interrupt daily activities and/or sleep

For the tolerability assessments of skin atrophy, striae, folliculitis, and telangiectasias, the investigator or designee will rate each of these parameters according to the scale shown in Table 4.

Table 4 Scale for Assessment of Skin Atrophy, Striae, Folliculitis, and Telangiectasias

Score	Definition
0	Absent
1	Present

Tolerability parameters will be reported as AEs only if they require intervention such as treatment with a medication, or interruption or discontinuation of study drug.

11.7 Adverse Event Evaluations

See Section 12.

11.8 Blood Sampling for Chemistry and Hematology

Blood samples for chemistry and hematology parameters will be taken in accordance with the schedule shown in Table 1.

Chemistry parameters will include alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, glucose, potassium, sodium, and total protein.

Hematology parameters will include red blood cells, white blood cells with differential (absolute neutrophil, eosinophil, basophil, lymphocyte, and monocyte counts), platelets, hemoglobin, and hematocrit.

11.9 PK Blood Sampling

PK blood samples will be taken at the times specified in Section 10.3. These blood samples will be taken and processed according to instructions provided in a separate laboratory manual.

11.10 Study Drug Administration

See Section 13.3.

11.11 Treatment Compliance

Subjects or their caregivers (as appropriate) will complete a diary documenting each study drug administration. Additionally, each bottle of study drug dispensed to a subject will be weighed by the investigator or designee both before dispensation and after the bottle is returned by the subject.

11.12 Protocol Deviations

The IRB-approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects.

The date of, nature of, and reason for deviations will be documented and explained by the investigator in all cases. Significant or major protocol deviations impacting the safety of the subject or the integrity of the data must be reported by the investigator to the sponsor and/or its designee and to the IRB immediately. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB.

All changes to the protocol will be made by the sponsor or designee as an approved amendment to the protocol, submitted to the FDA, and approved by the IRB prior to implementation. New or revised consent and assent forms required by the IRB due to a protocol amendment must be signed by the subject's legal representative(s) and the subject, as applicable, for all subjects currently enrolled in the study and must be used for any subsequent subject enrollment.

12 ADVERSE EVENTS

12.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject which does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease, whether or not considered related to the investigational or marketed study drug. AEs include any illness, sign, or symptom that has appeared or worsened during the course of the clinical trial, regardless of causal relationship to the study drug. Study drug includes the investigational drug under evaluation and any comparator product.

Medical conditions/diseases present before signing the informed consent form are only considered AEs if they worsen after the informed consent form is signed.

AEs may be either spontaneously reported or elicited during questioning and examination of a subject. At each examination or visit, study personnel will ask each subject and caregiver, as appropriate, the following question, "Have you had any problems since we last spoke?" If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms.

12.1.1 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence occurring at any dose that results in any of the following outcomes:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment may jeopardize the subject or may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to: allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasia or convulsions that do not result in inpatient hospitalization; the development of drug dependency or drug abuse.

Treatment on an outpatient emergency basis that does not result in hospital admission, or a hospitalization that is elective or is a preplanned treatment for a pre-existing condition that has not worsened since the start of the study, is not considered an SAE.

12.2 Severity of Adverse Events

The severity of an AE will be determined by the investigator according to the following definitions:

- **Mild:** Awareness of event, but easily tolerated and does not disrupt usual activity
- **Moderate:** Sufficient to cause interference with usual activity
- **Severe:** Incapacitating, with inability to perform usual activities

12.3 Relationship of Adverse Events to Study Drug

The relationship of AEs to the study drug will be assessed by the investigator according to the following definitions:

- **Not related:** The temporal relationship of the event to the study drug makes a causal relationship unlikely or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.
- **Related:** The temporal relationship of the event to the study drug makes a causal relationship possible or other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study drug and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE and the study drug is determined by the sponsor to be "related," the event will be considered to be related to the study drug for the purposes of expedited regulatory reporting.

12.4 Documentation of Adverse Events

All AEs must be completely recorded in the source documents and in the Adverse Events section of the eCRF. The collection of AE information should begin after the signing of informed consent and assent (as applicable) and continue up through the End of Treatment visit. Subjects experiencing AEs that cause interruption or discontinuation of study drug, or those experiencing AEs that are present at the end of their participation in the study or that resulted in permanent discontinuation will receive follow-up as appropriate until the AEs have either resolved or have stabilized.

For each AE, the investigator will evaluate and report the following:

- Event name (diagnosis preferred; if unknown, record the signs/symptoms)
- Onset (date);
- Resolution (date);
- Severity grade (mild, moderate, severe);
- Relationship to study drug (related or not related);

- Action taken (none, study drug temporarily interrupted, study drug permanently discontinued, concomitant medication taken, hospitalization/prolonged hospitalization, other);
- Serious (yes/no);
- Whether the AE occurred at the study drug application site (yes/no);
- Outcome.

12.4.1 Additional Reporting Requirements for Serious Adverse Events

All SAEs that occur from the signing of informed consent and assent (as applicable) until the End of Treatment visit will require expedited reporting. Additionally, any SAEs assessed as "related" to the study drug and discovered by the investigator at any time after the end of the study should be reported. Each of these SAEs must be reported to the sponsor and/or sponsor's designee within 24 hours of the investigator's awareness of the SAE. Information on recurrent episodes, complications, or progression of the initial SAE must also be reported within 24 hours of the investigator receiving the information.

Reporting may be by telephone, confirmed facsimile transmission, or confirmed email to the medical monitor. The investigator must assess the relationship of the SAE to study drug and must complete the SAE form. If only limited information is initially available, follow-up reports are required. Follow-up information (e.g., discharge summary) will be retained in the subject's chart and a copy (with the subject's personal information redacted and with the subject identified only by subject number) will be sent by confirmed facsimile transmission or confirmed email to the medical monitor. In the event of death, if an autopsy is performed, a copy of the report (with the subject's personal information redacted and with the subject identified only by subject number) should be sent to the medical monitor. Contact information for the medical monitor will be provided in a study reference manual.

As required and after the sponsor's review and determination of causality, the sponsor and/or designee will notify investigators of all AEs that are serious, unexpected, and considered by the investigator to be related to the study drug. An AE, whether serious or non-serious, is designated unexpected (unlabeled) if it is not reported in the Investigator's Brochure or if the event is of greater frequency, specificity or severity than reported in the Investigator's Brochure.

Upon receiving such notices, the investigator must review and retain the notice with the Investigator's Brochure and immediately submit a copy of this information to the responsible IRB according to local regulations. The determination will be made if the informed consent and assent (as applicable) require revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Follow-up reports should be submitted when requested or when pertinent information becomes available.

The sponsor will report all SAEs to the US FDA on the appropriate schedule depending on the event's expectedness and relationship to study drug based on the available information as presented in the Investigator's Brochure.

Any SAE occurring after the End of Treatment visit and which is not considered to be of "related" relationship to study drug does not need to be reported.

12.5 Pregnancy

Females of childbearing potential, as defined in Section 8.1, must use an effective method of contraception from screening up through the End of Treatment visit. Acceptable methods include the use of at least one of the following: 1) IUD; 2) hormonal contraceptives for at least 30 days prior to Day 1 (oral, injectable, implant, or ring); 3) barrier contraceptives (condom or diaphragm) with spermicide; or 4) abstinence.

Should a pregnancy occur, study drug must be discontinued, and the pregnancy must be recorded on the pregnancy form. The completed pregnancy form will be sent by confirmed facsimile or confirmed email to the medical monitor, within 24 hours of the investigator's awareness of the pregnancy. The pregnancy must also be documented in the eCRF. Pregnancy in itself is not regarded as an AE unless there is a suspicion that the study drug product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study. A spontaneous miscarriage or congenital abnormality will be reported as an SAE.

12.6 Study Contacts

Study contacts will be provided in a separate study reference manual.

13 STUDY TREATMENTS

13.1 Description of Study Drug

Clobetasol Topical Oil contains the active ingredient, CP 0.05%, formulated in an oil vehicle containing refined peanut oil, light mineral oil, oleth-2, and isopropyl myristate. Clobetasol Topical Oil is a clear, pale yellow, oily liquid, containing clobetasol propionate United States Pharmacopeia (USP) 0.05% by weight.

13.2 Area(s) of AD to Be Treated

For each subject, the investigator will specify the areas of moderate to severe AD to be treated with study drug and will communicate these to the subject, parent, guardian, and/or caregiver, as appropriate, at each visit in which study drug is dispensed. If after the start of treatment on Day 1 the investigator or designee identifies the emergence of any additional area(s) that qualify for study drug treatment that were not present on Day 1, the additional area(s) will also be treated with study drug up through the End of Treatment, provided the total BSA treated with study drug is ≤50%. Subjects will continue treating all body areas identified by the investigator up through the End of Treatment, even if clearing of the areas is observed.

13.3 Study Drug Administration

Subjects and/or their caregivers, as applicable, will treat all areas designated by the investigator or designee, in accordance with the instructions provided at the subject's most recent visit. For each application of study drug, subjects and/or their caregivers, as applicable, will:

- Blot dry the skin areas to be treated, using a towel.
- Moisten the skin areas to be treated, using the supplied spritzer, according to instructions which will be provided to each subject and/or caregiver, as applicable (see Section 17.3).
- Apply study drug as a thin film to the skin areas to be treated.
- Use only the amount of study drug necessary to cover the areas identified by the investigator, which should be no more than approximately 3.5 g per application, which equates to approximately four-fifths of a teaspoon, per application.
- Wash hands after each study drug application.
- Refrain from bathing, showering, or swimming for at least 2 hours after each study drug application.

Study drug will be applied twice daily (morning and evening). Study drug will continue to be applied to all areas identified by the investigator throughout the study and up through the End of Treatment visit, even if clearing of the affected areas is observed.

Subjects and their caregivers, as applicable, will also be instructed as follows:

- Keep study drug usage to less than 50 g in one week, which equates to approximately 3.5 g per application. If study drug is used in this manner, subjects will use slightly less than 1 bottle of study drug per week. Each bottle will contain approximately 60 g of study drug.
- Clothing may be worn over the treated areas but any coverings must not be occlusive, meaning that all coverings must allow air to reach the treated areas.
- For skin moisturization, subjects may use their regular non-medicated moisturizer or the Clobetasol Topical Oil vehicle moisturizer (which will be supplied to the subject if desired) including on the treatment areas. Moisturizer may be used as often as needed, in between treatments with study drug except that use of non-study skin products should be avoided within two hours before and one hour after application of study drug.
- Subjects may use their regular sunscreen as normal including on the treated areas except that use of non-study skin products should be avoided within two hours before and one hour after application of study drug.
- If a subject runs out of study drug before the next scheduled study visit, the subject or a parent, guardian, or caregiver must contact the site for a resupply of study drug so that study treatment may continue uninterrupted, if/as appropriate.

13.4 Randomization

Not applicable; this is a single-arm study.

13.5 Masking/Unmasking

Not applicable; this is an open-label study.

13.6 Study Drug Handling and Dispensing

13.6.1 Packaging and Labeling

Study drug will be supplied in 4-ounce opaque white fine ribbed polypropylene screw cap bottle with a pulp/Pharm-Seal V vinyl liner. Each bottle will contain ~60 g of product.

Study drug will be labeled with the following information:

- Protocol number
- Space for entry of the subject number
- Space for entry of the subject initials
- Space for entry of a bottle number
- Space for entry of date dispensed
- A statement reading, "For Topical Use Only. Not for Oral, Ophthalmic, or Intravaginal Use."

- A statement reading, "Store at controlled room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F). Protect from freezing."
- A statement indicating the sponsor, Hill Dermaceuticals, Inc.
- A statement indicating the quantity of product (approximately 60 grams)
- A statement reading, "Caution: New Drug - Limited by Federal Law to Investigational Use"
- A statement reading, "Keep out of Reach of Children"

13.6.2 Storage

The study drug is to be stored at room temperature (20°C to 25°C, or 68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F). All investigational study drug stored at the study site must be in a secure facility, with access limited to the investigator and authorized staff.

13.7 Accountability

The investigator or designee (e.g., study coordinator or pharmacist) is responsible for ensuring storage as per the label on the study drug and adequate accountability of all used and unused study drug. Adequate accountability includes acknowledgment of receipt of each shipment of study drug (quantity and condition), records of administration (including container number, date administered, subject number, and the initials of the person administering the drug), and documentation of quantities returned to the sponsor (or designee).

At time points during the course of the study and/or upon completion of the study, the sponsor or designee will review and verify the investigator's accountability records.

13.8 Return and Destruction

At the completion of the study, following verification of the investigator's accountability records by the sponsor and/or designee, all study drug must be returned to the sponsor or designee. This includes study drug returned by the subjects at the completion of the study, and reserve products that were not used.

14 STATISTICAL CONSIDERATIONS

14.1 Study Endpoints

14.1.1 Safety

Safety endpoints include the following:

- Number and percentage of subjects with HPA axis suppression, defined as a poststimulation serum cortisol concentration ≤18 µg/100 mL, at Screening and at the End of Treatment.
- Cortisol concentrations (stratified as prestimulation and poststimulation) at Screening and at End of Treatment, presented using descriptive statistics.
- 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.
- Number and percentage of subjects with shifts from normal (within the laboratory's normal range) to abnormal (outside of the laboratory's normal range) in each clinical laboratory parameter from Screening to the End of Treatment.

14.1.2 Pharmacokinetics (PK)

PK endpoints include the following parameters as assessed from blood samples taken at the End of Treatment visit, to the extent that each of these parameters can be calculated:

- Plasma clobetasol concentrations at each time point, presented using descriptive statistics.
- Maximum observed plasma concentration (C_{max}), presented using descriptive statistics including confidence interval (CI).
- Time of maximum observed plasma concentration (T_{max}), presented using descriptive statistics.
- Area under the curve from time 0 to 6 hours ($AUC_{(0-6)}$), presented using descriptive statistics including CI.

14.1.3 Exploratory

14.1.3.1 ISGA

The following parameters will be summarized by visit:

- Number and percentage of subjects in each ISGA category.
- Number and percentage of subjects with an ISGA score of either 0 or 1 (clear or almost clear).
- Number and percentage of subjects with an ISGA improvement of at least 2 grades from Baseline to each post-Baseline evaluation.
- Number and percentage of subjects with an ISGA score of either 0 or 1 (clear or almost clear) and an improvement of at least 2 grades from Baseline to each post-Baseline evaluation.

14.1.3.2 BSA

The following parameters will be summarized by visit:

- Percentage of total BSA affected by AD, presented using descriptive statistics.
- Percentage of total BSA affected by AD that is contained within areas that are eligible for treatment with study drug, presented using descriptive statistics.
- Number and percentage of subjects who applied study drug to additional areas during Week 2.

14.1.3.3 Tolerability

The following parameters will be summarized by visit:

- Number and percentage of subjects who experience each tolerability parameter (i.e., burning/stinging, skin atrophy, striae, folliculitis, and telangiectasias).

14.2 Sample Size and Definition of Evaluable Subjects

The sample size for this study (approximately 24 subjects in each of Cohorts 1, 2, and 3) is in order to achieve ≥20 evaluable subjects (as defined in Section 14.3.2) within each cohort. This sample size is 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. Additional subjects may be enrolled if necessary to achieve ≥20 evaluable subjects within each cohort.

14.3 Study Populations

14.3.1 Safety Population

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

14.3.2 Evaluable Populations

Inclusion of a subject in either of the evaluable populations below requires that the subject complete ≥80% of all planned doses of Clobetasol Topical Oil. The determination that a subject met this requirement will be primarily on the basis of the subject diary, along with observation by the study staff of the final dose which is administered at the End of Treatment visit. However, if the weight of the subject's returned supplies of study drug suggests noncompliance with study drug administration, the study team may judge a subject not to be evaluable for the purposes of inclusion in the evaluable populations described below and/or the purposes of achieving ≥20 evaluable subjects within each cohort.

14.3.2.1 HPA Axis Function

The evaluable population for HPA axis function will include all subjects:

1. Who completed the study without any major protocol deviations (e.g., deviations of the inclusion/exclusion criteria, or use of a prohibited medication), as determined by the study team;
2. Who were compliant with study drug use, defined as completion of ≥80% of all planned doses of Clobetasol Topical Oil including 100% of the last 5 doses (including the final dose administered at the End of Treatment visit), as determined by the study team; and
3. Whose HPA axis suppression tests were evaluable (i.e., blood samples were able to be analyzed and results reported).

14.3.2.2 PK

The evaluable population for PK analyses will include all subjects:

1. Who completed the study without any major protocol deviations (e.g., deviations of the inclusion/exclusion criteria, or use of a prohibited medication), as determined by the study team;
2. Who were compliant with study drug use, defined as completion of ≥80% of all planned doses of Clobetasol Topical Oil including 100% of the last 5 doses (including the final dose administered at the End of Treatment visit), as determined by the study team; and
3. Whose PK blood samples were taken within the required windows and processed without any known problems according to the instructions provided by the analytical laboratory.

14.4 Statistical Methods

All parameters will be analyzed based on the safety population. Additionally, HPA axis function will be analyzed on the population evaluable for HPA axis function, and PK data will be analyzed on the population evaluable for PK.

In general, categorical and binary variables will be summarized by the frequency count (n) and percentage (%) of subjects with non-missing data per category, and continuous measures will include the number of subjects (N), arithmetic and geometric mean (where appropriate), standard deviation (SD), median, minimum, maximum, and CI (where appropriate).

At the completion of Cohorts 1 and 2, interim results (i.e., cohort-specific data) will be summarized for both the safety and evaluable populations, by visit where appropriate. The parameters and statistics will be reviewed to determine enrollment of the subsequent cohort.

All analyses will follow a prospectively approved statistical analysis plan (SAP). The SAP will be approved before final data lock and before any analyses of the data. The SAP will include the details of all analyses, all database specifications and conventions, and all tables, listings and figures.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

All AEs will be recorded and classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA).

14.4.1 Safety Analyses

No subjects will be excluded from the safety population because of protocol deviations. Subjects who do not meet admission criteria prior to dosing or who have major protocol deviations after dosing that could significantly affect results will be excluded from the evaluable populations.

Cortisol concentrations, HPA axis suppression data, TEAEs, and clinical laboratory (chemistry and hematology) parameters will be summarized for the safety population (see Section 14.3.1).

TEAEs will be summarized by number of events and number and percentage of subjects experiencing TEAEs, across all subjects and by cohort. 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 SAEs will be summarized by the number of subjects reporting the event, system organ class, preferred term, severity, and relationship to study drug.

In addition to the safety population, cortisol concentrations and HPA axis suppression data will be summarized for the evaluable population for HPA axis function (see Section 14.3.2.1).

14.4.2 PK Analyses

PK summaries and analyses will be performed for the safety population (with available data) and also for the evaluable population for PK (see Section 14.3.2.2). Sensitivity analysis of PK results may be performed to assess any differences in estimates for the evaluable and safety populations. PK parameters will be calculated using validated software for non-compartmental analyses with actual sampling times as data allow. PK parameters will be summarized by age group (≥12 to <18, ≥6 to <12, and ≥2 to <6 years).

14.4.3 Exploratory Analyses

Exploratory analyses include several measures of efficacy and tolerability. Exploratory analyses will be performed for the safety population (see Section 14.3.1) and may also be performed for one or more evaluable populations (see Section 14.3.2). Statistical summaries will be presented by visit and may be further stratified as appropriate.

14.4.4 Sensitivity Analysis

Sensitivity analysis of safety endpoints may be performed and may include assessment of outcomes by use of specific concomitant medications and therapies.

14.4.5 Subject Demographic and Baseline Characteristics

Subject demographic and Baseline characteristics will be summarized descriptively for the safety (see Section 14.3.1) and evaluable (see Section 14.3.2) populations and will be supported with individual subject data listings.

14.4.6 Missing Data

Missing data will not be imputed.

14.4.7 Interim Analyses and Decision to Proceed to the Next Cohort

No interim analyses are planned for this study. However, safety data will be summarized (as necessary) and reviewed after each cohort, to support a decision as to whether to enroll the next, progressively younger age cohort. The decision to progress to the next cohort will be made by the medical monitor in conjunction with the sponsor.

Safety data that will be reviewed for the most recently completed cohort, before the decision is made to proceed with the next younger cohort, include at a minimum:

- Number and percentage of subjects with HPA axis suppression at the End of Treatment visit, in the safety population. The percentage of subjects with HPA axis suppression at the End of Treatment must be ≤40%; however, the medical monitor together with the sponsor may use judgment as to whether to exclude from this calculation subjects whose HPA axis suppression may have been due to administration of a prohibited medication (such as other topical corticosteroids) known to affect HPA axis function.

- Number and percentage of subjects with TEAEs in the safety population, and tolerability parameters in the safety population. The medical monitor together with the sponsor may decide not to proceed with enrollment into the next, progressively younger cohort if the frequency, severity, seriousness, and/or nature of TEAEs or tolerability findings are unexpected, taking into consideration the known effects of topical corticosteroids and the potency of CP 0.05%.
- Clinically significant treatment-emergent clinical laboratory (hematology and chemistry) findings in the safety population at the End of Treatment visit. The medical monitor together with the sponsor may decide not to proceed with enrollment into the next, progressively younger cohort if the frequency, severity, seriousness, and/or nature of clinical laboratory findings are unexpected, taking into consideration the known effects of topical corticosteroids.

The medical monitor and sponsor representative will document and communicate their joint decision to the investigator before enrollment of the next, progressively younger cohort is allowed to proceed.

15 ADMINISTRATIVE CONSIDERATIONS

Details of study administration will be provided in a study reference manual.

15.1 Institutional Review Board

The protocol, informed consent documents, any information provided to subjects, recruitment advertisements and any amendments to these items will have IRB approval prior to their use in the study.

Before study initiation, this protocol, the Clobetasol Topical Oil Investigator's Brochure, the informed consent and assent forms, any other written information given to subjects and/or their parent(s), guardian(s), and/or caregiver(s), and any advertisement for subject recruitment must have IRB approval. Documentation of IRB approval must be sent to the sponsor or designee before study drug will be shipped to the site. The investigator should also provide the Clobetasol Topical Oil Investigator's Brochure to the IRB.

The investigator must provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements and Institution procedures. The IRB must be notified of completion or termination of the study.

Copies of all correspondence with the IRB regarding this study must be sent to the sponsor or its designee. Additionally, the clinical site must maintain an accurate and complete record of all reports, documents, and other submissions made to the IRB concerning this protocol.

15.2 Ethics and Compliance with Good Clinical Practice

The investigator and all study staff will conduct the study in compliance with this protocol and compliance with FDA regulations, all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study, the ethical principles of the Declaration of Helsinki, and the current International Council for Harmonisation (ICH) GCP guidelines.

The rights, safety, and well-being of the study subjects are the most important considerations and prevail over the interests of science and society.

All personnel involved in the conduct of this study must be qualified by education, training and/or experience to perform their assigned responsibilities.

15.3 Informed Consent and Assent

Voluntary assent and informed consent will be given by every subject and/or the subject's legal representative(s), as applicable, prior to the initiation of any study related procedures. The IRB-approved assent and consent forms must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements. Sample assent and informed consent forms containing the required elements of informed consent or assent (as applicable) will be provided by the sponsor or designee. Any changes made to this sample must be approved by

the sponsor or its designee prior to submission to the IRB. After approval by the sponsor or its designee, the assent and informed consent forms must be submitted to and approved by the IRB.

The assent and informed consent forms must be written in a language in which the subject and/or the subject's legal representative(s), as applicable, are fluent. Regulations require that foreign language informed consent and assent forms be submitted to the IRB for approval. The foreign language translation is required to contain a statement of certification of the translation. The investigator must forward a copy of the assent and/or consent form, the certified foreign language translation, and an IRB approval letter to the sponsor.

Prior to the screening evaluation the investigator/designee will explain the study to each potential subject and the subject's legal representative(s). The subject's legal representative(s) must indicate voluntary consent by signing and dating the approved informed consent form. The subject will also indicate voluntary assent by signing and dating the approved assent form, as appropriate and practicable. The consent/assent process will be conducted prior to the start of any study-related procedure. The investigator must retain the original and provide the subject's legal representative with a copy of the consent/assent form(s).

The investigator will maintain documentation that informed consent and assent (as applicable) was obtained prior to the initiation of any study-related procedures.

15.4 Confidentiality of Subject Information

Subject data recorded on eCRFs during the study will be documented in a coded fashion, and all communications and reports regarding this study will identify subjects only by their subject numbers. Complete subject identification will be kept by the investigator for purposes of long-term follow-up, if needed. This information, as well as all medical information resulting from a subject's participation in this study, will be treated with strict adherence to professional standards of confidentiality. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

Data generated for the study should be stored in a limited-access file area and be accessible only to the investigator and authorized personnel, the sponsor and its designee(s), the IRB, and FDA or other relevant regulatory authorities. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare, but no information that can be related to a specific individual subject will be released or used in any fashion without the signed written consent of that subject's legal representative.

15.5 Study Monitoring

Representatives of the sponsor and designee(s) must be allowed to visit all study sites, to review study records and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the investigator and study staff and to verify that the investigator, study staff and facilities remain acceptable for the conduct of the study. Representatives of government regulatory authorities (i.e., FDA) may also evaluate the study records, source documents, investigator, study staff and facilities. All data generated

during this study and the medical records/documents from which they originated are subject to inspection by the sponsor, its designee(s), the FDA, and other regulatory agencies.

Prior to the start of the study, the sponsor and/or its designee will review the protocol, eCRF, regulatory obligations, and other material or equipment relevant to the conduct of the study with the investigator and relevant study site personnel.

Monitoring visits and telephone consultations will occur as necessary, during the course of the investigation to verify the following:

- the rights and well-being of subjects are protected
- the conduct of the investigation is in compliance with the currently approved protocol/amendment, ICH GCPs, and IRB requirements
- the integrity of the data, including adequate study documentation
- the facilities remain acceptable
- the investigator and site personnel remain qualified and able to conduct the study
- study drug accountability

The investigator must immediately notify the sponsor of any audits by any regulatory agency, and must promptly provide copies of any audit reports.

15.6 Case Report Form Requirements

Source documents will be created and retained at the clinical site.

Subject data during the course of the study will be recorded on eCRFs. The investigator and study site personnel will be responsible for completing the eCRFs. The investigator is required to verify that all of the requested information is accurately recorded in the eCRFs. All information requested in the eCRFs needs to be entered, including subject identification, date(s), assessment values, etc. Any omission or discrepancy will require explanation.

The sponsor or designee will review the data recorded in the eCRFs utilizing original source documentation, as applicable. Discrepant findings will be queried within the electronic data capture (EDC) system. The investigator and study site personnel will be responsible for answering all queries. Data reconciliation will be performed between the EDC data and the external data reported by the central laboratory. Any discrepancies in the data will be queried first with the clinical site and second with the central laboratory.

A copy of the eCRFs or archive of eCRFs will be retained by the investigator, who must ensure that it is stored in a secure place.

15.7 Quality Assurance Audits

Representatives from the sponsor and/or a third party selected by the sponsor or designee may conduct a quality assurance audit of this study at any time during or after completion of the study. The Investigator will be given adequate notice if he/she is selected for an audit. During the audit, the investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authority, the investigator must give the inspector direct access to relevant documents and discuss any findings with the inspector. If an inspection is requested by a regulatory authority and/or IRB, the investigator must inform the sponsor immediately that this request has been made.

15.8 Records Retention

The investigator must retain all study-related records for at least 2 years after a marketing application is approved for the drug. If an application is not approved for the drug, the investigator must retain all study-related records until at least 2 years after shipment and delivery of the drug for investigational use is discontinued, and FDA or regulatory agencies have been so notified.

The investigator must contact the sponsor prior to destroying any records associated with this study.

If the location of the study files changes from the address noted on the Form FDA 1572, written notification of the new location must be given to the sponsor. In the event the investigator withdraws from participation in the study, study records will be transferred to a mutually agreed upon designee of the investigator. The investigator must provide written notice to the sponsor of such transfer.

15.9 Publication of Results

All information concerning Clobetasol Topical Oil including study data and sponsor operations including but not limited to formulation information, manufacturing processes, basic scientific data, and patent applications will be regarded as confidential and will remain the sole property of the sponsor. The investigator agrees to use this information solely for the purposes of accomplishing this study and agrees not to use it for any other purposes without the written consent of the sponsor.

Study-related information must not be published or presented by the investigator without prior consultation with and written agreement from the sponsor.

16 REFERENCES

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Eichenfield LF, Ahluwalia J, Waldman A, et al. Current guidelines for the evaluation and management of atopic dermatitis: A comparison of the Joint Task Force Practice Parameter and American Academy of Dermatology guidelines. J Allergy Clin Immunol. 2017 Apr;139(4S):S49-S57. doi: 10.1016/j.jaci.2017.01.009.

Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014 Jul;71(1):116-32. doi: 10.1016/j.jaad.2014.03.023. Epub 2014 May 9.

Investigator's Brochure for Clobetasol Topical Oil Version 1.0 [2018].

17 APPENDICES

17.1 Criteria of Hanifin and Rajka

The clinical diagnosis of AD will be on the basis of the criteria of Hanifin and Rajka, as reported by Andersen [2016]. According to these criteria, a subject must have at least 3 of the 4 basic features, plus at least 3 or more of the 23 minor features, in order to fulfill the criteria for a diagnosis of AD. These criteria are described as follows.

Basic features, for which a subject must have at least 3 of the following 4, include:

1. Pruritus
2. Typical morphology and distribution:
    - Flexural lichenification or linearity in adults
    - Facial and extensor involvement in infants and children
3. Chronic or chronically relapsing dermatitis
4. Personal or family history of atopy (asthma, allergic rhinitis, AD)

Minor features, for which a subject must have at least 3 of the following 23, include:

1. Xerosis
2. Ichthyosis/palmar hyperlinearity/keratosis pilaris
3. Immediate (type I) skin test reactivity
4. Elevated serum IgE
5. Early age of onset
6. Tendency towards cutaneous infections (especially *Staphylococcus aureus* and *Herpes simplex*)/impaired cell-mediated immunity
7. Tendency towards non-specific hand or foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan intraorbital fold
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor/facial erythema
16. Pityriasis alba
17. Anterior neck folds

18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Course influenced by environmental/emotional factors
23. White dermographism/delayed blanch

17.2 Cortrosyn Package Insert

CORTROSYN - cosyntropin injection, powder, for solution
General Injectables & Vaccines, Inc

Cortrosyn (cosyntropin) 0.25 mg Injection, USP 1ml Vial

Description

FOR DIAGNOSTIC USE ONLY

CORTROSYN™ (cosyntropin) for Injection is a sterile lyophilized powder in vials containing 0.25 mg of CORTROSYN™ and 10 mg of mannitol to be reconstituted with 1 mL of 0.9% Sodium Chloride Injection, USP. Administration is by intravenous or intramuscular injection. Cosyntropin is a 1 – 24 corticotropin, a synthetic subunit of ACTH. It is an open chain polypeptide containing, from the N terminus, the first 24 of the 39 amino acids of natural ACTH. The sequence of amino acids in the 1 – 24 compound is as follows:

Ser	Tyr	Ser	Met	Glu	His	Phe	Arg	Trp	Gly	Lys
1	2	3	4	5	6	7	8	9	10	11
Pro	Val	Gly	Lys	Lys	Arg	Arg	Pro	Val	Lys	Val
12	13	14	15	16	17	18	19	20	21	22
Tyr	Pro									
23	24									

Clinical Pharmacology

CORTROSYN™ (cosyntropin) for Injection exhibits the full corticosteroidogenic activity of natural ACTH. Various studies have shown that the biologic activity of ACTH resides in the N-terminal portion of the molecule and that the 1 – 20 amino acid residue is the minimal sequence retaining full activity. Partial or complete loss of activity is noted with progressive shortening of the chain beyond 20 amino acid residues. For example, the decrement from 20 to 19 results in a 70% loss of potency.
The pharmacologic profile of CORTROSYN™ is similar to that of purified natural ACTH. It has been established that 0.25 mg of CORTROSYN™ will stimulate the adrenal cortex maximally and to the same extent as 25 units of natural ACTH. This dose of CORTROSYN™ will produce maximal secretion of 17-OH corticosteroids, 17- ketosteroids and / or 17 - ketogenic steroids.
The extra-adrenal effects which natural ACTH and CORTROSYN™ have in common include increased melanotropic activity, increased growth hormone secretion and an adipokinetic effect. These are considered to be without physiological or clinical significance.
Animal, human and synthetic ACTH (1–39) which all contain 39 amino acids exhibit similar immunologic activity. This activity resides in the C-terminal portion of the molecule and the 22–39 amino acid residues exhibit the greatest degree of antigenicity. In contrast, synthetic polypeptides containing 1–19 or fewer amino acids have no detectable immunologic activity. Those containing 1–26, 1–24 or 1–23 amino acids have very little immunologic although full biologic activity. This property of CORTROSYN™ assumes added importance in view of the known antigenicity of natural ACTH.

Indication and Usage

CORTROSYN™ (cosyntropin) for Injection is intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency. Because of its rapid effect on the adrenal cortex it may be utilized to perform a 30-minute test of adrenal function (plasma cortisol response) as an office or outpatient procedure, using only 2 venipunctures (seeDOSAGE AND ADMINISTRATION section).
Severe hypofunction of the pituitary - adrenal axis is usually associated with subnormal plasma cortisol values but a low basal level is not per se evidence of adrenal insufficiency and does not suffice to make the diagnosis. Many patients with proven insufficiency will have normal basal levels and will develop signs of insufficiency only when stressed. For this reason a criterion which should be used in establishing the diagnosis is the failure to respond to adequate corticotropin stimulation. When presumptive adrenal insufficiency is diagnosed by a subnormal CORTROSYN™ test, further studies are indicated to determine if it is primary or secondary.
Primary adrenal insufficiency (Addison's disease) is the result of an intrinsic disease process, such as tuberculosis within the gland.
The production of adrenocortical hormones is deficient despite high ACTH levels (feedback mechanism). Secondary or relative insufficiency arises as the result of defective production of ACTH leading in turn to disuse atrophy of the adrenal cortex. It is commonly seen, for example, as result of corticosteroid therapy, Sheehan's syndrome and pituitary tumors or ablation.
The differentiation of both types is based on the premise that a primarily defective gland cannot be stimulated by ACTH whereas a secondarily defective gland is potentially functional and will respond to adequate stimulation with ACTH. Patients selected for further study as the result of a subnormal CORTROSYN™ test should be given a 3 or 4 day course of treatment with Repository Corticotropin Injection USP and then retested. Suggested doses are 40 USP units twice daily for 4 days or 60 USP units twice daily for 3 days. Under these conditions little or no increase in plasma cortisol levels will be seen in Addison's disease whereas higher or even normal levels will be seen in cases with secondary adrenal insufficiency.

Contraindication

The only contraindication to CORTROSYN™ (cosyntropin) for Injection is a history of a previous adverse reaction to it.

Precautions

General

CORTROSYN™ (cosyntropin) for Injection exhibits slight immunologic activity, does not contain animal protein and is therefore less risky to use than natural ACTH. Patients known to be sensitized to natural ACTH with markedly positive skin tests will, with few exceptions, react negatively when tested intradermally with CORTROSYN™. Most patients with a history of a previous hypersensitivity reaction to natural ACTH or a pre-existing allergic disease will tolerate CORTROSYN™. Despite this however, CORTROSYN™ is not completely devoid of immunologic activity and hypersensitivity reactions including rare anaphylaxis are possible. Therefore, the physician should be prepared, prior to injection, to treat any possible acute hypersensitivity reaction.

Drug Interactions

Corticotropin may accentuate the electrolyte loss associated with diuretic therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility. A study in rats noted inhibition of reproductive function like natural ACTH.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with CORTROSYN™ (cosyntropin) for Injection. It is also not known whether CORTROSYN™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. CORTROSYN™ should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CORTROSYN™ (cosyntropin) for Injection is administered to a nursing woman.

Pediatric Use

(See DOSAGE AND ADMINISTRATION section.)

Adverse Reactions

Since CORTROSYN™ (cosyntropin) for Injection is intended for diagnostic and not therapeutic use, adverse reactions other than a rare hypersensitivity reaction are not anticipated. A rare hypersensitivity reaction usually associated with a pre-existing allergic disease and/or a previous reaction to natural ACTH is possible. Symptoms may include slight whealing with splotchy erythema at the injection site. There have been rare reports of anaphylactic reaction. The following adverse reactions have been reported in patients after the administration of CORTROSYN™ and the association has been neither confirmed nor refuted:

- bradycardia
- tachycardia
- hypertension
- peripheral edema
- rash

Dosage and Administration

CORTROSYN™ (cosyntropin) for Injection may be administered intramuscularly or as a direct intravenous injection when used as a rapid screening test of adrenal function. It may also be given as an intravenous infusion over a 4 to 8 hour period to provide a greater stimulus to the adrenal glands. Doses of CORTROSYN™ 0.25 to 0.75 mg have been used in clinical studies and a maximal response noted with the smallest dose.

A suggested method for a rapid screening test of adrenal function has been described by Wood and Associates (1). A control blood sample of 6 to 7 mL is collected in a heparinized tube. Reconstitute 0.25 mg of CORTROSYN™ with 1mL of 0.9% Sodium Chloride Injection, USP and inject intramuscularly. The reconstituted drug product should be inspected visually for particulate matter and discoloration prior to injection. Reconstituted CORTROSYN™ should not be retained. In the pediatric population, aged 2 years or less, a dose of 0.125 mg will often suffice. A second blood sample is collected exactly 30 minutes later. Both blood samples should be refrigerated until sent to the laboratory for determination of the plasma cortisol response by some appropriate method. If it is not possible to send them to the laboratory or perform the fluorimetric procedure within 12 hours, then the plasma should be separated and refrigerated or frozen according to need.

Two alternative methods of administration are intravenous injection and infusion. CORTROSYN™ can be injected intravenously in 2 to 5 mL of saline over a 2-minute period. When given as an intravenous infusion: CORTROSYN™, 0.25 mg may be added to glucose or saline solutions and given at the rate of approximately 40 micrograms per hour over a 6-hour period. It should not be added to blood or plasma as it is apt to be inactivated by enzymes. Adrenal response may be measured in the usual manner by determining page 3 of 3 urinary steroid excretion before and after treatment or by measuring plasma cortisol levels before and at the end of the infusion. The latter is preferable because the urinary steroid excretion does not always accurately reflect the adrenal or plasma cortisol response to ACTH.

The usual normal response in most cases is an approximate doubling of the basal level, provided that the basal level does not exceed the normal range. Patients receiving cortisone, hydrocortisone or spironolactone should omit their pre-test doses on the day selected for testing. Patients taking inadvertent doses of cortisone or hydrocortisone on the test day and patients taking spironolactone or women taking drugs which contain estrogen may exhibit abnormally high basal plasma cortisol levels. A paradoxical response may be noted in the cortisone or hydrocortisone group as seen in a decrease in plasma cortisol values following a stimulating dose of CORTROSYN™.

In the spironolactone or estrogen group only a normal incremental response is to be expected. Many patients with normal adrenal function, however, do not respond to the expected degree so that the following criteria have been established to denote a normal response:

1. The control plasma cortisol level should exceed 5 micrograms/100 mL.
2. The 30-minute level should show an increment of at least 7 micrograms/100 mL above the basal level.
3. The 30-minute level should exceed 18 micrograms/100 mL. Comparable figures have been reported by Greig and co-workers (2).

Plasma cortisol levels usually peak about 45 to 60 minutes after an injection of CORTROSYN™ and some prefer the 60-minute interval for testing for this reason. While it is true that the 60-minute values are usually higher than the 30-minute values, the difference may not be significant enough in most cases to outweigh the disadvantage of a longer testing period. If the 60-minute test period is used, the criterion for a normal response is an approximate doubling of the basal plasma cortisol value.
In patients with a raised plasma bilirubin or in patients where the plasma contains free hemoglobin, falsely high fluorescence measurements will result. The test may be performed at any time during the day but because of the physiological diurnal variation of plasma cortisol the criteria listed by Wood cannot apply. It has been shown that basal plasma cortisol levels and the post CORTROSYN™ increment exhibit diurnal changes. However, the 30-minute plasma cortisol level remains unchanged throughout the day so that only this single criterion should be used (3).
Parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.
Reconstituted CORTROSYN™ should not be retained.

How Supplied

Box of 10 vials of CORTROSYN™ (cosyntropin) for Injection 0.25 mg
NDC # 0548-5900-00

Storage
Store at 15–30°C (59–86°F).
CORTROSYN™ is intended as a single dose injection and contains no antimicrobial preservative. Any unused portion should be discarded.

Rx only

References

1. Wood, J.B. et al. LANCET 1.243, 1965.
2. Greig, W.R. et al. J. ENDOCR 34.411, 1966.
3. McGill, P.E. et al. ANN RHEUM DIS 26.123, 1967.

Amphastar Pharmaceuticals, Inc.
Rancho Cucamonga, CA 91730 U.S.A.
REV. 9-10

Sample Outer Package Label

CORTROSYN

cortrosyn injection, powder, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:52584-050(NDC:0548-5900)
Route of Administration	PARENTERAL, INTRAVENOUS, INTRAMUSCULAR	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Cosyntropin (Cosyntropin)	Cosyntropin	0.25 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52584-050-00	1 in 1 BAG		
1		1 mL in 1 VIAL		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA016750	03/01/2010	

Labeler - General Injectables & Vaccines, Inc (108250663)

Revised: 3/2012

General Injectables & Vaccines, Inc

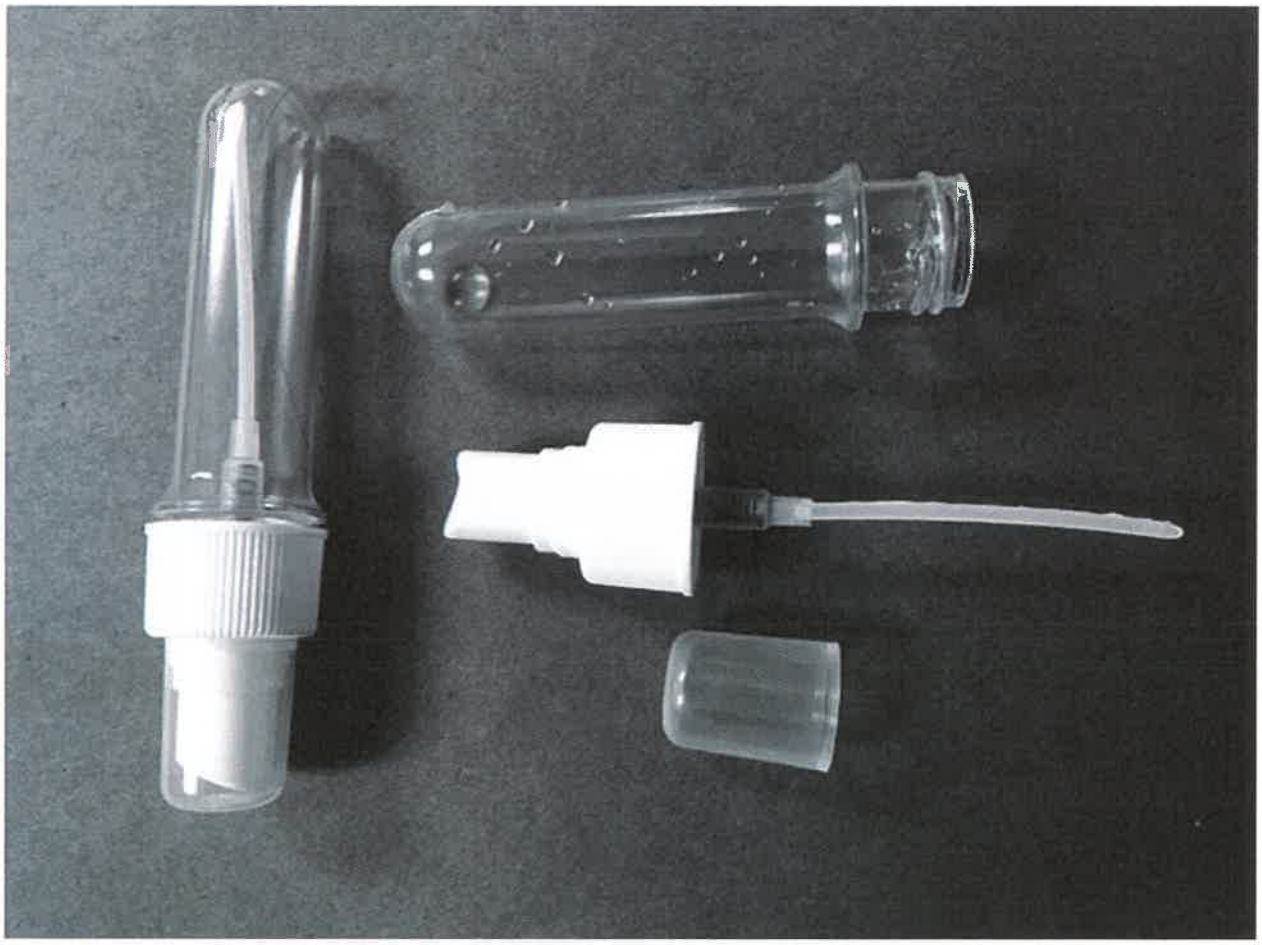
17.3 Use of Skin Spritzer

17.3.1 Description

The water spray bottle (spritzer bottle) has 3 removable parts (see Figure 1):

1. Sprayer pump, with plastic tubing; components are made of plastic;
2. Cap for the sprayer pump, made of see-through plastic;
3. See-through hard plastic tube (bottle) which can hold 25 mL of water.

Figure 1: Picture of Skin Spritzer



17.3.2 Use

How to use the skin spritzer:

1. Disassemble the spritzer into its component parts (if not done already).
2. Rinse each part with tap water.

3. Fill bottle with tap water up to the ridge of the neck of the bottle, and screw the sprayer pump back onto the bottle.
4. Make 2 to 3 initial sprays directed to the sink to prime the sprayer pump; do this immediately before using.
5. When ready to use, direct the sprayer to the area of the skin to be moistened. Hold sprayer approximately 6 inches away from the skin.
6. With one finger, press the pump all the way down to release water mist.
7. Repeat with a second spray over the same area.
8. Move to the next area and repeat Steps 6 and 7. Each area moistened by 2 sprays should measure approximately 3.5 × 3.5 inches. Repeat until the entire treatment area has been moistened.
9. Be sure to record the total number of sprays onto the subject diary.
10. Disassemble the spritzer, empty its contents into the sink, and leave the disassembled parts out to air dry.