# Clinical Study Protocol

# IDP-124

# Protocol V01-124A-301

# A Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Study to Evaluate the Efficacy and Safety of IDP-124 Lotion for the Treatment of Moderate to Severe Atopic Dermatitis in Pediatric and Adult Subjects

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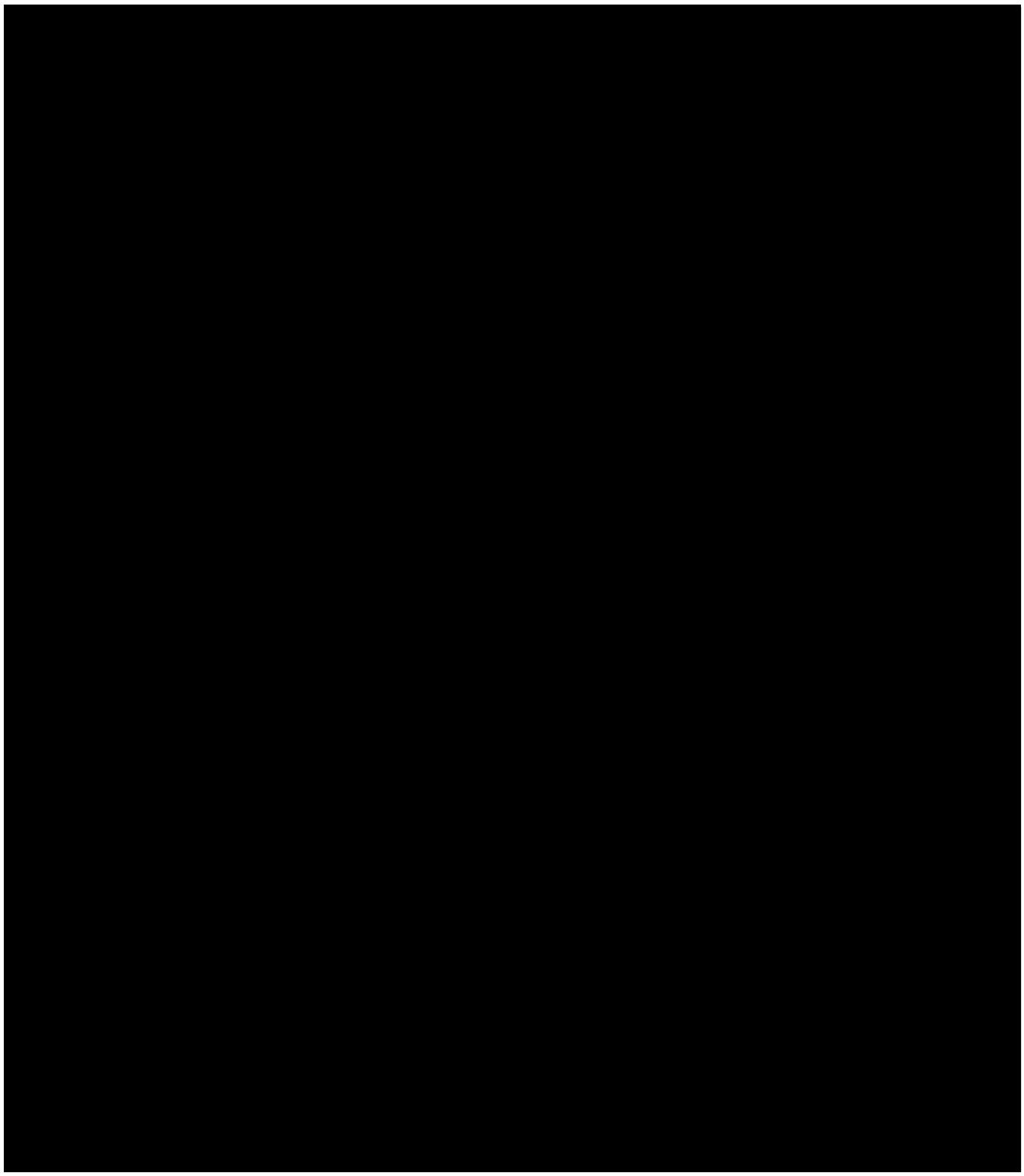
| Development phase of study: | 3 |
| Study design: | Multicenter, randomized, double-blind, vehicle-controlled efficacy and safety study |
| Date: | 25 November 2019 (Amendment 4)<br>28 August 2018 (Amendment 3)<br>18 June 2018 (Amendment 2)<br>02 May 2018 (Amendment 1)<br>16 May 2016 (Original) |
| Sponsor: | Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America, LLC<br>1330 Redwood Way, Suite C<br>Petaluma, CA 94954 |



VALEANT
Research & Development



# Personnel Responsible for Conducting the Study

**A Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Study to Evaluate the Efficacy and Safety of IDP-124 Lotion for the Treatment of Moderate to Severe Atopic Dermatitis in Pediatric and Adult Subjects**

**Contract Research Organization / Medical Monitor**

[redacted]

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## Principal Investigator Protocol Agreement Page

I agree:

- To assume responsibility for the proper conduct of this clinical study at this center and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor.
- That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practices (GCP) and all other applicable regulatory requirements to obtain written and dated approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the study protocol, written informed consent, consent form updates, subject-recruitment procedures (e.g., advertisements), and any other written information to be provided to the subjects, before initiating this clinical study.
- Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study.
- To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies).
- That I am thoroughly familiar with the appropriate use of the investigational products(s), as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current investigator Brochure or equivalent document and approved product label (if applicable).
- To provide sufficient time, and adequate numbers of qualified staff and facilities for the foreseen duration of the clinical study to conduct the study properly, ethically, and safely.
- To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions.

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Principal Investigator (print name)

_____ _____

Principal Investigator (signature) Date

# 2 Synopsis

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| **Name of Sponsor/Company:**<br>Dow Pharmaceuticals Sciences, a Division of Valeant Pharmaceuticals North America, LLC |
| **Name of Investigational Product:**<br>IDP-124 Lotion |
| **Name of Active Ingredient:**<br>Pimecrolimus, 1% |
| **Title of Study:**<br>A Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Study to Evaluate the Efficacy and Safety of IDP-124 Lotion for the Treatment of Moderate to Severe Atopic Dermatitis in Pediatric and Adult Subjects |
| **Number of Clinical Centers:**<br>Approximately 20 investigational centers in North America and Latin America |
| **Objectives:**<br>The objectives of this study are to evaluate the efficacy, safety, and tolerability of IDP-124 Lotion for the treatment of moderate to severe atopic dermatitis (AD) in pediatric and adult subjects, 2 years of age and older. |
| **Methodology:**<br>This is a multicenter, randomized, double-blind, parallel group, vehicle-controlled study to evaluate treatment success using a 5-point Investigator Global Assessment (IGA) scale from clear to severe; the improvement of Eczema Area Severity Index (EASI); improvement in total affected body surface area (TBSA); assessment of pruritus (itching) and sleep disturbance; Patient-Oriented Eczema Measure (POEM) from subjects and parents/legal guardians of pediatric subjects; and investigator's assessment of signs and symptoms of AD.<br>The study consists of a 6-week double-blind treatment period and 4-week post-treatment follow-up. Study visits include Screening, Baseline, and Weeks 1, 2, 4, 6, and 10 (subjects will return to the clinic at Week 10 for a post-treatment follow-up visit). At the Screening Visit, subjects or their parents/legal guardians (when applicable) will sign an informed consent/assent form, provide their medical histories, report their previous and concomitant medications/therapies, and be evaluated against the inclusion/exclusion criteria. For all pre-menses females (9 and older) and females of childbearing potential (FOCBP), urine pregnancy tests will be performed at specified visits. An abbreviated physical exam will be performed, vital signs measured (sitting blood pressure, respiration, pulse, and temperature), and blood and urine specimens will be collected for serum chemistry, hematology, and urinalysis evaluations (and serum pregnancy for all pre-menses females [9 and older] and females of childbearing potential). During this visit, the investigator will perform the IGA, evaluate the subject for TBSA affected by AD, and assess the subject for other signs and symptoms of AD.<br>At the Baseline Visit, prior to being evaluated by the investigator and study staff, subjects or parents/legal guardians (if applicable) are to complete the POEM. At this visit, medical histories and concomitant medication /therapy use will be updated, and the inclusion/exclusion criteria will be confirmed. Adverse events since the Screening Visit will be assessed, and all pre-menses females (9 and older) and FOCBP will have urine pregnancy tests performed. During the Baseline Visit, the IGA, EASI, Pruritus and Sleep Disturbances assessment, and Subject Assessment scale will be completed, and the investigator will evaluate the subject for other signs and symptoms of AD. |

After confirming eligibility at the Baseline Visit, subjects will be randomized using the interactive response technology (IRT) in a 2:1 ratio to receive either IDP-124 Lotion or IDP-124 Vehicle Lotion. Randomized Subjects or parents/legal guardians of pediatric subjects will apply the first administration of the assigned study drug to the affected areas of the skin (as identified in a body diagram in the source documentation) at the investigational center under the supervision of designated study personnel. Subjects will receive the study drug and given verbal and written instructions for treatment application. Specifically, the subjects will be instructed to apply the lotion to the affected areas twice daily, at approximately the same time each day, 12 hours apart. The subjects will also receive diaries, with instructions to complete a record of all applications and to note any missed applications of the study drug. In addition, at selected sites, standardized photography will be performed at Baseline and Weeks 2, 4, 6 and 10.

Throughout the study, safety will be assessed by reviewing the occurrence of adverse events (AEs), assessing vital sign measurements and abbreviated physical examination findings, and noting any additions or changes in concomitant medication uses. Blood and urine samples will be collected at Screening and Week 6 visits for routine safety laboratory evaluations (and serum pregnancy for pre-menses females [9 and older] and FOCBP); and urine pregnancy tests will be obtained for all pre-menses females (9 and older) and FOCBP at each study visit (with the exception of Week 1). Efficacy assessments of the IGA, EASI, Pruritus and Sleep Disturbances, TBSA affected by AD, Subject Assessment, and evaluation for signs and symptoms of atopic dermatitis will be performed throughout the study. In addition, the POEM will be completed by the subjects/parents/legal guardians at Week 6 and Week 10.

**Number of Subjects Planned:**

Approximately 348 subjects will be randomized 2:1 to the following treatment groups:

- 232 subjects to IDP-124 Lotion, twice daily application
- 116 subjects to IDP-124 Vehicle Lotion, twice daily application

**Inclusion Criteria:**

1. Male or female at least 2 years of age and older.
2. Written and verbal informed consent must be obtained; subjects less than age of consent must sign an assent (as required per IRB/IEC guidelines) for the study and a parent or a legal guardian must sign the informed consent (if subject reaches age of consent during the study they should be re-consented at the next study visit).
3. Nonimmunocompromized male or female who failed to respond adequately to other topical prescription treatment for AD or for whom those treatments are not advisable.
4. Clear diagnosis of AD fulfilling the diagnostic criteria of Hanifin and Rajka[13] that affects ≥ 5% of TBSA (see Appendix 17.4 for full list of diagnostic criteria to reference); subject should have had a diagnosis of AD for at least 3 months; ie, determined by subject-reported or parent-reported duration of subject experiencing itchy and dry skin for 3 months or longer (at Screening and Baseline visits).
5. Subject must have a score of 3 (moderate) or 4 (severe) on the IGA scale at the Screening and Baseline visits.
6. Subjects must be willing to comply with study instructions and return to the clinic for required visits; subjects under the age of consent must be accompanied by the parent or legal guardian at the time of assent/consent signing.

**Exclusion Criteria:**

1. Females who are pregnant, breast feeding, or who wish to become pregnant during the study period. Women of childbearing potential and females that are pre-menses (9 and older) must be willing to practice effective contraception for the duration of the study. (Effective contraception is defined as stabilized on oral contraceptive for at least 3 months, IUD, condom with spermicidal, diaphragm with spermicidal, implant, Nuvaring, injection, transdermal patch or abstinence.) Females on birth control must have taken the same type for at least three months prior to entering the study and must not change type during the study. Those who have used any hormonal contraception in the past must have discontinued usage at least three months prior to the start of the study.
2. Active cutaneous bacterial or viral infection in any treatment area at Baseline (e.g., clinically infected AD).
3. Sunburn, extensive scarring, extensive tattoo, or pigmented lesion(s) in any treatment area at Baseline, which would interfere with evaluations.
4. History of confounding skin conditions (e.g., psoriasis, rosacea, erythroderma, or ichthyosis [other than ichthyosis vulgaris]).
5. History or presence of:
    a. Basal/squamous cell carcinoma of skin and/or melanoma treated within the past 2 years
    b. carcinoma of cervix effectively treated less than 5 years ago
    c. immunological deficiencies or diseases, HIV, or serious recurrent infection
    d. clinically significant severe renal insufficiency or severe hepatic disorders
6. Current serious infection (including any skin infection).
7. Failure to respond to topical pimecrolimus/tacrolimus.
8. Use within 1 month prior to Baseline and/or expected use during the study:
    a. oral or injectable corticosteroids
    b. ultraviolet (UV) A/UVB therapy
    c. psoralen plus UVA therapy
    d. tanning booths
    e. nonprescription UV light sources
    f. systemic immunomodulators (except biologics, see #14(a)) or immunosuppressive therapies
    g. interferon
    h. cytotoxic drugs
    i. oral tacrolimus
9. Use within 14 days of Baseline and/or expected use during the study (in the affected area(s)):
    a. medicated topical products (e.g., containing urea, salicylic acid, ammonium lactate)
    b. topical antibiotics
    c. topical calcipotriene or other vitamin D preparations (stable dose of Vitamin D is allowed)
    d. topical retinoids
    e. topical antihistamines
    f. topical corticosteroids (other than hydrocortisone 1%, see #12)
    g. nonsteroidal topical prescription products for atopic dermatitis (e.g., Eucrisa)
    h. other topical prescription products
        - inhalation steroids and/or systemic antihistamines are allowed, as long as subjects are on stable dose for at least 2 weeks before Baseline

10. Subjects who are on an unstable dose of opioids, or who plan to start using opioids during the course of the study (stable dose is allowed, as long as it remains unchanged during the course of the study).
11. Use of systemic/oral antibiotics within 14 days of Baseline visit (oral antibiotics are permitted during the study [postbaseline]).
12. Use of 1% hydrocortisone cream within 3 days prior to Baseline and/or expected use during the study (in the affected area(s)).
13. Use of any nonmedicated topical product (e.g., sunscreens, lotions, creams, bland emollients) the morning of the Baseline Visit.
14. Has received systemic treatment for the skin, including but not limited to the following:
    a. For existing and new biologic agents (e.g., Stelara, Dupixent), should not be used within at least 3 months prior to Baseline
    b. Oral psoriasis medications (e.g., Otezla) should be considered systemic therapies and should not be used within at least 4 weeks prior to Baseline
15. Has received treatment with any investigational drug or device within 60 days or 5 drug half-lives (whichever is longer) prior to the Baseline Visit, or is concurrently participating in another clinical study with an investigational drug or device.
16. Subjects with a known hypersensitivity to pimecrolimus or any other ingredients in the study medication.
17. Subjects who are not willing to minimize or avoid excessive natural and artificial sunlight exposure during treatment.
18. Subjects who are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
19. Subjects with any underlying disease that the investigator deems uncontrolled, and poses a concern for the subjects safety while participating in the study.
20. Subjects who have a planned surgical or medical procedure that will overlap with participation in the study.

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| **Investigational Product, Dosage, and Mode of Administration:**<br>**Investigational Product and Dosage:** IDP-124 Lotion (Pimecrolimus, 1%)<br>**Mode of Administration:** Subjects and parents/legal guardians, when applicable, will be instructed to apply the study drug as a thin layer twice daily at approximately the same time each day and 12 hours apart to affected areas of the skin (see Appendix 17.1 for subject and parent/legal guardian instructions). The first administration of the assigned study drug will be applied to the affected areas of the skin at the investigational center at the Baseline visit, under the supervision of designated study personnel. Study drug will continue to be applied for the duration of the 6-week treatment period even if complete clearing of the affected areas is observed. On study visit days, subjects will apply one dose of study drug at the investigational site.<br>New areas of the skin that become affected during the study may be treated with study drug. The subject or parent/legal guardian may begin study drug application to new lesion/s without the investigator's confirmation, and must inform the investigator of new lesion treatment at their next study visit.<br>Bland emollients, such as CeraVe®, Eucerin®, or Aquaphor®, may be applied during the study at the discretion of the subject and/or parent/legal guardian, and investigator. Appendix 17.2 provides an example list of allowable bland emollients to be used during the study. Subjects will be instructed to apply the emollient (if needed) 20-30 minutes after study drug application. If subjects have been using bland emollients during the Screening period, they will be reminded to refrain from use on the morning prior to the Baseline Visit<br>Subjects may gently wash (e.g., take a bath or shower) the areas of treatment shortly before the application of study drug. Subjects should allow the skin to dry completely before application of the study drug. After application, the treated skin should not be washed for at least 3 hours.<br>Subjects will be instructed to record study drug treatment of affected areas identified at Baseline, new lesions during the study (if applicable), and bland emollient applications (if applicable) in the study diary each day. |
| **Duration of Treatment:**<br>6 weeks, twice daily |
| **Reference Therapy, Dosage and Mode of Administration:**<br>**Reference Therapy:** IDP-124 Vehicle Lotion (Vehicle)<br>**Mode of Administration:** Identical to the investigational product |

**Criteria for Evaluation:**

**Primary Efficacy:**

The primary efficacy variable is the IGA score at Week 6. Success of treatment is defined as achieving clear to almost clear (i.e., a score of 0 or 1) and at least a 2-grade improvement in the IGA score at the end of treatment compared with Baseline.

**Secondary Efficacy:**

The secondary efficacy variables are the following:

- Dichotomized IGA score at Week 4 where treatment success is defined as achieving clear to almost clear (i.e., score of 0 or 1) and at least a 2-grade improvement in the IGA from Baseline.
- The percentage of subjects with EASI 75 (at least a 75% reduction) at Week 6 where the EASI score is defined as a composite score based on the evaluated severity of 4 key signs of AD (i.e., erythema, infiltration/papulation, excoriation, and lichenification), and the extent of disease in each of the 4 body regions (i.e., head/neck, trunk, upper limbs, and lower limbs).
- The percentage of subjects with EASI 75 (at least a 75% reduction) at Week 4.
- Dichotomized IGA score at Week 10 where treatment success is defined as achieving clear to almost clear (i.e., score of 0 or 1) and at least a 2-grade improvement in the IGA from Baseline.
- The percentage of subjects with EASI 75 (at least a 75% reduction) at Week 10.
- Percentage of subjects with score of "None" or "Mild" and at least a one-grade improvement from Baseline in the severity of pruritus at Week 2
- Percentage of subjects with score of "None" or "Mild" and at least a one-grade improvement from Baseline in the severity of pruritus at Week 1Dichotomized IGA score at Week 2 where treatment success is defined as achieving clear to almost clear (i.e., score of 0 or 1) and at least a 2-grade improvement in the IGA from Baseline.

**Tertiary Efficacy**

- Percentage of subjects with at least a "2-grade improvement" (based on bandings as defined in the POEM scale) from Baseline in the POEM score at Week 6 – completed by the subject or parent/legal guardian (if applicable) prior to being seen by the investigator or study staff.
- Percentage of subjects with a score of "None" or "Mild" and at least a one-grade improvement from Baseline in the severity of Sleep Disturbance at Weeks 1, 2, 4, 6 and 10 – Overall sleep disturbance in the 24 hours prior to the visit as assessed by the subject and parent/legal guardian (if applicable).
- Percentage of subjects with a score of "None" or "Mild" and at least a one-grade improvement from Baseline in the severity of pruritus at Weeks 4, 6 and 10 – Overall pruritus in the 24 hours prior to the visit as assessed by the subject and parent/legal guardian (if applicable).
- Percentage of subjects with at least a 2-grade improvement from Baseline in the Subjects assessment score at Weeks 1, 2, 4, 6 and 10 – Overall AD disease control over the 7 days prior to the visit as assessed by the subject and parent/guardian using a score of 0 (complete disease control) to 3 (uncontrolled disease).
- Percentage of subjects with at least a 2-grade improvement from Baseline in the other signs and symptoms of AD at Weeks 1, 2, 4, 6 and 10 – Investigators assessment at each visit of hyperpigmentation, hypopigmentation, and dry skin.
- Mean percent change in the affected TBSA at each study visit.

**Safety:**

Safety and tolerability will be assessed throughout the study:

- Monitoring of AEs will be conducted at each study visit.
- Routine clinical laboratory results (hematology, serum chemistry, urinalysis, and serum pregnancy testing for pre-menses females [9 and older] and FOCBP), vital sign measurements (sitting blood pressure, respiration, pulse, and temperature), and abbreviated physical examination findings, will be conducted at Screening and Week 6 study visits.
- Urine pregnancy tests (FOCBP, females 9 and older) will be conducted throughout the study (with the exception of Week 1). If a subject becomes pregnant during the treatment period, the study drug will be discontinued immediately, the subject will be discontinued from the study, and the investigator will notify the sponsor. The pregnancy will be followed to term with the outcome reported to the sponsor.

Subjects will be followed for 4 weeks after either completion or early discontinuation from the study to assess those AEs ongoing at the time of study completion or leading to discontinuation. Description of AEs will include the dates of onset and resolution (if resolved), maximum severity, seriousness, action taken regarding the study drug, corrective treatment, outcome, and the investigator's assessment of causality. Any out-of-range laboratory result that is considered clinically significant by the investigator will be recorded as an AE and should be confirmed by repeat testing at the discretion of the investigator. Clinically significant laboratory abnormalities at any visit will be followed to resolution (return to normal or to the baseline state) or until clinically stable as determined by the investigator.

**Statistical Methods:**

All statistical processing will be performed using SAS® unless otherwise stated. No interim analyses are planned. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation, median, minimum, and maximum. Appropriate inferential statistics will be used for the primary, secondary, and tertiary efficacy variables.

The primary method of handling missing efficacy data will be the method of Markov Chain Monte Carlo multiple imputation. As a sensitivity analysis, the last observation carried forward method will be used (ie, the last available on-therapy observation for a subject will be used to estimate subsequent missing data points). Additionally, a tipping point analysis will be performed for the primary endpoint. No imputations will be made for missing safety data.

A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

*Primary efficacy analysis*: The primary efficacy endpoint will be used to compare twice daily application of IDP-124 Lotion and Vehicle Lotion. The percentage of subjects with treatment success at Week 6 will be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by analysis center.

*Secondary efficacy analysis*: Comparisons of secondary endpoints, will be performed using CMH tests stratified by analysis center. Evaluation of the secondary efficacy variables will use a gated sequential procedure starting with the comparisons in the predefined order as listed above. The process will terminate if a nonstatistically significant value is observed.

*Tertiary efficacy analysis*: For tertiary efficacy endpoints, all but the mean percent change from Baseline in the affected TBSA will be analyzed with the CMH test stratified by analysis center. The analysis of TBSA will use an Analysis of Covariance with factors of treatment and analysis center and a covariate of the Baseline TBSA score. Analyses of tertiary endpoints will be performed without adjusting for multiplicity.

Efficacy analyses will be performed using the intent-to-treat (ITT) population, the Week 6 per protocol (PP) population, and the Week 10 PP population. The ITT analysis set will be considered primary for the evaluation of efficacy. Safety analyses will be performed using the safety population.

All subjects who are randomized and dispensed study drug will be included in the ITT population.

All subjects who are randomized and receive at least 1 confirmed dose of study drug will be included in the safety population.

All subjects in the ITT population who complete the Week 6 visit without any major protocol violations will be included in the Week 6 PP population. The Week 6 PP population will include subjects in the ITT population who do not meet any of the following criteria:

- Violated the inclusion/exclusion criteria;
- Used an interfering concomitant medication prior to Week 6;
- Did not attend the Week 6 visit;
- Missed more than 1 post baseline study visit prior to Week 6;
- Have not been compliant with the dosing regimen (i.e., subjects must apply 80% - 120% of the expected applications of study medication during participation in the study);
- Out of visit window at the Week 6 visit by more than ± 5 days

Subjects who discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect (and/or worsening of condition) will be included in the Week 6 PP population.

All subjects in the Week 6 PP population who complete the Week 10 visit without any major protocol violations will be included in the Week 10 PP population. Specifically, the Week 10 PP population will include subjects in the Week 6 PP population who did not meet any of the following criteria:

- Used an interfering concomitant medication between Week 6 and Week 10
- Did not attend the Week 10 visit
- Out of visit window at the Week 10 visit by more than ± 5 days

Subjects that discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect will be included in the Week 10 PP population.
Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

**Sample Size Calculations:**

Power calculations were computed using the IGA efficacy results from the Pimecrolimus Cream, 1% (Elidel) New Drug Application 21-302. Considerations were given the change in expected entry level severity of the current study. Specifically, moderate to severe subjects enrolled in pivotal Elidel studies were used for analyses. Nquery Advisor Version 7.0 with the Fisher's exact test option was used to calculate the power using a two-sided test with an alpha of 0.05. Overall, 232 IDP-124 Lotion-treated subjects and 116 Vehicle Lotion-treated subjects will have greater than 95% power to detect a statistically significant outcome for a two-sided test with an alpha level of 0.05.

# 3 Table of Contents

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# 4 List of Abbreviations and Definitions of Terms

| Abbreviation or Specialist Term | Definition or Explanation |
|---|---|
| AD | atopic dermatitis |
| AE | adverse event |
| CBC/Diff | complete blood count/differential |
| CMH | Cochran Mantel-Haenszel |
| CRO | Contract Research Organization |
| EASI | Eczema Area Severity Index |
| eCRF | electronic case report form |
| ELIDEL Cream | ELIDEL® (pimecrolimus) cream, 1 % |
| ET | early termination |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonisation |
| IDP-124 Lotion | pimecrolimus Lotion, 1% |
| IEC | Independent Ethics Committee |
| IGA | Investigator's Global Assessment |
| IRB | institutional review board |
| IRT | Interactive response technology |
| ITT | intent-to-treat |
| LOCF | last observation carried forward |
| MCMC | Markov Chain Monte Carlo |
| MedDRA | Medical Dictionary for Regulatory Activities |
| POEM | Patient-Oriented Eczema Measure |
| PP | per protocol |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| TBSA | total body surface area |
| TEAE | treatment-emergent adverse event |
| US | United States |
| UV | ultraviolet |

# 5 Introduction

Atopic dermatitis (AD) is a very common chronic dermatosis with a prevalence of 10% to 20% in children and 1% to 3% in adults [1]; AD poses difficult therapeutic challenges and may have a profound effect on a patient's quality of life. The disease gives rise to itching and severely dry skin, and is characterized by an allergic predisposition, pruritus, erythema, oozing, crusting, excoriations, lichenification, sensitivity to allergens/irritants, and a susceptibility to secondary infections [2, 3].

Reactive treatment with topical corticosteroids is the classical paradigm of care, but while these compounds are effective, they are restricted in long-term use by local and systemic side effects. Specifically, the use of topical corticosteroids is associated with potential local and systemic side effects including skin atrophy, telangiectasia, dyspigmentation, suppression of the hypothalamic-pituitary-adrenal axis and the rebound effect. Aside from corticosteroids, there is only a limited armament of topical treatments available for AD, most of which have certain side effects that limit their use.

Ascomycin derivatives, such as pimecrolimus, represent a class of anti-inflammatory macrolactams that inhibit the phosphatase calcineurin [4-6]. Studies on the effect of ascomycin derivatives and other immunophilin ligands in animal models of skin inflammation provided evidence that they are effective in the treatment of skin diseases in humans such as chronic plaque psoriasis, without the well-known side effects of topical corticosteroids [7, 8]. Intensive studies on structure-activity relationships and comparative pharmacological evaluations resulted in the discovery and development of pimecrolimus [9, 10]. Pimecrolimus selectively acts on cells involved in skin inflammation, targeting T cells and mast cells, and inhibiting the production and release of proinflammatory cytokines.

ELIDEL® (pimecrolimus) Cream, 1% was approved by the Food and Drug Administration (FDA) in 2001 as second-line therapy for the short-term and noncontinuous chronic treatment of mild to moderate AD in nonimmunocompromized adults and children 2 years of age and older who fail to respond adequately to, or are advised against using, other topical prescription treatments. ELIDEL Cream is an innovative therapeutic agent with a mode of action different from topical corticosteroids; the product is generally safe and has been shown to be effective in the treatment of AD.

In order to improve patient satisfaction with use, the sponsor is developing a new formulation of pimecrolimus. This formulation will include the same concentration of the active ingredient as ELIDEL Cream (pimecrolimus 1%), but in a lotion form. It is expected that the safety profile of this new formulation, IDP-124 Lotion, will be similar to that of ELIDEL Cream. Additionally, the sponsor proposes to evaluate IDP-124 Lotion in patients with

moderate to severe AD in order to establish the safety and efficacy of the product for use in patients for whom there is no approved alternative. In this way, IDP-124 Lotion will enhance and extend the available therapeutic options for patients with AD.

The current clinical study is designed to evaluate the efficacy, safety, and tolerability of IDP-124 Lotion for the treatment of moderate to severe AD in pediatric and adult subjects.

# 6 Study Objectives and Purpose

The objectives of this study are to evaluate the efficacy, safety, and tolerability of IDP-124 Lotion for the treatment of moderate to severe AD in pediatric and adult subjects.

# 7 Investigational Plan

## 7.1 Investigators and Study Administrative Structure

Approximately 20 investigational centers are planned to participate in this study. Each clinical investigator will be required to provide a copy of his/her curriculum vitae and medical license, complete a financial disclosure statement, and generate a list of study personnel who will be involved in the study, with a summary of their roles and qualifications.

## 7.2 Summary of Study Design

This is a multicenter, randomized, double-blind, parallel group, vehicle-controlled study to evaluate treatment success using a 5-point Investigator Global Assessment (IGA) scale from clear to severe; the Eczema Area Severity Index (EASI); improvement in total affected body surface area (TBSA); assessment of pruritus (itching) and sleep disturbance; Patient-Oriented Eczema Measure (POEM) from subjects and parents/legal guardians of pediatric subjects, and investigator's assessment for presence or absence of signs and symptoms of AD.

Approximately 348 subjects, ages 2 and older, are planned for randomization (232 subjects to IDP-124 Lotion and 116 subjects to IDP-124 Vehicle Lotion). The study consists of a 6-week double-blind treatment period and 4-week, post-treatment follow-up. Study visits include Screening, Baseline, and Weeks 1, 2, 4, 6, and 10 (subjects will return to the clinic at Week 10 for a post-treatment follow-up visit).

At the Screening Visit, subjects or their parents/legal guardians (when applicable) will sign an informed consent/assent form, provide their medical histories, report their previous and concomitant medications, and be evaluated against the inclusion/exclusion criteria. Pre-menses females (ages 9 and older) and all females of childbearing potential will have urine pregnancy tests performed. An abbreviated physical examination will be performed, vital signs measured (sitting blood pressure, respiration, pulse, and temperature), and blood and urine specimens will be collected for serum chemistry, hematology, urinalysis evaluations

and serum pregnancy for pre-menses females (9 and older) and FOCBP. During this visit, the investigator will perform the IGA, evaluate the subject for TBSA affected by AD, and for the other signs and symptoms of AD.

At the Baseline Visit, prior to being evaluated by the investigator and study staff, subjects or parents/legal guardians (if applicable) are to complete the POEM. At this visit, medical histories and concomitant medication use will be updated, and the inclusion/exclusion criteria will be confirmed. Adverse events since the Screening Visit will be assessed, and all pre-menses females (9 and older) and FOCBP will have urine pregnancy tests performed. During the Baseline Visit, the IGA, EASI, pruritus and sleep disturbance, and subject's assessment of AD will be completed, and the investigator will assess TBSA affected by AD and evaluate the subject for other signs and symptoms of AD.

After confirming eligibility at the Baseline Visit, subjects will be randomized in a 2:1 ratio to receive either IDP-124 Lotion or IDP-124 Vehicle Lotion. Subjects or parents/legal guardians of pediatric subjects will apply the first dose of the assigned study drug to the affected areas of the skin at the investigational center under the supervision of designated study personnel. Subjects will receive the study drug and given verbal and written instructions for treatment application. Specifically, the subjects will be instructed to apply the lotion to the affected areas twice daily, at approximately the same time each day, about 12 hours apart. The subjects will also receive diaries, with instructions to complete a record of all applications (of study drug and bland emollient use) and to note any missed applications of the study drug.

Throughout the study, safety will be assessed by reviewing the occurrence of adverse events (AEs), assessing vital sign measurements and abbreviated physical examination findings (conducted at Baseline and Week 6), and noting any additions or changes in concomitant medication/therapies uses. Blood and urine samples will be collected at Screening and Week 6 visits for routine safety laboratory evaluations and serum pregnancy testing, as applicable, and urine pregnancy tests will be obtained for all pre-menses females (9 and older) and FOCBP at each study visit (except Week 1). Efficacy assessments of the IGA, EASI, Pruritus and Sleep Disturbances, TBSA affected by AD, evaluation for signs and symptoms of AD, and Subject Assessment, will be performed throughout the study. In addition, the POEM (Appendix 17.3) will be completed by the subjects/parents/legal guardians at Baseline, Week 6 and Week 10.

Additionally, at selected sites, standardized photography will be performed on subjects who provide photographic consent, at Baseline, Weeks 2, 4, 6, and 10.

The study design and schedule of assessments is presented in Table 1.

## Table 1: Study Design and Schedule of Assessments

| | Pre-Treatment | Treatment Period | | | | | Post-treatment |
|---|---|---|---|---|---|---|---|
| **Visit** | 1 | 2 | 3 [a] | 4 [a] | 5 [a] | 6 [a] | 7 [a] |
| **Week**<br>**PROCEDURES** | Screening<br>Day −35 to 0 | Baseline<br>Day 1 | Week 1<br>± 2 days | Week 2<br>± 2 days | Week 4<br>± 3 days | Week 6<br>-3/+5 days | Week 10<br>± 5 days |
| Obtain informed consent/assent | X | | | | | | |
| Review medical history | X | X [b] | | | | | |
| Review inclusion/exclusion criteria | X | X [b] | | | | | |
| Review previous therapies | X | X [b] | | | | | |
| Conduct urine pregnancy test (all pre-menses females [9 and older] and FOCBP)[c] | X | X | | X | X | X | X |
| Conduct abbreviated physical examination[d] | X | | | | | X | |
| Obtain vital signs[e] | X | | | | | X | |
| Collect blood and urine samples for hematology, serum chemistry, and urinalysis (including serum pregnancy)[f] | X | | | | | X[g] | |
| Evaluation of TBSA | X | X[h] | X | X | X | X | X |
| Perform IGA | X | X[h] | X | X | X | X | X |
| Photographs (select sites only)[i] | | X | | X | X | X | X |
| Assess other signs and symptoms of AD (hyper/hypopigmentation, dry skin) | | X[h] | X | X | X | X | X |
| Perform EASI assessment | | X[h] | X | X | X | X | X |
| Assess pruritus and sleep disturbance[j] | | X[h] | X | X | X | X | X |
| Subject's assessment of AD | | X[h] | X | X | X | X | X |
| POEM for adult subjects or parents of pediatric subjects[k] | | X[h] | | | | X | X |
| Randomize qualified subjects via IRT | | X | | | | | |
| Review dosing instructions (Appendix 17.1) | | X | X | X | X | | |
| Dispense study drug | | X | | X | X | | |

| | Pre-Treatment | Treatment Period | | | | | Post-treatment |
|---|---|---|---|---|---|---|---|
| **Visit** | 1 | 2 | 3 [a] | 4 [a] | 5 [a] | 6 [a] | 7 [a] |
| **Week**<br>**PROCEDURES** | Screening<br>Day −35 to 0 | Baseline<br>Day 1 | Week 1<br>± 2 days | Week 2<br>± 2 days | Week 4<br>± 3 days | Week 6<br>-3/+5 days | Week 10<br>± 5 days |
| Weigh study drug | | X | X | X | X | X | |
| Dispense subject diary | | X | X | X | X | X[l] | |
| Application of (one of two doses of) study drug in clinic | | X | X | X | X | | |
| Apply study drug[m] | | ◄ | ——— | ——— | ——— | ► | |
| Collect study drug | | | | X | X | X | |
| Collect/review subject diary | | | X | X | X | X | X |
| Review concomitant medications / therapies | | X | X | X | X | X | X |
| Review adverse events | | X | X | X | X | X | X |
| Exit study | | | | | | | X |

Abbreviations: CBC/Diff = complete blood count/differential; EASI = Eczema Area Severity Index; IGA = Investigator's Global Assessment; POEM = Patient-Oriented Eczema Measure; TBSA = total body surface area

a Post-baseline Visits 3-6 are to be scheduled in reference to Visit 2 (Baseline Visit) and within the designated window for each visit. Visit 7 (4-week post-treatment visit) is to be scheduled 4 weeks following Visit 6 and within the designated window.

b Confirmation of evaluations conducted at the Screening Visit.

c For pre-menses females (9 and older) and FOCBP, the urine pregnancy test must be completed at all scheduled visits, as per schedule. Serum pregnancy testing will be completed at Screening and Week 6 only. Subjects with a positive pregnancy test at any time during the study will be discontinued.

d The abbreviated physical examination at the Screening and Week 6 Visits includes height and weight.

e Vital sign measurements include temperature, pulse, respirations, and sitting blood pressure.

f Refer to Appendix 17.5 for a list of analytes that will be analyzed for the blood and urine sample collections.

g Any clinically significant laboratory abnormality present at Week 6 (or Early Termination) is to be followed to resolution or until clinically stable as determined by the investigator.

h Perform assessment prior to study drug application or application of any other approved products on the affected areas.

i For select sites performed photography, include target lesion and full-front/back images (reference photography manual).

j Pruritus and sleep disturbance to be collected based on a 24 hour window prior to assessment.

k The POEM is to be completed by the subject or subject's parent/legal guardian prior to the subject being seen by the investigator or study staff.

l A different subject diary will be dispensed at Week 6 to track blank emollient use only (i.e,. IP use will not be tracked after end of treatment/Week 6).

m On study visit days, subjects will apply their one of the two doses of study drug at the investigational site (i.e., if study visit is in the morning, they will not apply prior to coming in for their study visit). Subject will apply last dose of study drug on the day prior to Week 6 visit.

# 8 Selection and Withdrawal of Subjects

## 8.1 Subject Inclusion Criteria

Subjects meeting all of the following criteria will be eligible for study entry:

1. Male or female at least 2 years of age and older.
2. Written and verbal informed consent must be obtained; subjects less than age of consent must sign an assent (as required per IRB/IEC guidelines) for the study and a parent or a legal guardian must sign the informed consent (if subject reaches age of consent during the study they should be re-consented at the next study visit).
3. Nonimmunocompromized male or female who failed to respond adequately to other topical prescription treatment for AD or for whom those treatments are not advisable.
4. Clear diagnosis of AD fulfilling the diagnostic criteria of Hanifin and Rajka[13] that affects ≥ 5% of TBSA (see Appendix 17.4 for full list of diagnostic criteria to reference); subject should have had a diagnosis of AD for at least 3 months; i.e., determined by subject-reported or parent-reported duration of subject experiencing itchy and dry skin for 3 months or longer (at Screening and Baseline visits).
5. Subject must have a score of 3 (moderate) or 4 (severe) on the IGA scale at the Screening and Baseline visits.
6. Subjects must be willing to comply with study instructions and return to the clinic for required visits; subjects under the age of consent must be accompanied by the parent or legal guardian at the time of assent/consent signing.

## 8.2 Subject Exclusion Criteria

Subjects meeting any one of the following criteria will be excluded from the study:

1. Females who are pregnant, breast feeding, or who wish to become pregnant during the study period. Women of childbearing potential[1] and females that are pre-menses (9 and older) must be willing to practice effective contraception for the duration of the study[2]. (Effective contraception is defined as stabilized on oral contraceptive for at least 3 months, IUD, condom with spermicidal, diaphragm

[1] Pre-menses females and FOCBP include any female who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea > 12 consecutive months; or women on hormone replacement therapy with documented plasma follicle-stimulating hormone level > 35mLU/mL). Even women who are using oral, implanted, or injectable contraceptive hormones, an intrauterine device, barrier methods (diaphragm, condoms, spermicidal) to prevent pregnancy, practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.

[2] Urine pregnancy tests must have a minimum sensitivity of 25mIU HCG/mL of urine and must be performed within 72 hours prior to the start of study drug. Kits will be provided by the CRO/designee.

with spermicidal, implant, Nuvaring, injection, transdermal patch or abstinence.) Females on birth control must have taken the same type for at least three months prior to entering the study and must not change type during the study. Those who have used any hormonal contraception in the past must have discontinued usage at least three months prior to the start of the study.

2. Active cutaneous bacterial or viral infection in any treatment area at Baseline (e.g., clinically infected AD).
3. Sunburn, extensive scarring, extensive tattoo, or pigmented lesion(s) in any treatment area at Baseline, which would interfere with evaluations.
4. History of confounding skin conditions (e.g., psoriasis, rosacea, erythroderma, or ichthyosis, other than ichthyosis vulgaris).
5. History or presence of:
    a. Basal/squamous cell carcinoma of skin and/or melanoma treated within the past 2 years
    b. carcinoma of cervix effectively treated less than 5 years ago
    c. immunological deficiencies or diseases, HIV, or serious recurrent infection
    d. clinically significant severe renal insufficiency or severe hepatic disorders
6. Current serious infection (including any skin infection).
7. Failure to respond to topical pimecrolimus/tacrolimus.
8. Use within 1 month prior to Baseline and/or expected use during the study:
    a. oral or injectable corticosteroids
    b. ultraviolet (UV) A/UVB therapy
    c. psoralen plus UVA therapy
    d. tanning booths
    e. nonprescription UV light sources
    f. systemic immunomodulators (except biologics, see #14(a)) or immunosuppressive therapies
    g. interferon
    h. cytotoxic drugs
    i. oral tacrolimus
9. Use within 14 days prior to Baseline and/or expected use during the study (in the affected area(s)):
    a. medicated topical products (e.g., containing urea, salicylic acid, ammonium lactate)
    b. topical antibiotics
    c. calcipotriene or other vitamin D preparations (stable dose of Vitamin D use is allowed)
    d. topical retinoids

e. topical antihistamines
f. topical corticosteroids (other than hydrocortisone, see #12)
g. nonsteroidal topical prescription products for atopic dermatitis (e.g., Eucrisa)
h. other topical prescription products
    - inhalation steroids and/or systemic antihistamines are allowed, as long as subjects are on stable dose for at least 2 weeks before Baseline

10. Subjects who are on an unstable dose of opioids, or who plan to start using opioids during the course of the study (stable dose is allowed, as long as it remains unchanged during the course of the study).
11. Use of systemic/oral antibiotics within 14 days of Baseline visit (oral antibiotics are permitted during the study [postbaseline]).
12. Use of 1% hydrocortisone cream within 3 days prior to Baseline and/or expected use during the study (in the affected area(s)).
13. Use of any nonmedicated topical product (e.g., sunscreens, lotions, creams, bland emollients) the morning of the Baseline.
14. Has received systemic treatment for the skin, including but not limited to:
    a. For existing or new biologic agents (e.g., Stelara, Dupixent), should not be used within at least 3 months prior to baseline.
    b. Oral psoriasis medications (e.g., Otezla) should be considered systemic therapies and should not be used within at least 4 weeks prior to baseline.
15. Has received treatment with any investigational drug or device within 60 days or 5 drug half-lives (whichever is longer) prior to the Baseline Visit, or is concurrently participating in another clinical study with an investigational drug or device
16. Subjects with a known hypersensitivity to pimecrolimus or any other ingredients in the study medication.
17. Subjects who are not willing to minimize or avoid excessive natural and artificial sunlight exposure during treatment.
18. Subjects who are unable to communicate or cooperate with the investigator due to language problems, poor mental development, or impaired cerebral function.
19. Subjects with any underlying disease that the investigator deems uncontrolled, or poses a concern for the subjects safety while participating in the study.
20. Subjects who have a planned surgical or medical procedure that will overlap with participation in the study.

## 8.3 Subject Withdrawal Criteria

When possible, subjects who discontinue from the study prior to completing the 6-week treatment period should return to the clinical center to perform the assessments scheduled for

the ET visit. If appropriate, discontinued subjects may be placed on other conventional therapy upon request or whenever clinically necessary, as determined by the physician. The End of Study source documents and all relevant data should be entered into the electronic case report form (eCRF) system at the time the subject discontinues from the study.

Reasons for subject withdrawal may include, but are not limited to, the following:

- Progression of AD, as determined by the investigator, which requires treatment with a prohibited therapy
- At the investigator's discretion for safety reasons (e.g., severe adverse reactions or unauthorized concomitant therapy)
- Subject withdrawal
- When the requirements of the protocol are not followed
- When a concomitant therapy likely to interfere with the results of the study is reported or required by the subject (the investigator will report all such information on the source documents/eCRFs and decide, in accordance with the sponsor, whether the subject is to be withdrawn)
- When a subject is lost to follow-up; the investigator (or designee) will try twice to reach the subject by telephone, email and/or text message, and will send a follow-up letter by certified mail before considering the subject as lost to follow-up. These actions will be documented on the End of Study source documents, and a copy of the follow-up letter maintained in the investigator's file
- If a subject becomes pregnant during the treatment period, the study drug will be discontinued immediately, the subject will be discontinued from the study, and the investigator will notify the sponsor. The pregnancy will be followed to term with the outcome reported to the sponsor.

# 9 Treatment Plan

## 9.1 Methods of Assigning Subjects to Treatment Groups

Eligible subjects will be randomized to receive one of the two study products in a ratio of 2:1 (IDP-124 Lotion : Vehicle Lotion). The study center will assign each screened subject a unique 6-digit study number. The number will consist of the 3-digit study center number (pre-assigned by Sponsor/designee) and the 3-digit chronological screening number, starting with 001 (e.g., 101001, 101002). The IRT system will assign the study drug kit to subjects based on a randomization code at Baseline. One kit will be dispensed to the subjects at

Baseline, and Weeks 2, and 4 after accessing IRT, at each visit for kit number assignment, by the designated study center staff. For subjects who require more than one kit of study drug, an option of an unscheduled visit for dispensing study drug at the Week 1 visit will be available in addition to the options of dispensing two kits at Weeks 2 and 4. A study drug log will document the inventory, dispensing, and collection of study drug at each study center. The assigned investigational product is to be applied twice daily beginning on Day 1 for 6 weeks.

## 9.2 Randomization and Blinding

All eligible subjects will be assigned to treatment groups in accordance with a computer-generated randomization schedule prepared by the sponsor's statistical programming group. Approximately 348 subjects are planned for enrollment in a 2:1 ratio in the 2 treatment groups (IDP-124 Lotion or Vehicle Lotion).

This is a double-blinded study in which IDP-124 Lotion or Vehicle Lotion will be packaged and labeled identically. This level of blinding will be maintained throughout the conduct of the study. As a double-blinded study, the investigators, the staff at each investigational center, the sponsor, the clinical monitors, and the subjects will be unaware of the assigned treatment given to each subject. Designated staff at each investigational center will dispense and collect the investigational products as appropriate to minimize inadvertent unblinding.

The treatment assignments for all randomized subjects will be unblinded only after the conclusion of the study. Specifically, the blind will be broken only after: all data are verified, entered into the database, and validated; subject evaluability assessments are performed and entered into the database; and the database is locked.

In case of a medical emergency, the investigator can contact the medical monitor and sponsor (or sponsor designee) to obtain the treatment assignment for an individual subject. The sponsor is to be informed if the randomization code is broken, along with the reasons for unblinding.

## 9.3 Treatment Compliance

Subjects and/or their parents/legal guardians will be dispensed one kit (containing 2 tubes) of study drug at the Day 1 (Baseline), Week 2, and Week 4 study visits (see Section 9.1 for IRT dispensing at these visits). Using a calibrated scale, designated study personnel will weigh and record each tube of study drug within the kit, separately (with cap on) to the nearest tenth of a gram, before dispensing both tubes to the subject and/or their parent/legal guardian. Subjects will be instructed to return their dispensed study drug tubes at the subsequent visits, and weights will be collected. Used, partially used, and unused study drug tubes will be

collected and recorded. Tube weights will be recorded in the individual study drug log and in the appropriate eCRF.

Subjects will also receive diaries, with instructions to complete a record of all applications of study drug and bland emollients, if applicable (Section 10.1.3), and to note any missed applications of the study drug. The study drug application will be in accordance with the body diagram marked with the AD lesions that will be provided to the subjects at the Baseline visit (note: any new lesions as identified by the subject in between study visits should be recorded on the body diagram and treated). Subjects will be instructed to return their completed diary at each visit. Note: a new subject diary will be dispensed at the Week 6 visit, specifically for the off drug period, and will require recording of bland emollient use only; and this diary will be collected at the Week 10 visit. At the Week 1, 2, 4, and 6 study visits, designated study personnel will collect and review the completed diaries for treatment compliance. Any missed doses of study drug should include an explanation for each missed dose. A subject who has deviated from the twice daily dosing regimen will be counseled.

The dates of missed study drug application will be recorded in the appropriate eCRF.

## 9.4 Concomitant Medications / Therapies

Concomitant medications / therapies refer to all medications / therapies used by the subject during the study. During the course of the study, if appropriate, every attempt should be made to keep the dosing and regimen of concomitant medications / therapies constant, and any change to a medication / therapy during the study must be recorded. Information on concomitant medications / therapies (including indication, dosing, and start and stop dates) will be recorded in the source document and on the appropriate eCRF. All concomitant medications / therapies used during the study will be recorded under Concomitant Medications / Therapies source documents and eCRF.

Disease-related (atopic dermatitis) prior medications / therapies (used within 2 years prior to Screening) will be collected/recorded in the eCRF (e.g., Eucrisa, topical corticosteroids, biologics, etc).

All other prior medications / therapies (those used and stopped within 30 days prior to Screening) will be recorded under Prior Medications / Therapies in the eCRF (e.g., aspirin, acetaminophen, birth control pills, vitamins, herbal products, homeopathic preparations).

Concomitant medications / therapies (prescription or over-the-counter) that are considered necessary for the subject's welfare and do not interfere with study assessments and evaluations will be allowed during the study at the investigator's discretion.

### 9.4.1 Prior and Prohibited Concomitant Medications / Therapies

No systemic or topical treatments for atopic dermatitis (except for use of non-medicated allowable bland emollients) should be used during the study. If any prohibited medication is used by the subject, it must be recorded as a protocol deviation. Subjects will be encouraged to limit their exposure to sunlight and avoid tanning beds or sunlamps for the duration of their participation in the study.

The following table outlines the concomitant medications that are prohibited during the study/treatment period.

| Medication | Prohibited Prior to Baseline |
|---|---|
| Systemic treatment for the skin including but not limited to:<br>• Biologic agents (e.g., Stelara, Dupixent)<br>• Oral psoriasis agents (e.g., Otezla) | <br>• At least 3 months prior to baseline visit<br>• At least 1 month prior to baseline |
| Oral or intravenous corticosteroids | 1 month prior to baseline visit |
| Ultraviolet (UV)A/UVB therapy | 1 month prior to baseline visit |
| Psoralen plus UVA therapy | 1 month prior to baseline visit |
| Tanning booths | 1 month prior to baseline visit |
| Nonprescription UV light sources | 1 month prior to baseline visit |
| Systemic immunomodulators (except biologics, see Exc #13(a)) or immunosuppressive therapies | 1 month prior to baseline visit |
| Interferon | 1 month prior to baseline visit |
| Cytotoxic drugs | 1 month prior to baseline visit |
| Oral tacrolimus | 1 month prior to baseline visit |
| Medicated topical products (e.g., containing urea, salicylic acid, ammonium lactate) | 14 days prior to baseline visit |
| Systemic/oral antibiotics* | 14 days prior to baseline visit |
| Topical antibiotics | 14 days prior to baseline visit |
| Calcipotriene/other vitamin D preparations (stable dose of Vitamin D use allowed) | 14 days prior to baseline visit |
| Topical retinoids | 14 days prior to baseline visit |
| Topical antihistamines | 14 days prior to baseline visit |
| Topical corticosteroids (other than hydrocortisone 1%, see Exc #11) | 14 days prior to baseline visit |
| Nonsteroidal topical prescription products for atopic dermatitis (e.g., Eucrisa) | 14 days prior to baseline visit |
| Topical prescription products | 14 days prior to baseline visit |

| Medication | Prohibited Prior to Baseline |
|---|---|
| 1% Hydrocortisone cream | 3 days prior to baseline visit |
| Opioids | Permitted if on stable dose at Screening/Baseline; not permitted if unstable dose |

*Systemic/oral antibiotic use during the study will be permitted at the investigator's discretion.

### 9.4.2 Permitted Medications / Therapies

Non-medicated topical products, such as sunscreen and bland emollients are permitted during the screening and treatment periods, however, subjects should refrain from using these products the morning of the Baseline visit.

Inhalation steroids and inhaled/systemic antihistamines are permitted provided subjects are on a stable dose for at least 2 weeks prior to the baseline visit.

Opioids are permitted provided subjects are on a stable dose and are not willing to change the dose during the course of the study. Unstable dosing or if a subject starts using opioids during the study is not permitted.

Topical or oral antifungals may be used if antifungal treatment is indicated. Topical or oral antiviral therapy also is permitted as required.

## 9.5 Protocol Deviations and Violations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the sponsor and the institutional review board (IRB)/IEC and agreed to by the investigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria.

A protocol violation occurs when there is nonadherence to the protocol that results in a significant, additional risk to the subject, when the subject or investigator has failed to adhere to significant protocol requirements (inclusion/exclusion criteria) and the subject was enrolled without prior sponsor approval, or when there is nonadherence to United States FDA regulations and/or International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline.

The investigator or designee must document and explain in the patients' source documentation any deviations from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol

amendment(s) should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

# 10 Study Drug Materials and Management

The study drug will be provided to the investigational centers by the sponsor (or sponsor designee) and will be dispensed to the subject and their parent/legal guardian (as required) by the pharmacy or an appropriately qualified member of the study staff assigned by the investigator.

All laboratory kits containing materials necessary to collect blood and urine for routine clinical laboratory tests and urine for pregnancy testing will be supplied to the clinical centers by the designated central laboratory.

## 10.1 Study Drug

A description of the study drug is included in Table 2.

**Table 2: Study Drug Identification**

| | Investigational Product | Vehicle |
|---|---|---|
| Study Drug Name | IDP-124 Lotion | IDP-124 Vehicle Lotion |
| Name of Active Ingredient | Pimecrolimus 1% | N/A |
| Manufacturer | Valeant Pharmaceuticals International, Inc.<br>2150 St. Elzear Boulevard West<br>Laval (Quebec), Canada H7L 4A8 | |
| Chemical Name | (1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-2-{(1R,3R,4S)-4-chloro-3-methoxycyclohexyl}-1-methylvinyl]-17-ethyl-1, 14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.0]octacos-18-ene-2,3,10,16-tetraone | N/A |
| Chemical Formula/Molecular Weight | C43H68ClNO11/810.45 g/mol | N/A |
| Therapeutic Category | Anti-inflammatory ascomycin macrolactam derivative | N/A |
| Appearance | White to off white lotion | |
| Packaging | White tube with a white cap | |
| Storage Requirements | Store at 20°C to 25°C (68°F to 77°F)<br>Excursions permitted between $15^0$C and $30^0$C ($59^0$F and $86^0$F) | Store at 20°C to 25°C (68°F to 77°F); same per-mitted excursions |
| Dosing Schedule | Twice a day, for 6 weeks | Twice a day, for 6 weeks |
| Route of Administration | Topical application | Topical application |

### 10.1.1 Packaging and Labeling

Study drug will be packaged and labeled in a manner consistent with the study design and according to a computer generated randomization scheme. For blinding purposes, the investigational product and vehicle lotion will be provided in matching tubes containing 90 g of product. One kit will be provided for each randomized subject at each of the following visits: Baseline, Week 2 and Week 4. Each kit will contain two (2) tubes of either IDP-124 Lotion or Vehicle Lotion and will be dispensed at the noted visits. Designated site personnel will access IRT for kit assignments at each of the dispensing visits listed above.

The label on the study drug kits and individual tubes will contain at minimum the following information:

- Protocol number
- Kit Number
- Tube Number
- Contents
- Space for entry of the subject initials and subject number
- Space for entry of date dispensed
- The sponsor name, Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals N.A., LLC
- The quantity of product (90 grams)
- A statement reading, “For external use only. Avoid contact with eyes and lips.”
- A statement reading, “Store at controlled room temperature 20°C to 25°C (68ºF to 77ºF), with excursions permitted between 15ºC and 30ºC (59ºF and 86ºF)”
- A statement reading, “Caution: New Drug Limited by Federal Law to Investigational Use”

Additional information may be included on the kit and tube labels as necessary.

### 10.1.2 Storage, Handling, and Disposal of Study Drug

Study drug should be stored in a secure area at the investigational center according to local regulations, at controlled room temperature (20°C to 25°C [68ºF to 77ºF]), with excursions permitted between 15°C and 30ºC (59ºF and 86ºF).

Subjects and their parents/legal guardians will be instructed to keep their study drug at room temperature, not to share the study drug with anyone else, and to use it only on the affected areas of the skin as directed by the investigator. Subjects and their parents/legal guardians will be asked to notify the investigational center immediately if a study drug tube is damaged or lost.

All used and unused study drug supplies will be returned to the sponsor (or sponsor designee) for destruction.

### 10.1.3 Treatment Administration

Subjects and their parents/legal guardians will receive both verbal and written instructions (Appendix 17.1) on the application of the study drug. Study drug will be applied as a thin layer to the affected areas of the skin, twice daily at approximately the same time each day and about 12 hours apart. The subject and/or their parent/legal guardian will apply the first dose of study drug at the investigational center during the Baseline Visit under the supervision of designated study personnel. On subsequent study visit days, subjects will apply one dose of study drug at the investigational center, depending on time of study visit (subjects should not apply study drug prior to coming in to the center for their study visit if the scheduled visit is in the morning). All of the remaining study drug doses will be applied at home. Study drug will continue to be applied for the duration of the 6-week treatment period, even if complete clearing of the affected areas has been observed; i.e., all originally identified lesions will continue to be treated even if cleared (refer to Appendix 17.1).

New areas of the skin that become affected during the study may be treated with study drug. The subject or parent/legal guardian may begin study drug application to new lesion/s without the investigator's confirmation. They must record new lesions on the same body diagram provided and in the study diary, and inform the investigator of new lesion treatment at the next study visit.

Non-medicated bland emollients, such as CeraVe®, Eucerin®, or Aquaphor®, may be applied during the study at the discretion of the subject and/or parent/legal guardian, and investigator. Appendix 17.2 provides an example list of allowable non-medicated bland emollients to be used during the study. Subjects will be instructed to apply the emollient (if needed) at least 20-30 minutes after study drug application. If subjects have been using bland emollients during the screening period, they will be reminded not to apply emollients the morning of the Baseline visit. All emollients used should be captured in the source documents and eCRF.

Subjects may gently wash (e.g., take a bath or shower) the areas of treatment shortly before the application of study drug. Subjects should allow the skin to dry completely before application of the study drug. After application, the treated skin should not be washed for at least 3 hours.

## 10.2 Study Drug Accountability

The investigator or designee will be responsible for keeping current and accurate records of the amount of study drug received and dispensed, and its disposition. The study drug must be stored under the appropriate conditions in a secure area and is to be dispensed only to subjects enrolled in the study, in accordance with the conditions specified in this protocol.

During the course of the study, the investigator or designee must maintain an inventory of all study drug dispensed to or returned by the subject, including subject identifiers.

A study drug accountability log will be completed by the investigator or designee to document the receipt, dispensation, and return of study drug tubes.

At the end of the study, the sponsor will provide instructions as to disposition of any remaining used and unused study drug tubes, and any other ancillary supplies.

# 11 Study Procedures and Evaluations

## 11.1 Schedule of Evaluations and Procedures

All subject information and data obtained during the study visit procedures must be recorded in the source documents, applicable study logs, and eCRFs.

### 11.1.1 Screening Visit (Visit 1, Day −35 to 0)

After signing the informed consent/assent, subjects will undergo the screening procedures to confirm eligibility to participate in the study.

The following procedures will be conducted at this visit:

1. Review and explain the nature of the study. Provide a visit schedule with the length of each visit to ensure that the subject can meet the requirements and has adequate transportation.
2. Obtain verbal and written informed consent/assent from the subject and the subject's parent or legal guardian prior to performing any study-related procedures. Provide signed copies of the consent and assent forms to the subject/parent or legal guardian.
3. Assign a 6-digit study number by accessing IRT which includes the 3-digit investigational center number plus a unique 3-digit subject number beginning with 001 (e.g., 101001, 101002, 101003, etc.; in this example site number is 101).
4. Record subject's demographic information (sex, date of birth, age, ethnicity, and race).
5. Record subject's medical history.
6. Collect a detailed history of AD, including an estimated start date, duration, and all previous medications/therapies used for AD treatment within the last 2 years.
7. Review all prior medications (those used within 30 days prior to the Screening Visit) and previous medications used by the subject.
8. Review inclusion/exclusion criteria.

9. Perform a urine pregnancy test[3] for all females who are pre-menses (9 and older) and female subjects of childbearing potential.[4] Exclude the subject if the pregnancy test result is positive.

   **Urine pregnancy testing is mandatory for all female subjects who are pre-menses (9 and older) and females of childbearing potential at Screening, Baseline, and at the Week 2, 4, 6 and 10 study visits. The decision may be made by the investigator to do additional urine pregnancy tests during the course of the study.**

10. Obtain vital sign measurements. Vital signs will be measured after the subject is seated for at least 5 minutes, and will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and oral body temperature (for younger pediatric subjects, aural or temporal temperatures will be allowed provided the same method is used for all study visits).
11. Measure height and weight.
12. Conduct an abbreviated physical examination (excluding urogenital/reproductive systems).
13. Perform an evaluation of the subject's TBSA affected by AD (using diagnostic criteria in Appendix 17.4).
14. Perform an IGA.
15. Collect blood and urine samples for routine safety laboratory analysis (hematology, serum chemistry, urinalysis, and serum pregnancy testing for pre-menses females [9 and older] and FOCBP).[5] Process and ship the samples to the central safety laboratory per instructions provided in the laboratory manual.
16. If eligible to return for the Baseline visit, if applicable, remind the subject to refrain from using nonmedicated topical products (e.g.(e.g., sunscreens, lotions, creams, bland emollients) the morning of the Baseline visit.
17. Schedule subject to return for the Baseline Visit (Visit 2, Day 1).

    **If a subject fails screening, either at the Screening or Baseline visit (prior to first dose of study drug), the subject may be rescreened at a later date.**

[3] Urine pregnancy tests must have a minimum sensitivity of 25 mIU of human chorionic gonadotropin per mL of urine. Urine pregnancy test kits will be provided by the sponsor.

[4] Premenses females and FOCBP include any female who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea for > 12 consecutive months or women on hormone replacement therapy with documented plasma follicle-stimulating hormone levels > 35 mIU/mL). Even women who are using oral, implanted, or injectable contraceptive hormones, an intrauterine device, barrier methods (diaphragm, condoms, spermicidal) to prevent pregnancy, practicing abstinence, or where partner is sterile (e.g., vasectomy) should be considered to be of childbearing potential.

[5] Refer to Appendix 17.5 for a list of analytes that will be analyzed for the blood and urine sample collections.

**Subjects who are rescreened will be assigned a new screening number, must be re-consented, and undergo all screening procedures per protocol**.

### 11.1.2 Baseline Visit (Visit 2, Day 1)

The following procedures will be conducted at this visit:

1. Prior to conducting any evaluations, instruct the subject or their parent/legal guardian to complete the appropriate POEM.
2. Record any AEs (query subjects and their parents/legal guardians, "Are there any changes in your health since the last visit?").
3. Review the safety laboratory test results.

   **If any safety laboratory test results obtained at the Screening Visit, which will be received by the investigator prior to conducting the Baseline Visit, are abnormal and clinically significant as determined by the investigator, the investigator should discuss with the medical monitor whether it is in the subject's best interest to participate in the study prior to enrolling.**
4. Confirm the subject's medical history and prior medication uses.
5. Review all concomitant medications or therapies and new medications / therapies started since the last study visit, including use of bland emollients.
6. Perform a urine pregnancy test for all female subjects who are pre-menses (9 and older) and females of childbearing potential. Exclude the subject if the pregnancy test result is positive.
7. Perform an evaluation of the subject's TBSA affected by AD.
8. Perform an IGA.
9. Perform EASI evaluations.
10. Perform an evaluation of the other signs and symptoms of AD (hyper/hypopigmentation, dry skin).
11. Assess pruritus and sleep disturbance.
12. Instruct the subject or their parent/legal guardian to assess the degree to which the subject's AD was controlled in the 7 days immediately prior to the visit (i.e., the subject's assessment of AD).
13. Review inclusion/exclusion criteria. If the subject continues to meet all inclusion criteria and none of the exclusion criteria, randomize the subject by accessing the interactive response technology (IRT) system.
14. *At select sites only* – obtain standardized representative photos (refer to the study-specific photography manual for further details). Photos taken will include a target lesion and full front/back images (please refer to photography manual for details).

15. Obtain the IRT-assigned study drug kit (containing two tubes), remove and weigh the tubes (individually) to be dispensed to the nearest tenth of a gram, and complete the study drug accountability record. Dispense both tubes to the subject and/or their parent/legal guardian and review the dosing instructions.
16. Instruct the subject and their parent/legal guardian on diary completion and dispense diary. The subject, or parent/legal guardian as necessary, will record daily study drug applications and if applicable, bland emollient applications.
17. The subject or their parent/legal guardian will apply the first dose of study drug in the investigational center. Instruct the subject and their parent/legal guardian in the proper application technique for the study drug and provide the appropriate Subject Instruction Sheet with dosing instructions (Appendix 17.1).
18. Record any AEs following the initial treatment application.
19. Remind the subject, or parent/legal guardian, to refrain from applying the study drug and non-medicated topical products (e.g., sunscreens, lotions, creams, bland emollients) the morning of the next study visit.
20. Schedule the next study visit (Visit 3 [Week 1]) in 7 days (± 2 days).

### 11.1.3 Visit 3 (Week 1 [± 2 days]), Visit 4 (Week 2 [± 2 days]), Visit 5 (Week 4 [± 3 days]), and Visit 6/Early Termination (ET) Visit (Week 6 [-3/+5 days])

Visits are to be scheduled in reference to Visit 2 (Baseline). The following procedures will be conducted at these visits:

1. Record any AEs (query subjects and their parents/legal guardians, “Are there any changes in your health since the last visit?”).
2. Review concomitant medications.
3. With the exception of Week 1 (Visit 3), conduct a urine pregnancy test on all pre-menses females (9 and older) and female subjects of childbearing potential (discontinue any subject from the study who has a positive test result).
4. Perform an evaluation of the subject’s TBSA affected by AD.
5. Perform an IGA.
6. Perform EASI evaluations.
7. Perform an evaluation of the other signs and symptoms of AD (hyper/hypopigmentation, dry skin).
8. Assess pruritus and sleep disturbance.
9. Instruct the subject or their parent/legal guardian to assess the degree to which the subject’s AD was controlled in the 7 days immediately prior to the visit (i.e., the subject’s or parent’s/legal guardian’s assessment of AD).

10. At Visits 4, 5, and 6 (Weeks 2, 4, and 6) only: Collect used/unused study drug tubes and completed diary from the subject or parent/legal guardian. At Visits 3-6 (Weeks 1, 2, 4 and 6), review the diary for treatment compliance with the subject/ parent/legal guardian.
11. *For select sites only: At Visits 4, 5, and 6 (Weeks 2, 4, and 6) only* – obtain representative photos of the affected area(s). Please refer to the photography manual for details.
12. At Visits 4, and 5 (Weeks 2 and 4) only: Obtain assigned kit using IRT and dispense both tubes of study drug from the assigned kit, weigh the tubes (with the cap on) individually, to the nearest tenth of a gram, and complete the drug accountability log. New tubes of study drug will **not** be dispensed at Visit 3 (Week 1) or Visit 6 (Week 6).
13. At Visit 3 (Week 1) only, re-dispense the two tubes (dispensed at Baseline) and a new diary to the subject and/or their parent/legal guardian. Review the dosing instructions with the subject and/or parent/legal guardian.
14. Remind the subject to refrain from applying the study drug and any allowed non-medicated topical products (e.g., sunscreens, lotions, creams, bland emollients) the morning of the next study visit.
15. At Visit 6 (Week 6) only:
    a. Prior to conducting any evaluations, instruct the subject or their parent/legal guardian to complete the appropriate POEM.
    b. Obtain vital sign measurements.
    c. Measure height and weight.
    d. Conduct an abbreviated physical examination (excluding urogenital/reproductive systems).
    e. After all AD assessments, collect blood and urine samples for routine safety laboratory analysis (hematology, serum chemistry, urinalysis, and serum pregnancy for pre-menses females (9 and older) and FOCBP). Process and ship the samples to the central safety laboratory per instructions provided in the study-specific laboratory manual.
    f. Instruct the subject to continue use of bland emollient (if applicable) between Week 6 and Week 10 (post-treatment phase). Dispense new subject diary with bland emollient use application only.
    g. If this is the ET Visit, record the reason for subject discontinuation from the study in the source document. All other subjects should be scheduled to return for Visit 7 (Week 10 [± 5 days])/ Post-Treatment Follow-Up Visit.

### 11.1.4 Visit 7 (Week 10 [± 5 days])/Post-Treatment Follow-Up Visit

The following procedures will be conducted at this visit:

1. Prior to conducting any evaluations, instruct the subject or their parent/legal guardian to complete the appropriate POEM.
2. Record any AEs (query subjects and their parents/legal guardians, "Are there any changes in your health since the last visit?").
3. Review concomitant medications/therapies.
4. Conduct a urine pregnancy test on all female subjects who are pre-menses (9 and older) and females of childbearing potential.
5. Perform an evaluation of the subject's TBSA affected by AD.
6. Perform an IGA.
7. Perform EASI evaluations.
8. Perform an evaluation of the other signs and symptoms of AD (hyper/hypopigmentation, dry skin).
9. Assess pruritus and sleep disturbance.
10. Instruct the subject or their parent/legal guardian to assess the degree to which the subject's AD was controlled in the 7 days immediately prior to the visit (i.e., the subject's assessment of AD).
11. Collect and review subject diary (dispensed from Visit 6 (Week 6)).
12. *At select sites only* – obtain standardized representative photos (refer to the study-specific photography manual for further details). Photos taken will include a target lesion and full front/back images (please refer to photography manual for details).
13. Exit the subject from the study and complete the end of study eCRFs.

### 11.1.5 Unscheduled Visits

Additional visits may be scheduled, as necessary, to ensure the safety and wellbeing of subjects. All additional examinations should be fully documented in the source documents and on Unscheduled Visit eCRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit range, are not unscheduled visits. In these cases, the visit data will be collected and transcribed to the appropriate scheduled visit eCRF.

## 11.2 Evaluation of Efficacy

### 11.2.1 Total Body Surface Area (TBSA)

The investigator will assess the percent of TBSA (≥5% required to qualify at Screening and Baseline) affected by AD in the allowed treatment areas for each subject at Screening/Baseline and at all study visits. The percent of TBSA will be assessed by utilizing the handprint (palm including all the digits) method.

When utilizing the handprint (palm including all the digits) method to asses a subject's TBSA estimation, the outstretched hand (including all five digits adducted together) equals approximately 1% of the subject's TBSA. NOTE: The subject's hand is the hand of reference and not the assessor's hand.

### 11.2.2 Investigators Global Assessment

At Screening, Day 1 (Baseline), Week 1, 2, 4, 6 and 10 study visits (all visits), AD severity will be determined by the investigator/evaluator based on a global assessment of the inflammatory signs of AD. Evaluations will be graded on a static scale ranging from 0 (clear) to 4 (severe) as shown in the following table:

| Score | Grade | Description |
|---|---|---|
| 0 | Clear | No inflammatory signs of AD (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present. |
| 1 | Almost clear | Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting. |
| 2 | Mild | Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting. |
| 3 | Moderate | Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present. |
| 4 | Severe | Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is wide-spread in extent. Oozing or crusting may be present. |

The primary efficacy variable is the IGA score at Week 6. Treatment success is defined as achieving clear to almost clear (i.e., a score of 0 or 1) and at least a 2-grade improvement in the IGA score at the end of treatment compared with Baseline.

### 11.2.3 Eczema Area Severity Index (EASI)

At Day 1 (Baseline), and Weeks 1, 2, 4, 6, and 10, the EASI will be calculated. The EASI is defined as a composite score based on the evaluated severity of 4 key signs of AD (i.e., erythema, infiltration/papulation, excoriation and lichenification), and the extent of disease in each of the 4 body regions (i.e., head/neck, trunk, upper limbs, and lower limbs).

The area of involvement (affected by inflammation, not including dry skin) of each of the 4 body regions will be determined and represented by a numeric coded value based on a scale from 0 to 6 as described below (the investigator is required to record the affected TBSA on the eCRF).

| Score | Area of Involvement |
|---|---|
| 0 | No eruption |
| 1 | < 10% |
| 2 | 10%-29% |
| 3 | 30%-49% |
| 4 | 50%-69% |
| 5 | 70%-89% |
| 6 | 90%-100% |

The 4 body regions are assessed separately for each sign/symptom, and the average degree of severity of each sign in each of the 4 body parts is assigned a score of 0 (none) to 3 (severe) on a scale that allows half-unit increments.

**Signs and Symptoms of Atopic Dermatitis**

| Score | Grade | Description |
|---|---|---|
| *Erythema* | | |
| 0 | None | No erythema present |
| 1 | Mild | Mild erythema, very light pink |
| 2 | Moderate | Pink red clearly distinguishable perceptible erythema |
| 3 | Severe | Bright red |
| *Infiltration/Papulation* | | |
| 0 | None | None |
| 1 | Mild | Barely perceptible elevation |
| 2 | Moderate | Clearly perceptible but not extensive |
| 3 | Severe | Marked and extensive elevation |
| *Excoriation* | | |
| 0 | None | None |
| 1 | Mild | Scant evidence of excoriations with no signs of deeper skin damage (erosion, crust) |
| 2 | Moderate | Severe linear marks of skin with some showing evidence of deeper skin injury (erosion, crust) |
| 3 | Severe | Many erosive or crusty lesions |
| *Lichenification* | | |
| 0 | None | None |
| 1 | Mild | Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated |
| 2 | Moderate | Definite thickening of the skin with skin marking exaggerated so that they form a visible crisscross pattern |
| 3 | Severe | Thickened indurated skin with skin markings visibly portraying an exaggerated crisscross pattern |

The EASI score (range from 0 to 72) will then be calculated using the following formula:

| **Body Region** | **EASI Score** |
|---|---|
| Head/neck | (E+I+EX+L) x Area x P* |
| Upper limbs | (E+I+EX+L) x Area x P* |
| Trunk | (E+I+EX+L) x Area x P* |
| Lower limbs | (E+I+EX+L) x Area x P* |
| **Total body score =** | **Sum of each region score** |

E = erythema; I = infiltration/papulation; EX = excoriation; L = lichenification
Area is defined on a 7-point scale, where 0 = no eruption, 1 = < 10%, 2 = 10%-29%, 3 = 30%-49%, 4 = 50%-69%, 5 = 70%-89%, 6 = ≥ 90%
* Note that a value is assigned to P based on subject age as shown below:

| | **Head/neck** | **Upper limbs** | **Trunk** | **Lower limbs** |
|---|---|---|---|---|
| ≥ 8 years | 0.1 | 0.2 | 0.3 | 0.4 |
| < 8 years | 0.2 | 0.2 | 0.3 | 0.3 |

### 11.2.4 Pruritus and Sleep Disturbance

At Day 1 (Baseline), and Weeks 1, 2, 4, 6, and 10, the subject or parent/legal guardian of pediatric subjects will assess pruritus and sleep disturbance on 4-point scales as described below. Subjects will be instructed to recall the severity based on a 24-hour period prior to the study visit.

| **Score** | **Grade** | **Description** |
|---|---|---|
| *Pruritus* | | |
| 0 | None | None |
| 1 | Mild | Occasional, slight itching/scratching |
| 2 | Moderate | Constant or intermittent itching/scratching/discomfort which is not disturbing sleep |
| 3 | Severe | Bothersome itching/scratching/discomfort which is disturbing sleep |
| *Sleep Disturbance* | | |
| 0 | None | None |
| 1 | Mild | Occasional, few disturbances |
| 2 | Moderate | Intermittent disturbances |
| 3 | Severe | Bothersome and disruptive disturbances |

In addition, at the Week 1 only visit subjects or parent/legal guardian will be asked to assess how quickly relief of pruritus was experienced (if so) after study drug application was initiated. Assessment will be asked by the study site based on the below scale:

| Window of Relief Experienced (Days) | Yes/No |
|---|---|
| 1 – 2 Days post first application | Yes □ No □ |
| 3 – 4 Days post first application | Yes □ No □ |
| 5 – 6 Days post first application | Yes □ No □ |

### 11.2.5 Other Signs and Symptoms of AD

Other signs and symptoms of AD to be assessed by the investigator will include hyperpigmentation, hypopigmentation, and dry skin. These assessments will be performed at Baseline, and Weeks 1, 2, 4, 6, and 10. The scales used for assessing these signs and symptoms are as follows:

| Score | Grade | Description |
|---|---|---|
| *Hypopigmentation* | | |
| 0 | None | No evidence |
| 1 | Mild | Slight, barely perceptible |
| 2 | Moderate | Definite, evident |
| 3 | Severe | Marked, prominent |

| | | |
|---|---|---|
| *Hyperpigmentation* | | |
| 0 | None | No evidence |
| 1 | Mild | Slight, barely perceptible |
| 2 | Moderate | Definite, evident |
| 3 | Severe | Marked, prominent |
| *Dry Skin* | | |
| 0 | None | No dryness |
| 1 | Mild | Slight, but definite roughness |
| 2 | Moderate | Definite roughness |
| 3 | Severe | Marked roughness |

### 11.2.6 Subject's Assessment

At Day 1 (Baseline), and Weeks 1, 2, 4, 6, and 10, overall AD disease control will also be assessed by the subject or parent/legal guardian of pediatric subjects. The evaluation consists of a 4-point scale in which the degree to which the disease was controlled in the 7 days immediately prior to the assessment is rated.

| Score | Description |
|---|---|
| 0 | Complete disease control |
| 1 | Good disease control |
| 2 | Limited disease control |
| 3 | Uncontrolled disease |

### 11.2.7 Patient-Oriented Eczema Measure (POEM)

At Day 1 (Baseline), Week 6 (end of treatment) and Week 10 (end of study), adult subjects and parents/legal guardians of pediatric subjects will complete the POEM questionnaire (see Appendix 17.3). The POEM questionnaire is a self-assessment of atopic eczema symptoms for adult subjects and for parents/legal guardians of children (11, 12). The POEM for Self-Assessment questionnaire should be completed by subjects ≥8 years of age, and the POEM for Proxy Completion should be completed by parents/legal guardians of pediatric subjects less than 8 years of age.

### 11.2.8 Photography

At select sites, photographs will be taken at Baseline, and at Weeks 2, 4, 6 and 10. Only subjects who provide written photographic consent for photographs will be included in photography. Reference shall be made to the photographic manual for this study.

## 11.3 Evaluation of Safety

### 11.3.1 Clinical Laboratory Tests

Blood and urine samples will be collected for routine safety laboratory tests (hematology, serum chemistry, and urinalysis) at Screening and Week 6 (or ET). Any subject with a screening laboratory abnormality that is determined by the investigator to be clinically significant must be approved for inclusion in the study by the medical monitor. All results will be reported, including abnormal results. Clinically significant changes in lab results from Screening, in the opinion of the investigator, should be reported as AEs. Clinically significant changes present at Week 6 (or ET) are to be followed to resolution or until clinically stable as determined by the investigator. If an AE should require laboratory testing, the results of the test must be obtained by the investigational center and filed in the subject's documentation.

Materials for sample collection will be provided to the investigational centers by the sponsor or central laboratory. Instructions for processing and shipping samples to the central laboratory are contained in the study-specific laboratory manual.

For all female subjects who are pre-menses (9 and older) and females of childbearing potential, a serum pregnancy test will be conducted at Screening and Week 6 (or ET). Additionally, urine pregnancy testing will be performed at all study visits (except Week 1). The results at the Screening and Baseline visits must be negative for a subject to enter the study. Materials for pregnancy testing will be provided to the investigational centers by the sponsor, CRO or central laboratory.

### 11.3.2 Vital Sign Measurements

Measurement of vital signs will be performed at Screening and Week 6 (or ET). After the subjects have been sitting for at least 5 minutes, systolic and diastolic blood pressures, pulse rates, respiration rates, and oral temperatures will be recorded (for younger pediatric subjects, aural or temporal temperatures will be allowed provided the same method is used across all study visits).

### 11.3.3 Physical Examinations

An abbreviated physical examination will be performed at Screening and Week 6 (or ET). Height and weight will be measured at both visits.

### 11.3.4 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the study drug. Thus, AEs include any unfavorable and unintended illness, sign, symptom, clinically significant laboratory test abnormality, or disease temporally associated with the use of a medicinal product that has appeared or worsened during the course of the clinical study, regardless of causal relationship to the study drug(s) under study. The collection of non-serious AEs and serious AEs (SAEs) should begin following the subject's completion of the consent/assent process to participate in the study.

Descriptions of AEs will include the dates of onset and resolution, maximum severity, seriousness, action taken regarding study drug, corrective treatment, outcome, and investigator's assessment of causality. Worsening of disease will not be considered an AE unless it results in discontinuation of the subject from the study or requires medical intervention prohibited by the protocol. All AEs will be followed to resolution or until stable as determined by the investigator.

#### 11.3.4.1 Serious Adverse Events

All AEs will be assessed as either serious or non-serious. An SAE or serious adverse reaction is defined as any untoward medical occurrence that at any dose:

- Results in death

- Is immediately life-threatening, (the term "life-threatening" in the definition of "serious" refers to an event in which the subject is 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 in subject hospitalization or prolongation of existing hospitalization (hospitalization for elective surgery for a baseline condition is not considered an AE)
- Results in persistent or significant disability/incapacity (permanent or substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is a medically important event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the above listed outcomes

Important medical events that may not have resulted in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalization is a criterion for assessment of seriousness. To qualify as serious under the criteria of "hospitalization," a hospital admission of at least a 24-hour period is required. If a subject is retained the emergency room greater than 24 hours, but not admitted for medical care, these cases should be evaluated individually, as criteria such as "medically significant" may also apply.

Hospitalization without a medical AE should not be considered either serious or an AE. Examples include the following:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with worsening of the pre-existing condition (e.g., for work-up of persistent pretreatment lab abnormality)
- Hospitalization for a purpose unrelated to the study (e.g.,, "planned" or elective surgery scheduled prior to study participation) would not ordinarily need to be reported, unless a complication occurred which otherwise caused prolongation of this hospitalization

- Protocol-specified admission or procedure (e.g., cataract surgery required by a study protocol; or overnight stay for monitoring due to protocol required surgery, with no associated SAE or complication necessitating prolonged stay)
- Social admission (e.g., social hospitalization for purposes of respite care)

Note: A spontaneous abortion and elective abortion will be considered as SAEs, and must be reported to the sponsor within 24 hours of your awareness of the event.

#### 11.3.4.2 Assessment of Severity and Causality of Adverse Events

The severity assigned to an AE should be determined by the maximum severity of the AE. The categories described below should be used to estimate the severity of AEs:

- Mild: Awareness of a sign or symptom but is easily tolerated, requires no treatment and does not interfere with subject's daily activities.
- Moderate: Low level of concern to the subject and may interfere with daily activities, but can be relieved by simple therapeutic care.
- Severe: Interrupts the subject's daily activity and requires systemic therapy or other treatment.

The investigator should assess the relationship of the AE, if any, to the study drug as either "Related" or "Not Related."

- **Related:** There is at least a reasonable possibility that the AE/SAE is related to the study drug. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the AE.
- **Not Related:** There is little or no reasonable possibility that the AE/SAE is related to the study drug. This assessment implies that the AE/SAE has little or no temporal relationship to the study drug and/or a more likely or certain alternative etiology exists.

The following should be taken into account when assessing AE/SAE causality:

- Positive temporal relationship to study drug, such as if the study drug was withdrawn and the SAE resolved or the event recurred after re introduction
- If there is a reasonable possibility that the AE is associated with an underlying or concomitant illness
- Possible association with previous or concomitant therapy

- No temporal relationship to the study drug and/or a more likely alternative etiology exists
- If the AE is directly related to study procedures or there is a lack of efficacy

#### 11.3.4.3 Procedures for Reporting Adverse Events and Serious Adverse Events

Throughout the course of the study, efforts will be made by the investigator to remain alert to possible AEs that are either systemic or ocular in nature. The period of observation for collection of AEs extends from the time the subject and parent/legal guardian gives informed consent/assent until the last study visit or discontinuation from the study. The first concern will be the safety of the subject, and appropriate medical intervention will be made.

The investigator or designee will elicit reports (i.e., via direct questioning, observation, clinical evaluation) of AEs from the subject at each study visit and record all AEs. The investigator will document the dates of onset, progress, outcome, and resolution of such AEs. The investigator will also provide an assessment of all AEs as to the severity, causal relationship to study drug, and causal relationship to study protocol.

It is the investigator's responsibility to document all AEs that occur during the study. The AEs should be documented as a single medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject and/or their parent/legal guardian at each study visit.

All AEs occurring after the subject and their parent/legal guardian signs the assent/informed consent through the last study visit must be reported, regardless of whether or not the AEs are considered drug-related. All AEs, whether in response to a query, observed by the clinical center personnel, or reported spontaneously by the subject and/or their parent/legal guardian, will be recorded.

At each visit during the study, the subject will be assessed for the occurrence of new and ongoing AEs. Cutaneous tolerability signs and symptoms that result in the subject's requiring a concomitant therapy or discontinuation from the study will be reported as an AE. The following data will be collected on all AEs and recorded on the appropriate eCRF:

- Event name (diagnosis preferred, if unknown, record the signs/symptoms)
- Onset date and end date
- Maximum intensity (severity)
- Seriousness
- Action taken regarding study drug

- Corrective treatment, if given
- Outcome

In addition, the investigator's assessment of causality will be recorded.

Any SAE must be reported to the sponsor, independent of the circumstance or suspected cause, within 24 hours from the time the event was reported to the investigator. All SAEs experienced from the date of consent through at least 30 days after the last dose of study drug must be reported to the sponsor regardless of the relationship to the study drug or the protocol. For events occurring beyond the minimum 30-day period after the last dose of study drug, or for any timeframe afterward deemed medically significant, only SAEs considered related to the study drug should be reported promptly to the sponsor.

Within 24 hours of notification the investigator will fax or email a completed Serious Adverse Event Report to the following:

Investigators should not wait to receive additional information to document the event before notifying the sponsor of an SAE. If only limited information is initially available, follow-up reports are required. If the investigator becomes aware of any new information regarding a SAE (ie, resolution, change in condition, or new treatment), a new SAE Form must be completed and faxed/emailed to the sponsor within 24 hours. The original SAE Form is not to be altered. The report should be marked as a "follow-up report" and describe whether the event has resolved or continues and how the event was treated. Additional relevant information such as hospital records and autopsy reports should be provided to the sponsor as soon as they are available.

Should the investigator become aware of an SAE (regardless of its relationship to investigational product) that occurs within 30 days after stopping the study drug, the SAE must be reported in accordance with procedures specified in this protocol.

The investigator should take all appropriate measures to ensure the safety of the subjects, notably he/she should follow a subject with an SAE until the event has resolved or the condition has stabilized. This may imply that follow-up will continue after the subject has left the study, and that additional investigations may be requested by the sponsor.

#### 11.3.4.4 Submitting an Expedited Safety Report to the Institutional Review Board

Any suspected unexpected serious adverse reaction warrants expedited reporting. In addition, any unexpected SAE related to a subject's participation in the study (or conduct of study), regardless if the study drug was administered, will be evaluated by Global Safety and Vigilance to determine if expedited reporting is required. For example, an unexpected, serious and severe reaction which could be associated to the study procedures, and which could modify the study conduct requires expedited reporting.

Each expedited safety report will routinely include a brief cover memorandum, the completed MedWatch Form FDA 3500A or Council for International Organizations of Medical Sciences I Form, a clinical analysis of the event with any similar events that have occurred with the product, and any additional pertinent information recommended by the study medical monitor. Once the report is compiled, the clinical center investigator must submit the expedited safety report to the local IRB/IEC within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available. The principal investigator must retain a complete copy of each expedited safety report as it was submitted to the IRB/IEC. It is important that the principal investigator review these expedited reports, as they contain safety information that may be relevant to each of the participating subjects.

### 11.3.5 Pregnancy

All pre-menses females (9 and older) and female subjects of childbearing potential must use an effective method of birth control during the course of the study, in a manner such that risk of contraceptive failure is minimized. Abstinence is allowed as a birth control method.

Before enrolling a female subject of childbearing potential in this clinical study, the investigator must review the following information about study participation:

- Informed consent/assent requirements.
- Contraceptives in current use.

Following review of this information and appropriate counseling for the subject and their parent/legal guardian, the investigator or designee and the subject and parent/legal guardian must sign the assent/informed consent before study enrollment.

During the study, all pre-menses females (9 and older) and female subjects of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period).

If a subject or investigator suspects that the subject may be pregnant prior to study enrollment, the study drug must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive study drug and must not be enrolled in the study. If pregnancy is suspected while the subject is receiving study treatment, the study drug must immediately be withheld until the result of pregnancy testing is known. If pregnancy is confirmed, the study drug will be permanently discontinued and the subject will be followed until the pregnancy comes to term. A Pregnancy Report form will be submitted to the sponsor, initially within 24 hours of the investigator's awareness and at the end of the pregnancy, which includes the outcome of the pregnancy and any complications occurring during the pregnancy or the delivery. If a pregnancy is associated with an SAE, and SAE report form and the pregnancy report form should be submitted to the sponsor within 24 hours of the investigators awareness.

# 12 Statistics

All statistical processing will be performed using SAS® unless otherwise stated. No interim analyses are planned. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation, median, minimum, and maximum. Appropriate inferential statistics will be used for the primary, secondary, and tertiary efficacy variables.

The primary method of handling missing efficacy data will be the method of Markov Chain Monte Carlo (MCMC) multiple imputation. As a sensitivity analysis, the last observation carried forward method (LOCF) will be used (i.e., the last available on-therapy observation for a subject will be used to estimate subsequent missing data points). Additionally, a tipping point analysis will be performed for the primary endpoint. No imputations will be made for missing safety data.

A statistical analysis plan (SAP), describing all statistical analyses will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

### 12.1 Subject Disposition

A tabulation of subject disposition will be provided. The tabulation will include the numbers of subjects who enter the study, complete the study, and discontinue the study. The reasons for discontinuation will be included.

### 12.2 Demographics and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized by treatment group for the intent-to-treat (ITT) population, the Week 6 per protocol (PP) population, and the Week 10 PP population. For continuous variables (e.g., age) comparisons among the 2 treatment groups will be conducted using a 2-way analysis of variance with factors of treatment and analysis center. Ethnicity and race will be analyzed with a Cochran-Mantel-Haenszel (CMH) test stratified by analysis center. Past and current medical conditions, as well as history of disease will not be compared statistically.

### 12.3 Protocol Deviations

All protocol deviations will be reported to the sponsor and recorded throughout the study. A data listing of protocol deviations will be included in the final study report.

### 12.4 Compliance

The extent of exposure to study drug in each treatment group will be summarized by total number of days of exposure, total number of applications, number of missed applications, percentage of expected applications applied and number and percentage of subjects who are compliant. A subject will be considered compliant with the dosing regimen if the subject applied 80% to 120% of the expected number of applications while enrolled in the study.

### 12.5 Efficacy

The primary efficacy endpoint will be the percent of subjects with treatment success, defined as at least a 2-grade improvement from Baseline in IGA score and an IGA score equating to clear or almost clear.

#### 12.5.1 Primary Efficacy

The primary efficacy endpoint will be used to compare twice daily application of IDP-124 Lotion and Vehicle Lotion.

The percentage of subjects with treatment success at Week 6 will be analyzed using CMH test stratified by analysis center.

#### 12.5.2 Secondary Efficacy

The secondary efficacy endpoints will be:

- Dichotomized IGA score at Week 4 where treatment success is defined as achieving clear to almost clear (i.e., a score of 0 or 1) and at least a 2-grade improvement in the IGA. These data will be analyzed using the CMH test stratified by analysis center.
- The percentage of subjects with EASI 75 (at least a 75% reduction) at Week 6 where the EASI score is defined as a composite score based on the evaluated severity of 4 key signs of AD (i.e., erythema, infiltration/papulation, excoriation, and lichenification), and the extent of disease in each of the 4 body regions (i.e., head/neck, trunk, upper limbs, and lower limbs) will be analyzed using the CMH test stratified by analysis center.
- The percentage of subjects with EASI 75 (at least 75% reduction) at Week 4 will be analyzed using the CMH test stratified by analysis center.
- Dichotomized IGA score at Week 10 where treatment success is defined as achieving clear to almost clear (i.e., score of 0 or 1) and at least a 2-grade improvement in the IGA from Baseline. These data will be analyzed using the CMH test stratified by analysis center.
- The percentage of subjects with EASI 75 (at least 75% reduction) at Week 10 will be analyzed using the CMH test stratified by analysis center.
- Percentage of subjects with score of "None" or "Mild" and at least a one-grade improvement from Baseline in the severity of pruritus at Week 2
- Percentage of subjects with score of "None" or "Mild" and at least a one-grade improvement from Baseline in the severity of pruritus at Week 1Dichotomized IGA score at Week 2 where treatment success is defined as achieving clear to almost clear (i.e., score of 0 or 1) and at least a 2-grade improvement in the IGA from Baseline. These data will be analyzed using the CMH test stratified by analysis center.

Evaluation of the secondary efficacy variables will use a gated sequential procedure starting with the comparisons of the first bulleted item and proceeding onto the next item. The process will terminate if a nonstatistically significant value is observed.

### 12.5.3 Tertiary Efficacy

The following tertiary efficacy endpoints will be analyzed to further characterize the treatment effect of IDP-124 Lotion over the Vehicle Lotion.

- Percentage of subjects with at least a "2-grade improvement" (based on bandings as defined in the POEM scale) from Baseline in the POEM score at Week 6 – completed by the subject or parent/legal guardian (if applicable) prior to being seen by the investigator or study staff.
- Percentage of subjects with score of "None" or "Mild" and at least a one-grade improvement from Baseline in the severity of Sleep Disturbance at Weeks 1, 2, 4, 6 and 10 – Overall sleep disturbance in the 24 hours prior to the visit as assessed by the subject and parent/legal guardian (if applicable).

- Percentage of subjects with score of "None" or "Mild" and at least a one-grade improvement from Baseline in the severity of pruritus at Weeks 4, 6 and 10 – Overall pruritus in the 24 hours prior to the visit as assessed by the subject and parent/legal guardian (if applicable).
- Percentage of subjects with at least a 2-grade improvement from Baseline in the Subjects assessment score at Weeks 1, 2, 4, 6, and 10 – Overall AD disease control over the 7 days prior to the visit as assessed by the subject and parent/ guardian using a score of 0 (complete disease control) to 3 (uncontrolled disease).
- Percentage of subjects with at least a 2-grade improvement from Baseline in the other signs and symptoms of AD at Weeks 1, 2, 4, 6 and 10 – Investigators assessment at each visit for hyperpigmentation, hypopigmentation, and dry skin.
- Mean percent change from Baseline in the affected TBSA at each study visit.

All but the mean percent change from Baseline in the affected TBSA will be analyzed with the CMH test stratified by analysis center. The analysis of TBSA will use Analysis of Covariance with factors of treatment and analysis center and a covariate of the baseline TBSA score. Analyses of tertiary endpoints will be performed without adjusting for multiplicity.

### 12.5.4 Pooling Analysis

The clinical study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analysis. Every effort will be made to promote consistency in study execution at each study site. The study is intended to be conducted in a manner such that a minimum of 15 subjects will be randomized and included in the ITT population (i.e., approximately at least 10 subjects in the IDP-124 Lotion arm and at least 5 subjects in the Vehicle Lotion arm) for any investigational site. In the event that there are too few subjects in a treatment arm for an investigator, then the investigator's data will be combined to achieve the desired sample size minimum per treatment arm. The combining of investigator data will be accomplished, within geographic region, by taking the investigator with the smallest enrollment and combining it with the investigator with the largest, restricted to investigational sites that did not meet minimum enrollment. If there is a further need to combine data, then the data of the investigator with the second smallest enrollment will be combined with the investigator's data which had the second largest enrollment, and so on. This process will continue for all investigators who did not have a minimum of 15 subjects enrolled. The process of combining investigator data that have insufficient subjects per treatment arm will result in redefining the groups of investigators for the purposes of

statistical analyses. These combined groups will be referred to as "analysis centers" in the statistical analyses.

The consistency of treatment response will be investigated across the analysis centers subsequent to combining the data as described above. Statistical tests will be conducted to identify if there are extreme analysis centers that could affect the interpretation of common statistical and clinical conclusions. For the purpose of testing consistency of treatment response, the primary efficacy variable will be considered. The percent of subjects with treatment success at Week 6 will be analyzed with a logistic regression with factors of treatment group, analysis center, and the interaction term of treatment group by analysis center. Further examination will follow if the analysis results in a significant interaction term.

In the event that the logistic regression interaction p-value is less than or equal to 0.10, a sensitivity analysis that excludes analysis centers with the extreme efficacy result will be performed to determine the robustness of the treatment effect. On the other hand, if the analysis results in an interaction terms with p-value greater than 0.10, then the conclusions from the pooled data will be considered to be free of the impact of extreme analysis centers.

The first step in conducting a sensitivity analysis is to identify the extreme analysis center or centers that contribute to the statistical significance of the interaction term of the logistic regression. The process involves submitting subsets of analysis centers to the logistic regression and observing the interaction p-value for the subset. Subsets resulting in interaction p-values greater than 0.10 are considered homogeneous.

The search for an extreme analysis center begins by analyzing all subsets that can be created by excluding 1 analysis center. If 1 or more of the subsets result in an interaction p-value greater than or equal to 0.10, then the analysis center excluded from the subset with the largest interaction p-value is deemed the extreme analysis center.

If all subset interaction p-values are less than or equal to 0.10, then the process will analyze the interaction for all subsets that can be created by excluding 2 analysis centers. If 1 or more of these subsets generate interaction p-values larger than 0.10, then the analysis centers excluded from the subset with the largest interaction p-value are deemed the extreme analysis centers.

Thus, the process of identifying the extreme analysis centers will continue in a stepwise manner by first excluding 1, then 2, then 3, etc, analysis centers until the logistic regression interaction p-value exceeds 0.10.

Once the extreme analysis center or centers have been identified, then the treatment p-values of the remaining analysis centers will be computed. Inferences will be drawn from the treatment p-value, as well as any pertinent observations regarding the extreme analysis center

or centers. Additionally, it is noted that this process excludes subjects from the analysis in a nonrandom manner and has an unpredictable impact on the power of the treatment effect test.

In the event that the treatment effect of the remaining subset is not statistically significant, due consideration of the post hoc aspects of the process will be given when the results are interpreted. Conclusions will be presented by the sponsor as appropriate to the findings of the sensitivity analysis.

Prior to investigating the treatment effect within the analysis centers, the magnitude of the site main effect will be investigated to determine if the main site-to-site variability is such that it could mask the analysis center effects. Thus, prior to pooling, the percent of subjects with treatment success at Week 6 will be analyzed with a logistic regression with factors of treatment group, site, and the interaction term of treatment group by site. If the analysis is not computationally feasible due to some sites having very few subjects enrolled, the low enrolling sites will be excluded from the analysis.

### 12.5.5 Sensitivity Efficacy Analyses

#### 12.5.5.1 Analyses Using Last Observation Carried Forward

In the first set of sensitivity analyses, missing IGA values will be imputed using LOCF. Treatment success at Week 6 will be analyzed as it was in the primary analyses. Comparisons will be performed on imputed data using CMH tests stratified by analysis center.

#### 12.5.5.2 Repeated Measures Analysis on Observed Data

As a second sensitivity analysis, treatment success at Week 6 will be analyzed with a repeated measures logistic regression model (generalized estimating equations), with treatment success as the dependent variable and treatment, analysis center and visit (Weeks 1, 2, , 4 and 6) as independent factors.

#### 12.5.5.3 Tipping Point Analysis

A tipping point analysis of the primary endpoint will be performed as a sensitivity analysis for the handling of missing data.

### 12.5.6 Subgroup Analyses

Subgroup analyses will be conducted for the ITT population for the following subgroups: Baseline IGA, sex, age, ethnicity, race, and geographic region. Subgroup analyses will be conducted on the primary efficacy endpoint and will contain only descriptive statistics.

## 12.6 Safety

### 12.6.1 Adverse Events

The primary analysis of safety will be conducted at Week 6. There will be a separate tabulation of the AEs that start in the period post Week 6, to Week 10 visit. All AEs occurring during the study will be recorded and classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All reported treatment-emergent adverse events (TEAEs), defined as any AE with an onset on or after the date of first study drug application, will be summarized by treatment group and will provide the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to study drug. 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.

All information pertaining to AEs noted during the study will be listed by treatment group and subject and will include a verbatim description of the event as reported by the investigator, as well as the preferred term, system organ class, start date, stop date (if stopped), seriousness, severity, action taken regarding the study drug, corrective treatment, outcome, and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided as well as a listing of subjects who reported an SAE.

### 12.6.2 Clinical Laboratory Tests

Changes from Baseline in safety laboratory values (hematology, serum chemistry, and urinalysis) will be summarized with descriptive statistics for each treatment group at all applicable study visits.

Shift tables will be presented for changes in safety laboratory values to summarize laboratory test results collected at Screening and Week 6. Normal ranges established by the central laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at any assessment time point will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by each investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

### 12.6.3 Vital Signs

Changes from Baseline in vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits.

### 12.6.4 Concomitant Medications

All previous therapies and concomitant medications will be classified based on terminology from the World Health Organization Drug Dictionary. Previous therapies and concomitant medications data will be presented in data listings.

## 12.7 Interim Analyses

No interim analyses are planned.

## 12.8 Additional Statistical Considerations

All statistical processing will be performed using SAS® version 9.3 or higher unless otherwise stated. A SAP, describing all statistical analyses, will be provided as a separate document prior to database lock.

### 12.8.1 Analysis Populations

Approximately 348 subjects with moderate or severe atopic dermatitis (defined as an IGA score of 3 or 4) will be enrolled and randomized in the study. With a 2:1 randomization ratio, it is anticipated that:

- Approximately 232 subjects will be randomized to receive IDP-124 Lotion
- Approximately 116 subjects will be randomized to receive IDP-124 Vehicle Lotion

Efficacy analyses will be performed using the ITT population, the Week 6 PP population, and the Week 10 PP population. The ITT analysis set will be considered primary for the evaluation of efficacy. Safety analyses will be performed using the safety population during the treatment period (Baseline to Week 6), and during the post treatment period (Week 6 to Week 10).

All subjects who are randomized and dispensed study drug will be included in the ITT population.

All subjects who are randomized and receive at least 1 confirmed dose of study drug will be included in the safety population.

All subjects in the ITT population who complete the Week 6 visit without any major protocol violations will be included in the Week 6 PP population. The Week 6 PP population will include subjects in the ITT population who did not meet any of the following criteria:

- Violated the inclusion/exclusion criteria
- Used an interfering concomitant medication prior to Week 6
- Did not attend the Week 6 visit
- Missed more than 1 post-baseline study visit prior to Week 6

- Have not been compliant with the dosing regimen (i.e., subjects must apply 80% 120% of the expected applications of study medication during participation in the study)
- Out of visit window at the Week 6 visit by more than ± 5 days

Subjects that discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect (and/or worsening of condition) will be included in the Week 6 PP population.

All subjects in the Week 6 PP population who complete the Week 10 visit without any major protocol violations will be included in the Week 10 PP population. Specifically, the Week 10 PP population will include subjects in the Week 6 PP population who did not meet any of the following criteria:

- Used an interfering concomitant medication between Week 6 and Week 10
- Did not attend the Week 10 visit
- Out of visit window at the Week 10 visit by more than ± 5 days

Subjects that discontinue from the study due to an adverse event related to study treatment or documented lack of treatment effect will be included in the Week 10 PP population.

Prior to breaking the blind, other additional criteria may be added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

The number of subjects in each analysis population will be summarized. Reasons for study withdrawal during the blinded study will be summarized using frequencies and percentages by treatment group.

### 12.8.2 Sample Size Determination

The following power calculations were computed using the IGA efficacy results from the Pimecrolimus Lotion, 1% (Elidel) NDA 21-302. Considerations were given the change in expected entry level severity of the current study. Nquery Advisor Version 7.0 with the Fisher's exact test option was used to calculate the power using a 2-sided test with an alpha of 0.05. The following table presents the efficacy estimates used in this power calculation.

**Percent Dichotomized IGA Success* for Treatment Groups**

| | Pimecrolimus Lotion, 1% | Vehicle |
|---|---|---|
| Percent Success | 23.6% | 6.3% |

* Success was defined as at least a 2-grade improvement from Baseline in the IGA score and an IGA score equating to “Clear” or “Almost Clear”.

Overall, 232 IDP-124 Lotion treated subjects and 116 vehicle lotion treated subjects will have greater than 95% power to detect a statistically significant outcome for a 2-sided test with an alpha level of 0.05.

It was noted that the estimates extracted from the above studies are based on the LOCF method of handling missing values while the proposed Phase 3 analysis will account for missing values using multiple imputations. The power stated above sufficiently exceeds 95% which will compensate for the difference in handling of missing data.

### 12.8.3 Handling of Missing Data

The primary method of handling missing efficacy data will be MCMC multiple imputation. This method does not rely on the assumption of data missing at random. Additionally, imputation will be conducted within each treatment group independently, so the pattern of missing observations in 1 treatment group cannot influence missing value estimations in another.

For each efficacy variable (IGA, EASI, pruritus severity), the following steps will be performed to impute missing data:

1. For each treatment group, create a data set containing subjects with observed values and those needing estimation by MCMC. The missing efficacy data in each data set will be filled in using the MCMC method 5 times to generate 5 data sets. The resulting data set for each treatment group will be combined into 1 complete data set for each imputation.
2. Syntax:

```
proc mi data=datain out=dataout seed=&seed. nimpute=5 <options>;
    where trtpn=(1 or 2);
    mcmc chain=multiple;
    var baseline week1 week2 week4 week6 week10;
run;
```

3. Imputed data will be used to determine dichotomized success/failure values, as appropriate.
4. Each complete data set will be analyzed with the appropriate test (CMH, Analysis of Covariance).
5. CMH statistics will be normalized using the Wilson-Hilferty transformation.
6. The results from these analyses will be combined into a single inference using SAS PROC MIANALYZE.

A total of 6 random seeds will be needed for the multiple imputation process for the primary and secondary variables. The 6 random seeds have been prespecified by using a random number generator:

- Seed for IGA endpoints for IDP-124 = 144527508
- Seed for IGA endpoints for Vehicle = 622040939
- Seed for EASI endpoints for IDP-124 = 1706910659
- Seed for EASI endpoints for Vehicle = 2030081039
- Seed for pruritus severity endpoints for IDP-124 = 1758840189
- Seed for pruritus severity endpoints for Vehicle = 566468919

### 12.8.4 Multicenter Issues

The study will be conducted at multiple investigational centers in North America and Latin America with the intention of pooling the results for analysis.

### 12.8.5 Multiplicity Issues

Not applicable.

### 12.8.6 Windowing Rules

The timing of study visits during the treatment period is relative to Baseline (Day 1). The Week 1 and 2 visits should occur within ± 2 days of the Day 1 visit, and Week 4 visit should occur within ± 3 days of the Day 1 visit, and Week 6 visit should occur within -3/+5 days of the Day 1 visit. The 4-week post-treatment visit, Week 10, should occur within ± 5 days of the Week 6 visit.

## 13 Quality Control and Quality Assurance

This study will be conducted under the sponsorship of Valeant (sponsor), in conformation with all appropriate local and federal regulations as well as ICH guidelines.

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, GCP guidelines, and applicable regulatory requirements. In addition, the sponsor will be responsible for securing agreement from all involved parties to ensure direct access to all study-related clinical centers, source data/documents, eCRFs, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

Central laboratory services will be performed by qualified, licensed facility(ies) that will be listed on the US FDA Form 1572 or equivalent. Copies of all normal values (as applicable),

laboratory certifications, and the director's curriculum vitae will be provided to each investigational center and to the sponsor.

### 13.1 Study Monitoring

The conduct of the study will be closely monitored. Sponsor representatives must be permitted to visit all clinical center locations to assess the data, quality of study performance, and study integrity in a manner consistent with applicable health authority regulations and the procedures described in this protocol.

Prior to the start of the study, the sponsor or its designee(s) will review the protocol, eCRFs, regulatory obligations, and other material or equipment relevant to the conduct of the study with the investigator/sub-investigator/co-investigator and relevant clinical center personnel.

Monitoring visits and telephone consultations will occur as necessary, or per the study monitoring plan, during the course of the investigation to verify the following:

- The rights and wellbeing of subjects are protected
- The conduct of the investigation is in compliance with the currently approved protocol/amendment, ICH GCPs, and IRB/IEC requirements
- The integrity of the data is maintained, including adequate study documentation
- The facilities remain acceptable
- The investigator and clinical center personnel remain qualified and able to conduct the study
- Study drug accountability is documented properly

During the course of the study, if the sponsor determines that an investigator is noncompliant with the study plan and/or applicable regulatory requirements, the sponsor will take action to secure or reinstate compliance. In addition, the sponsor may terminate the investigator's participation in the study if appropriate, or if the investigator remains noncompliant despite the remedial actions of the sponsor.

### 13.2 Audits and Inspections

Interim and End of Study audits of raw data, study files, and the final report may be conducted by the sponsor's quality assurance department or its designee. A certificate attesting to the audit(s) will be issued as applicable. In addition, inspections or on-site audits may be carried out by local authorities. The investigators will allow the sponsor's representatives and any regulatory agency to examine all study records and logs, eCRFs, corresponding subject medical records, study drug dispensing records, study drug storage

area, and any other documents considered source documentation. The investigators agree to assist the representative, if required

### 13.3 Data Quality Assurance

All assessments performed will be accurately documented in the subject's source documents and eCRFs. The investigator or designee will enter the information required by the protocol into the source documents and eCRFs provided by the sponsor or designee. Subjects will be identified in the eCRFs by their assigned subject number and initials only.

The investigators must read the protocol thoroughly and must follow the instructions exactly. Any deviations should be agreed to by prior discussion between the sponsor and the investigator, with appropriate written protocol amendments made prior to effecting the agreed upon changes. Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB/IEC before it may be implemented. No change in the conduct of the study can be instituted without written approval from the sponsor.

## 14 Ethics and Administrative Issues

### 14.1 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, ICH guidelines, GCP guidelines, and in compliance with local and federal regulatory requirements. The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP.

### 14.2 Ethics Review

This protocol, proposed informed consent/assent form and other information to the subjects, and all appropriate amendments, will be properly reviewed, and approved by an IRB/IEC. A signed and dated notification of the IRB/IEC approval will be provided to the sponsor and investigator prior to study initiation. The name and occupation of the chair and members of the IRB/IEC will be supplied to the sponsor. The investigator will provide required progress reports and report all SAEs to the IRB/IEC as required.

Written informed consent/assent, in accordance with local clinical investigation regulations, must be obtained prior to participation in the study. The investigator or designee will discuss the purpose of the study with each subject and their parent/legal guardian and will provide a description of the study drug (including any potential and possible side effects) and the study procedures. Information must be given both in oral and written form. The subject information

provided will be in a language understandable to the subject and their parent/legal guardian and may not include any language that appears to waive any of the subject's legal rights or appears to release the investigator, the sponsor, or the institution from liability or negligence.

The investigator or designee will provide the prospective subject and the subject's parent or legal guardian sufficient time to consider whether to participate, minimizing the possibility of coercion or undue influence and will discuss any questions the subject and/or their parent/legal guardian may have. The investigator or designee will explain to the subject and their parent/legal guardian that participation in the study is voluntary and that withdrawal from the study is possible at any time without detriment to care. The consent must include acknowledgment that medical records and medical data derived from the study may be forwarded to the sponsor or to the responsible authorities or federal authorities.

No subject can enter the study or have any study-related procedures performed before his/her written informed consent/assent has been obtained. Subjects under the age of consent must sign an assent form and their parents/legal guardians must sign the informed consent form. Subjects over the age of consent must sign the informed consent form. At selected sites, subjects and their parents/legal guardians will also provide written consent/assent to obtain optional photographs of the specified areas. The original signed and dated informed consent and assent forms will be retained with the study records, and a copy of the signed forms will be given to the subject and their parent or legal guardian as applicable.

An informed consent/assent template will be supplied by the sponsor to the investigator. Any changes to the informed consent/assent form must be agreed to by the sponsor prior to submission to the IRB/IEC, and a copy of the approved version must be provided to the sponsor after IRB/IEC approval.

### 14.3 Subject Data Protection

Subject data will be protected by ensuring that no captured data contain subject names, addresses, telephone numbers, email addresses, or other direct personally identifying information. It is acknowledged that subject initials, demographics (including birthdates), medical histories, and prior concomitant medication uses, along with the name and address of the enrolling investigator may allow for personal identification of study participants. Other than where necessary to meet regulatory requirements, all data collected in this study will be presented in tabulated (i.e., aggregate) form and listings containing information that could be used to identify an individual subject will not be included in any public disclosures of the study data or the study results.

### 14.4 Financial Disclosure

Financial disclosures will be obtained from all investigators in order to document any potential conflicts of interest.

### 14.5 Essential Documents

The investigator must maintain essential documents during the conduct of the study and retain these documents after the completion of the study in accordance with the sponsor's record retention instructions. The investigator agrees to adhere to the document retention procedures when signing the protocol's Investigator Statement of Approval.

Essential documents include, but are not limited to, the following:

- IRB/IEC approvals for the study protocol, all amendments, informed consent forms, and advertisements
- IRB/IEC annual study review
- IRB/IEC correspondence and reports (e.g., SAE reports, protocol deviations, and safety updates)
- Regulatory documents (e.g., financial disclosure and delegation of authority forms)
- All source documents
- eCRFs
- Subject's signed informed consent/assent form
- FDA Form 1572 or equivalent
- Accountability records for the study drug
- Correspondence from and to the sponsor
- Any other documents relevant to the conduct of the study

In the event that the investigator withdraws from the study (e.g., retirement or relocation), study records will be transferred to a mutually agreed upon designee (e.g., another investigator or IRB/IEC). The investigator will provide notice of such transfer in writing to the sponsor.

### 14.6 Investigator Obligations

The investigators must read the protocol thoroughly, complete and sign the protocol signature page, and must follow the instructions exactly, and adhere to the principles of GCP.

## 14.7 Changes to the Protocol

Any amendment containing major modifications (particularly if it may involve an increased risk to the subjects) will be approved by the IRB/IEC before it may be implemented. No change in the conduct of the study can be instituted without prior written approval from the sponsor.

## 14.8 Confidentiality/Publication of the Study

All the data furnished to the investigator and his/her staff and all data obtained through this protocol will be regarded as confidential and proprietary in nature and will not be disclosed to any third party, except for the US FDA or other regulatory body, without written consent from the sponsor.

The results of the study may be published or presented by the investigator(s) after the review by, and in consultation and agreement with the sponsor, and such that confidential or proprietary information is not disclosed. Prior to submission for publication or presentation, a copy of the final text should be forwarded by the investigator(s) to the sponsor or its designee for review and comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to the sponsor products and activities receive fair, accurate, and reasonable presentation.

## 14.9 Study Termination

The sponsor reserves the right to discontinue the study overall or at a particular clinical center at any time for reasons including but not limited to:

- Emergence of effects that do not justify the benefit/risk relationship to the study population as a whole
- Failure to comply with the protocol, GCP, or any other violation disturbing the appropriate conduct of the study
- Failure to meet enrollment goals overall or at a particular clinical center

If a study is terminated, the sponsor will promptly notify the investigator. After notification, the investigator must contact all participating subjects and their parents/legal guardians within a reasonable timeframe agreed upon by the sponsor. All study materials must be collected and all eCRFs completed to the greatest extent possible.

# 15 Data Handling and Record Keeping

## 15.1 Inspection of Records

Investigators must maintain detailed records on all study subjects who are enrolled in the study or who undergo screening. Data will be recorded in the subject's source documents and in applicable study logs provided by the sponsor. Source documents include subject's medical records, hospital charts, clinic charts, and the investigator's subject study files, as well as the results of diagnostic tests (e.g., laboratory tests). All medical information obtained at each study visit must be recorded in the subject's source documentation in real time as it is collected and then entered onto the eCRF by clinical center personnel.

Subject-completed forms such as diaries and questionnaires are also considered source data. Only subjects are to record information in subject diaries and questionnaires. In no instance, should an investigator or clinical center personnel record any data or make changes to subject-completed forms. The investigator or designee should review subject-completed forms during study visits. If an entry is found to be illegible or a mistake is found (e.g., an incorrect year was recorded), the subject should be instructed to edit the entry by drawing a single line through the original entry, entering the new information, dating, and writing subject's year of birth to acknowledge.

Upon study completion or at any other time specified by the sponsor or designee, the appropriate study documents must be submitted to the sponsor.

Telephone conversations and electronic mail with the subject, the sponsor, or the sponsor's designee concerning the study must be recorded or kept on file.

The investigator will allow representatives of the sponsor's monitoring team, the governing IRB/IEC, the FDA, and other applicable regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's clinic and/or hospital medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness and accuracy of the data being entered onto the eCRF, and compliance with FDA or other regulatory agency regulations.

## 15.2 Case Report Forms

Subject data required by this protocol are to be recorded on eCRFs. Subject data recorded on eCRFs during the study will be documented in a coded fashion. The subject will only be identified by the subject number and by their year of birth if also required. Confidentiality of subject records must be maintained to ensure adherence to applicable local privacy regulations.

The investigator and clinical center personnel will be responsible for completing the eCRFs. The investigator is required to verify that all of the requested information is accurately recorded on the eCRFs. All information requested on the eCRFs needs to be supplied, including subject identification, date(s), assessment values, etc, and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

The study monitor will be responsible for reviewing and verifying the data recorded on the eCRFs, utilizing the original source documentation and will query discrepant findings. The investigator and clinical center personnel will be responsible for answering all queries. The eCRFs will be submitted to the sponsor or its designee(s) for quality assurance review, and statistical analysis.

A copy of the eCRFs will be retained by the investigator at the conclusion of the study, who must ensure that it is stored in a secure place

### 15.3 Retention of Records

The investigator should properly store and maintain all study records in accordance with sponsor directives. All records relating to the conduct of this study are to be retained by the investigator until notified by the sponsor in writing that the records may be destroyed.

# 16 References


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# 17 Appendices

## 17.1 Subject Instruction Sheet

A thin layer of study drug should be applied twice daily at about the same time each day (approximately 12 hours apart) over the affected treatment areas indicated by the investigator for 6 weeks. A body diagram will be provided with your instructions and your study drug at your Baseline visit.

Wash your hands before using the study drug. If you apply study drug after a bath or shower, make sure your skin is dry before application.

Subjects and/or parent/legal guardian will squeeze study drug (about the size of a pea) onto a fingertip and then spread a thin layer of the study drug over the affected treatment area. If necessary, additional pea-sized amounts of study drug may be applied in increments (one pea size gently rubbed over a treatment area at a time) to cover all affected treatment areas. This is to be followed twice a day (at each application) over a 6 week period. Be sure to wash your hands after you apply the product.

Refer to the body diagram to identify and document study drug application in the affected areas. It is important to continue to apply the study drug in all the areas that are identified in the body diagram even if improvement of signs and symptoms are noted.

If new lesions are observed in between study visits, please document the new area(s) on the body diagram and bring with you to the next study visit. The study doctor will review the body diagram and any new lesions with you.

The amount of study drug used by the subjects will be monitored by weighing each newly dispensed study drug container and weighing each returned study drug container at all applicable study visits.

Reminders:

- On study visit days (Weeks 1, 2, 4 and 6) bring your study drug (both tubes regardless of whether they are used or unused), diary and body diagram with you.
- On your Baseline visit the first application of your two daily applications of the study drug will be done at the investigational site. Your second dose of study drug will be applied in the PM (evening).
- On study visit days (Weeks 1, 2, and 4) one of your two daily applications of the study drug will be done at the investigational site. If your study visit is in the AM (morning), please do not apply your first dose of the study drug before your visit. Your second dose of study drug will be applied in the PM (evening).
- Last dose of study drug is applied on the evening prior to Week 6 visit. Do not apply study drug on the day of your Week 6 visit.

- Avoid contact with the eyes, inside the nose, mouth and all mucous membranes including the vagina and the rectum. If contact with eyes occurs, rinse thoroughly with water.
- Do not bathe, shower or swim right after applying the study drug for at least three hours. This could wash off the lotion.
- Tubes of study drug must be returned to the study facility, even if they are empty.
- If you miss any doses, at your next visit inform the study doctor of the date(s) of the missed dose(s).
- Continue to use the same, study doctor approved, cleanser, moisturizer and sunscreen throughout the study.
- Study doctor will approve the use of bland emollients that you may use during the course of the study, if applicable. If you apply the emollients, please wait for 20 to 30 minutes after study drug application.
- You must complete the diary on a daily basis to record study drug applications, including missed doses and bland emollient use (if applicable). You will continue to record this throughout the 6 week treatment period.
- For the follow up period between Week 6 and Week 10, continue to record bland emollient use in your diary (if applicable). Please ensure to bring your study diary back with you on your last visit (Week 10).
- You must not use any other treatment for your atopic dermatitis while you are participating in this study.
- Do not cover the affected areas with any type of dressing, such as gauze.
- THE STUDY DRUG SHOULD BE USED ONLY BY THE PERSON FOR WHOM IT WAS PRESCRIBED and it should be kept out of the reach of others of limited capacity to read or understand.
- DO NOT USE THE STUDY DRUG IN CHILDREN UNDER THE AGE OF 2.
- 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). Do not refrigerate or freeze. Avoid excessive heat or cold.
- Avoid unnecessary sun exposure and tanning booths. Use Investigator-approved sunscreen with at least SPF 15 and wear protective clothing during the day (e.g., hat) if you have to be in the sunlight.
- It is important that you inform the study site about any medications (i.e., prescriptions, over-the-counter medications, street drugs, or herbal medications) that you have taken during the study.

If you have any questions or have a potential research-related side effect or injury you may contact _____ at _____.

## 17.2 Guidelines for Allowable Emollients for Use

Subjects may use the following products as examples of approved products. The Investigator may use his/her discretion on what products each subject may use in the treatment area during the study. Subjects may use the below set of examples or other Investigator approved nonmedicated products on the treatment area. Information regarding products used should be captured in the source document and recorded on the eCRF.

Approved Cleanser Examples:

- CeraVe cleanser
- Cetaphil daily cleaner and gentle cleansing bar
- Purpose gentle cleansing wash

Approved Bland emollients /Moisturizer Examples:

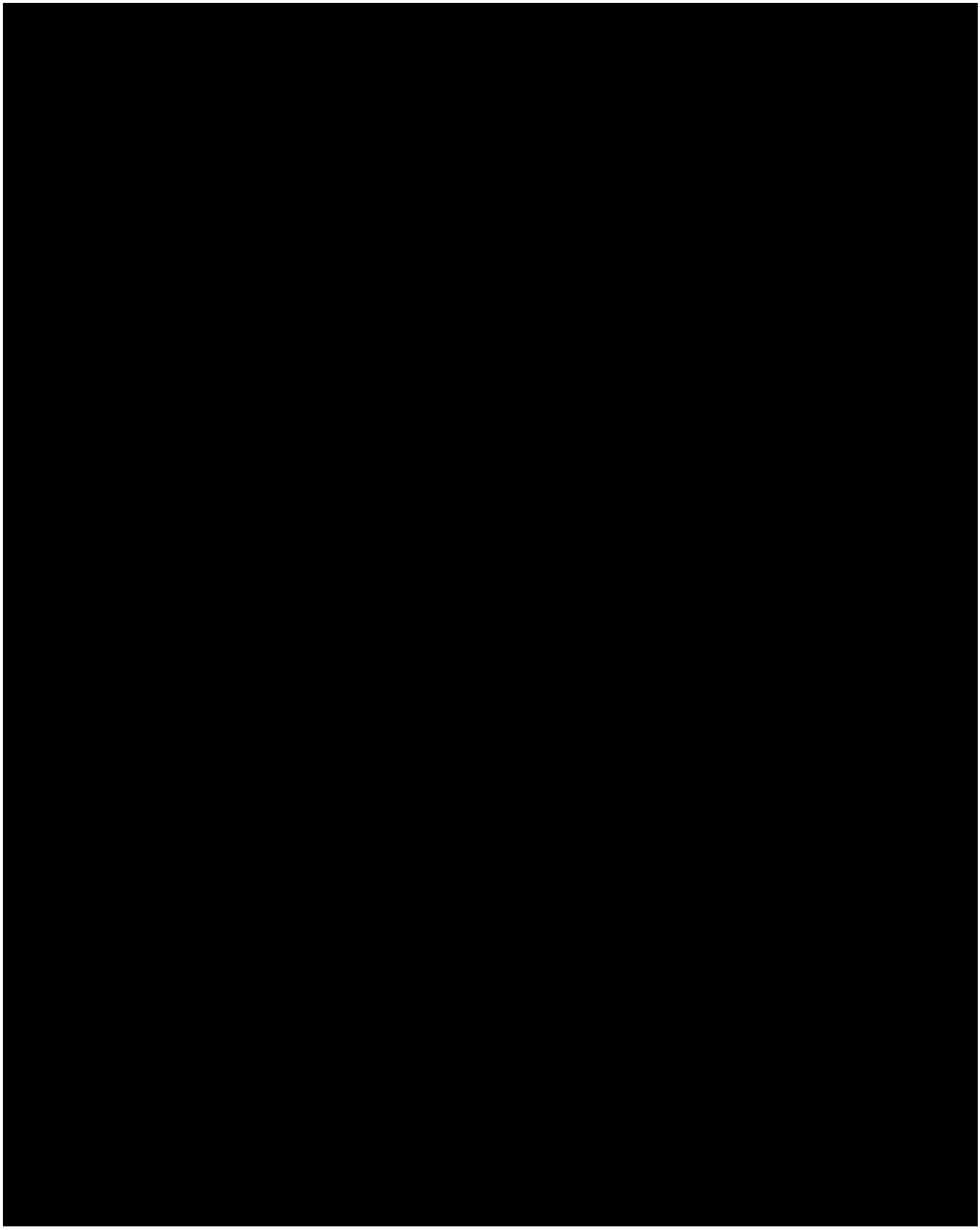
- Aquaphor
- CeraVe Cream or Lotion
- Moisturel cream or lotion
- Nutraderm
- Cetaphil lotion or cream
- Eucerin lotion or cream
- Purpose

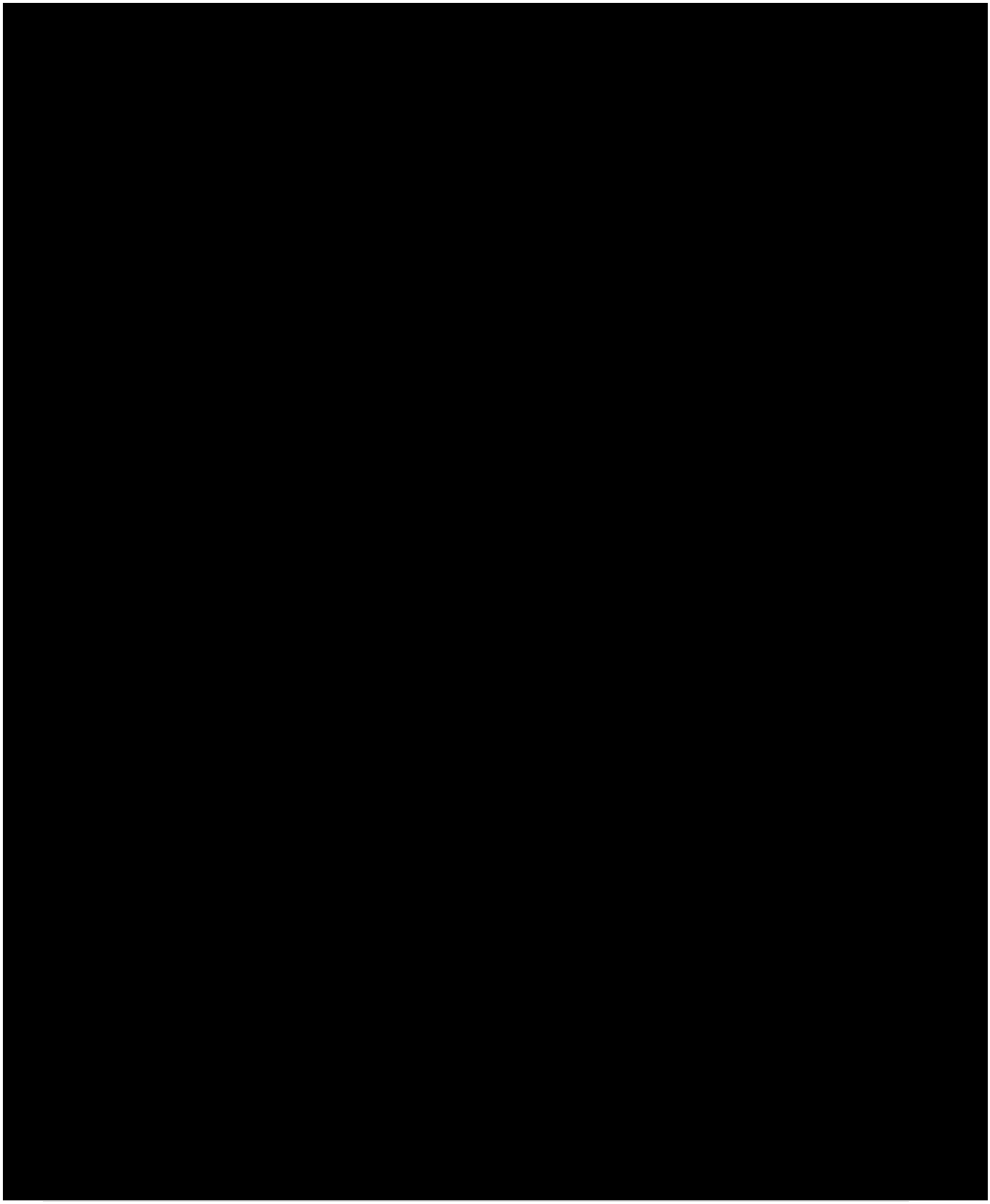
Approved Moisturizer/Sunscreen Combination Product Examples:

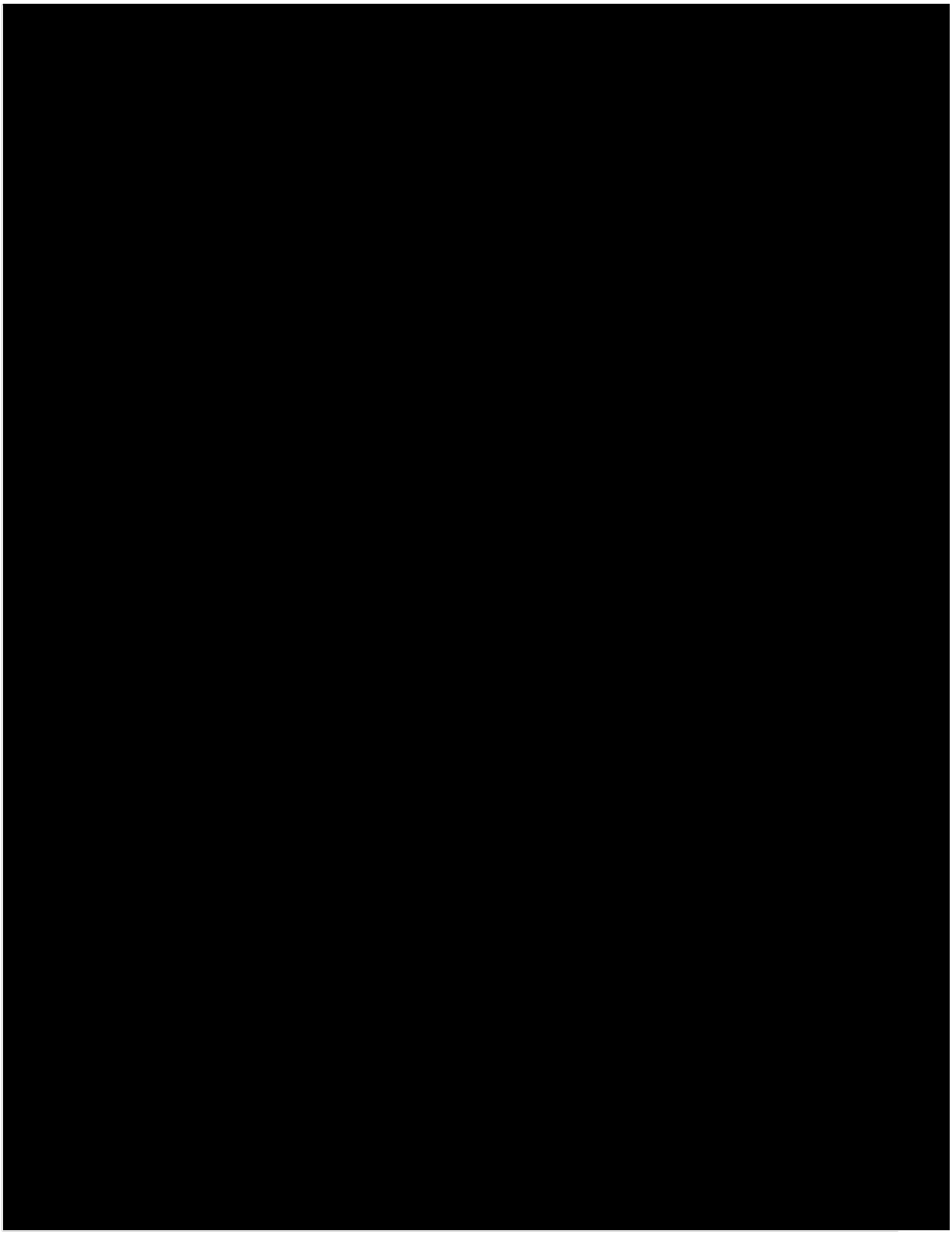
- CeraVe Lotion A.M.
- Olay Complete (SPF 15)
- Neutrogena Health Defense Daily Moisturizer (SPF 30)
- Cetaphil Daily Facial Moisturizer (SPF 15)

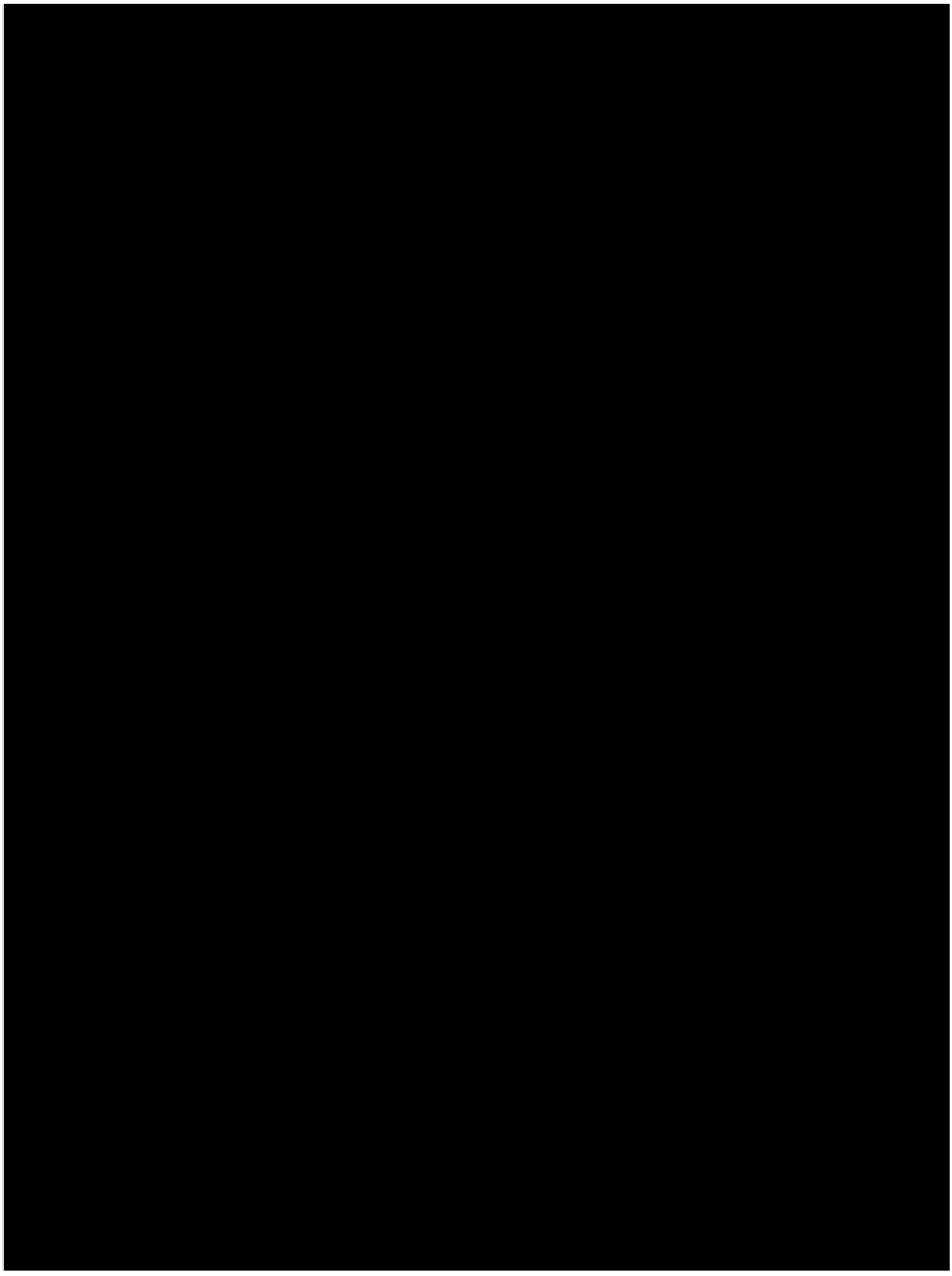
Approved Sunscreen Examples:

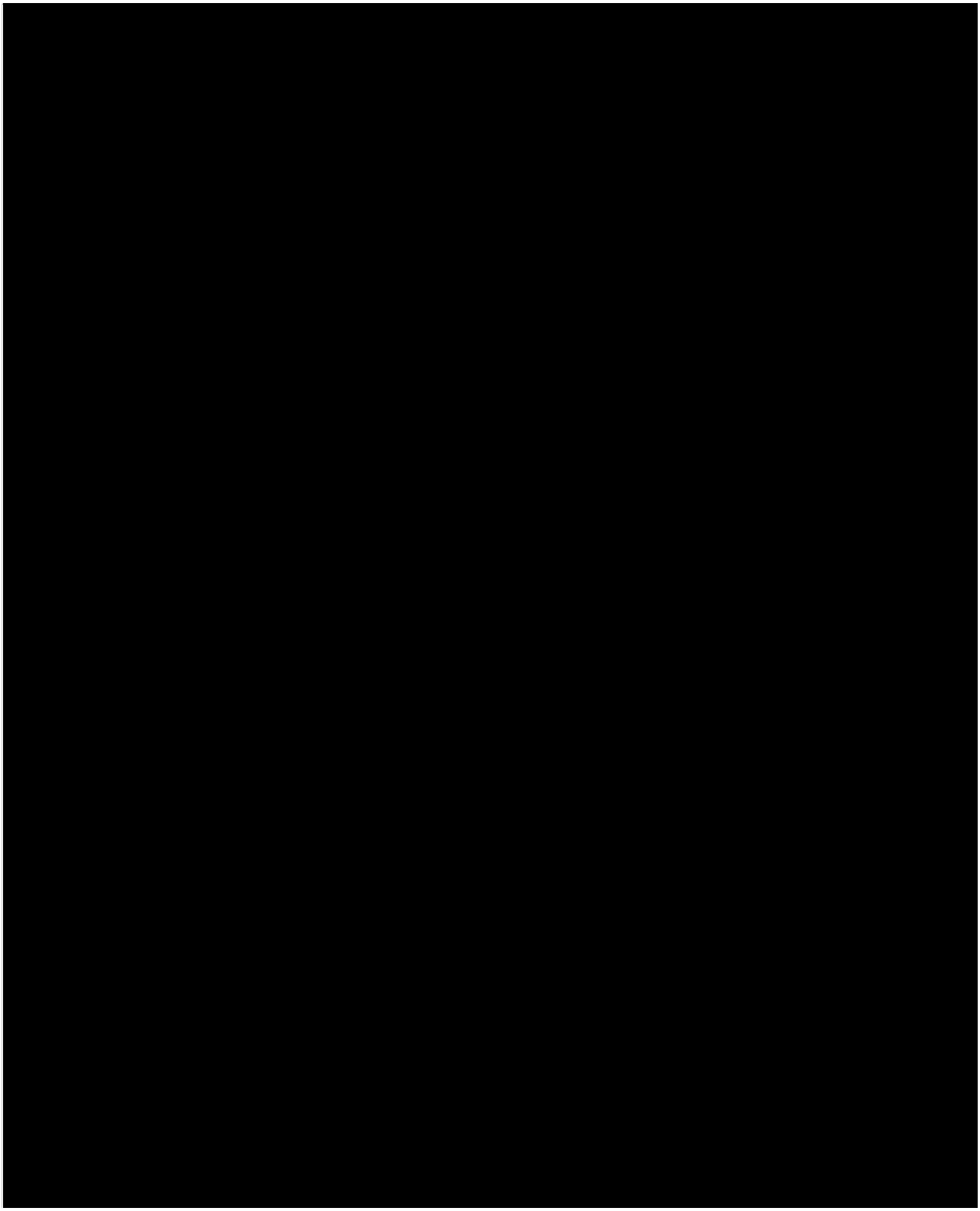
- Banana Boat Sport Sunblock Lotion (SPF 15, 30+ or 50)
- Neutrogena UVA/UVB (SPF 30 or 45)
- Neutrogena Sensitive Skin Sunblock Lotion (SPF 17)
- Neutrogena Healthy Defense Oil-Free Sunblock Lotion (SPF 30 or 45)
- Coppertone Water Babies UVA/UVB Sunblock Lotion (SPF 45)

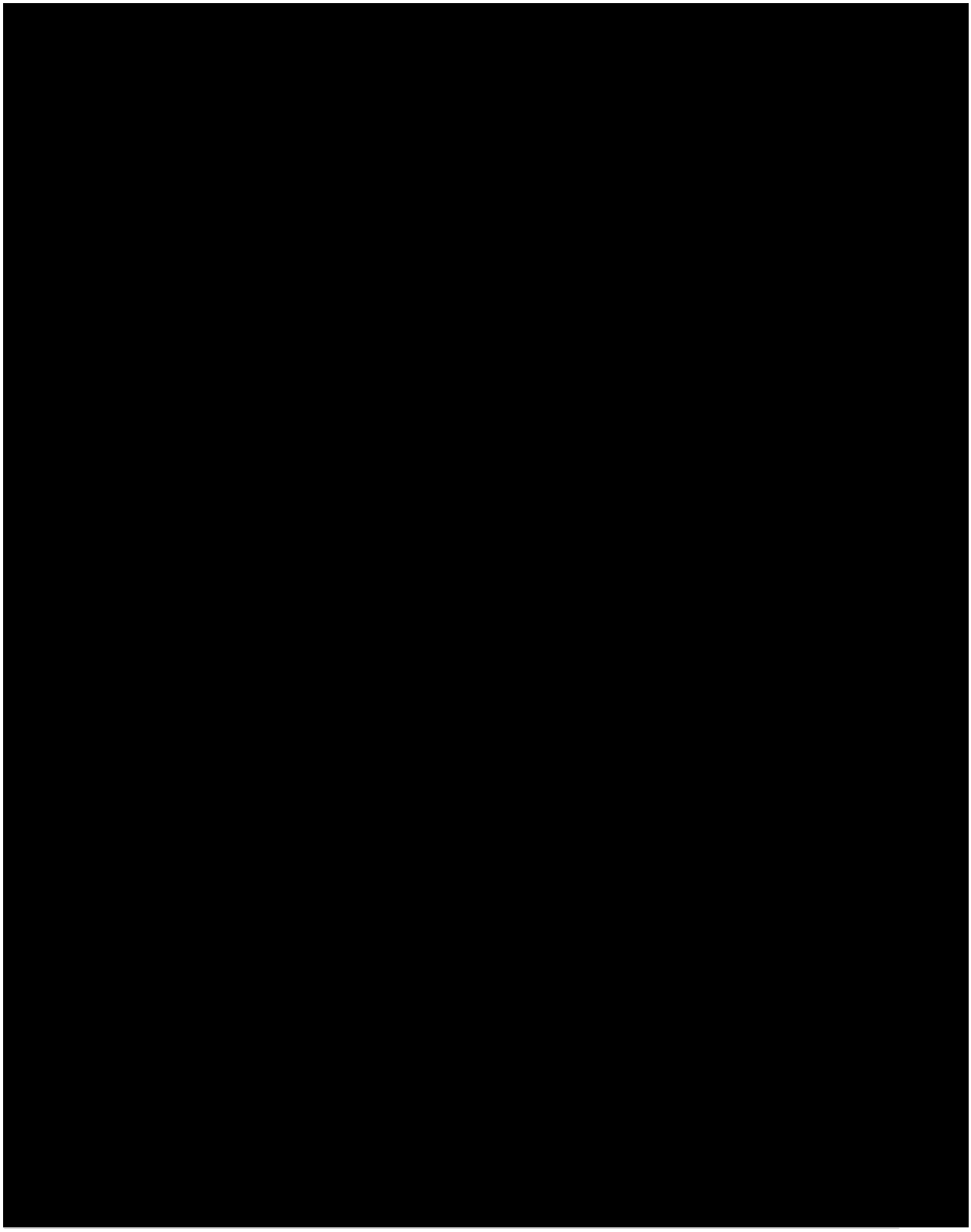


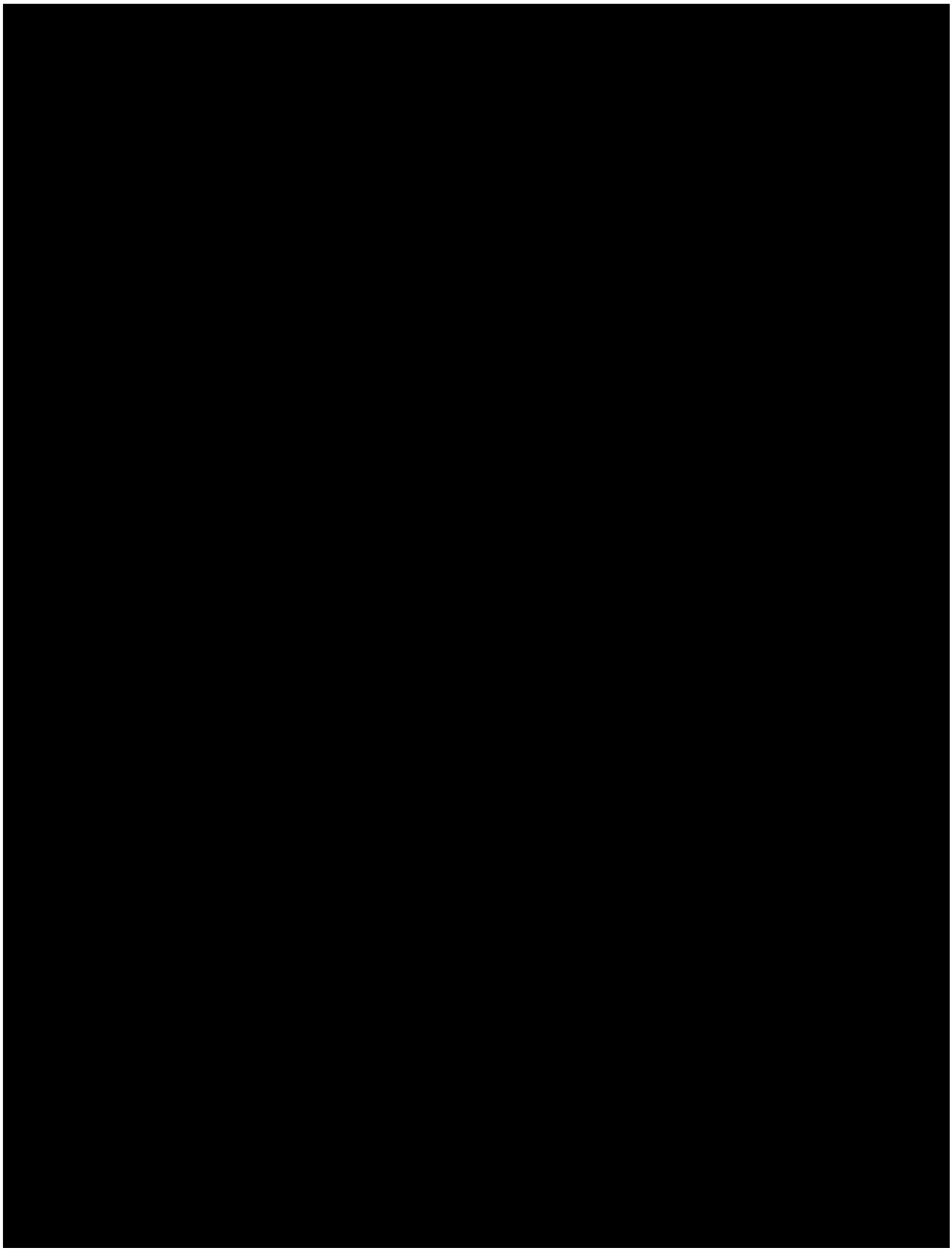


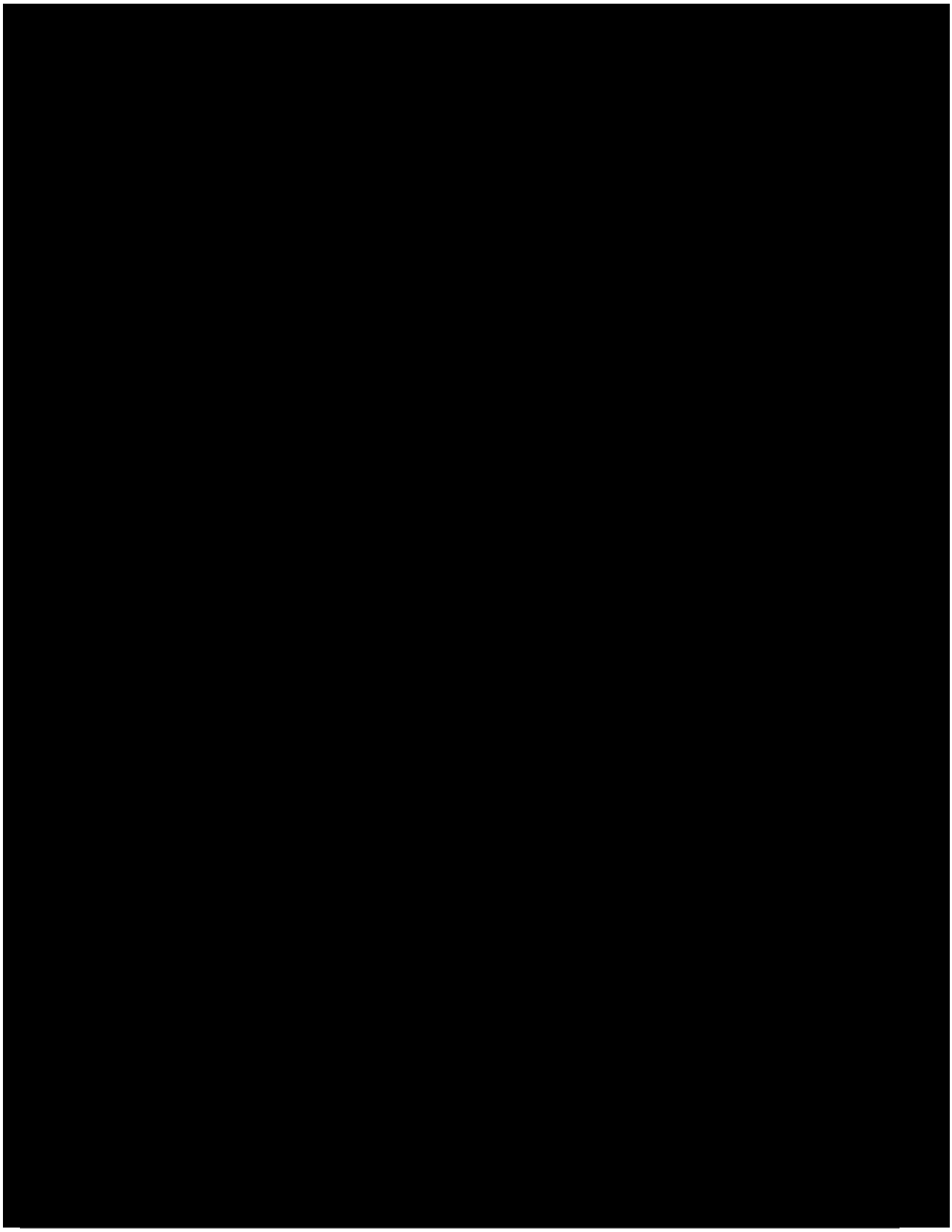


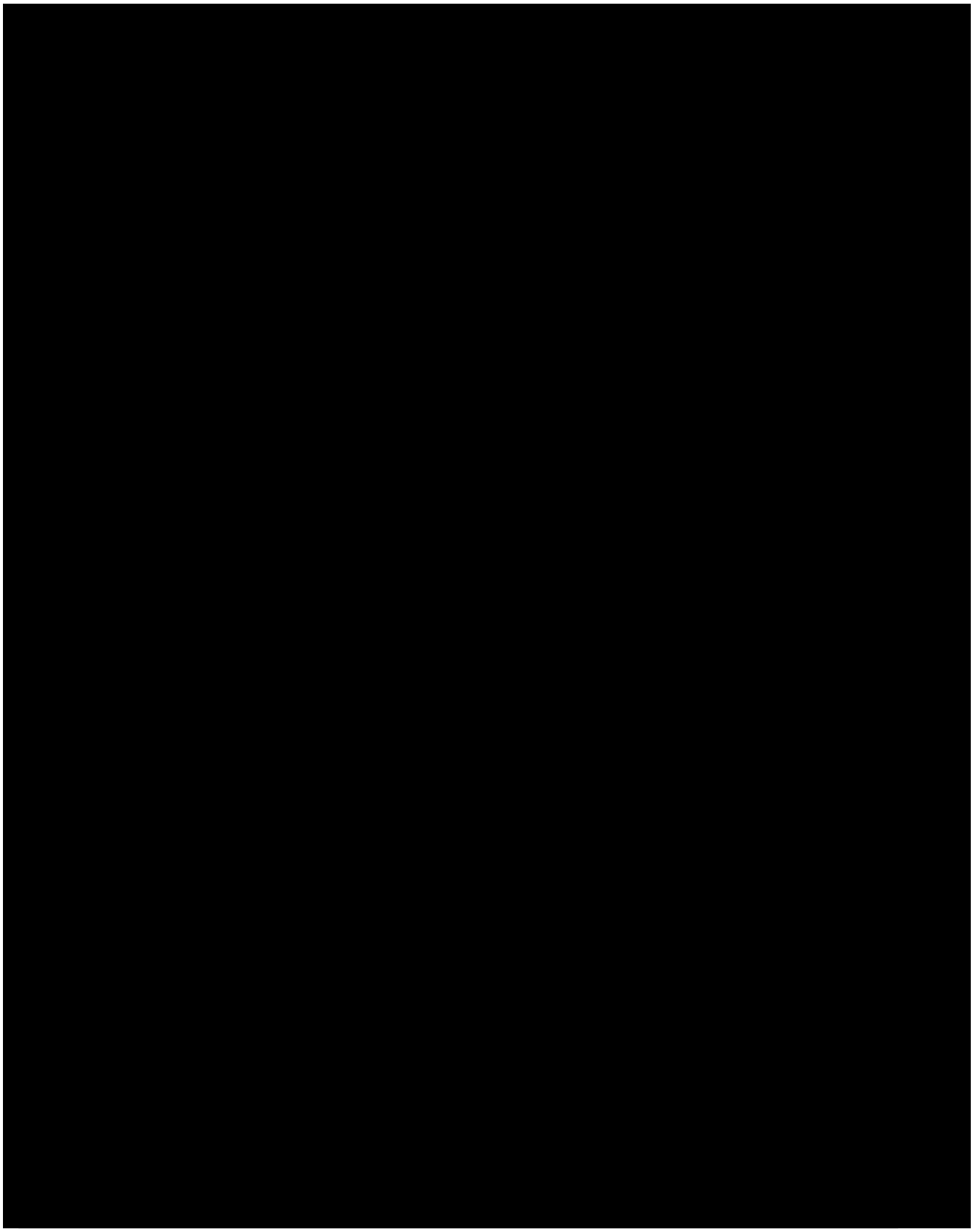


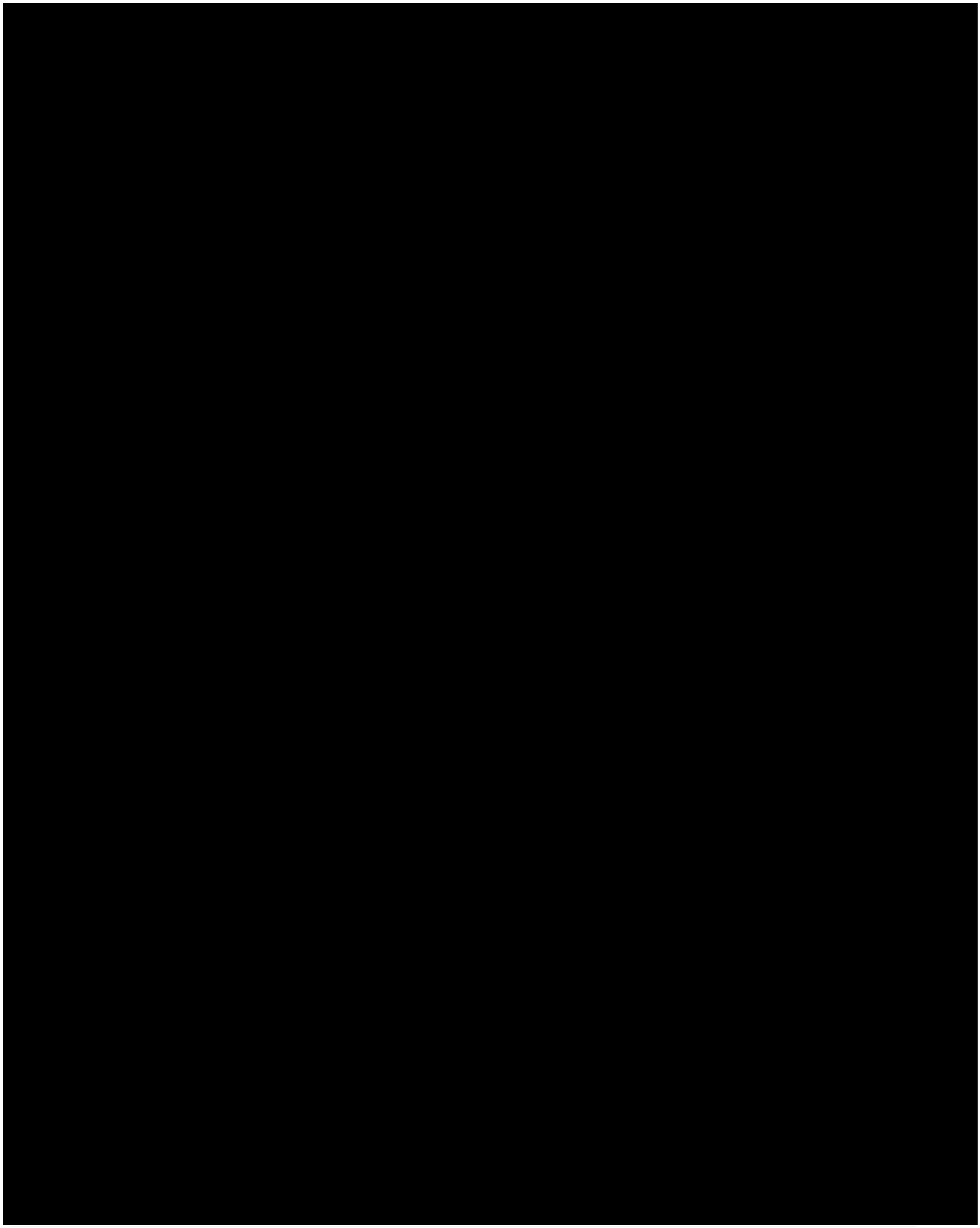


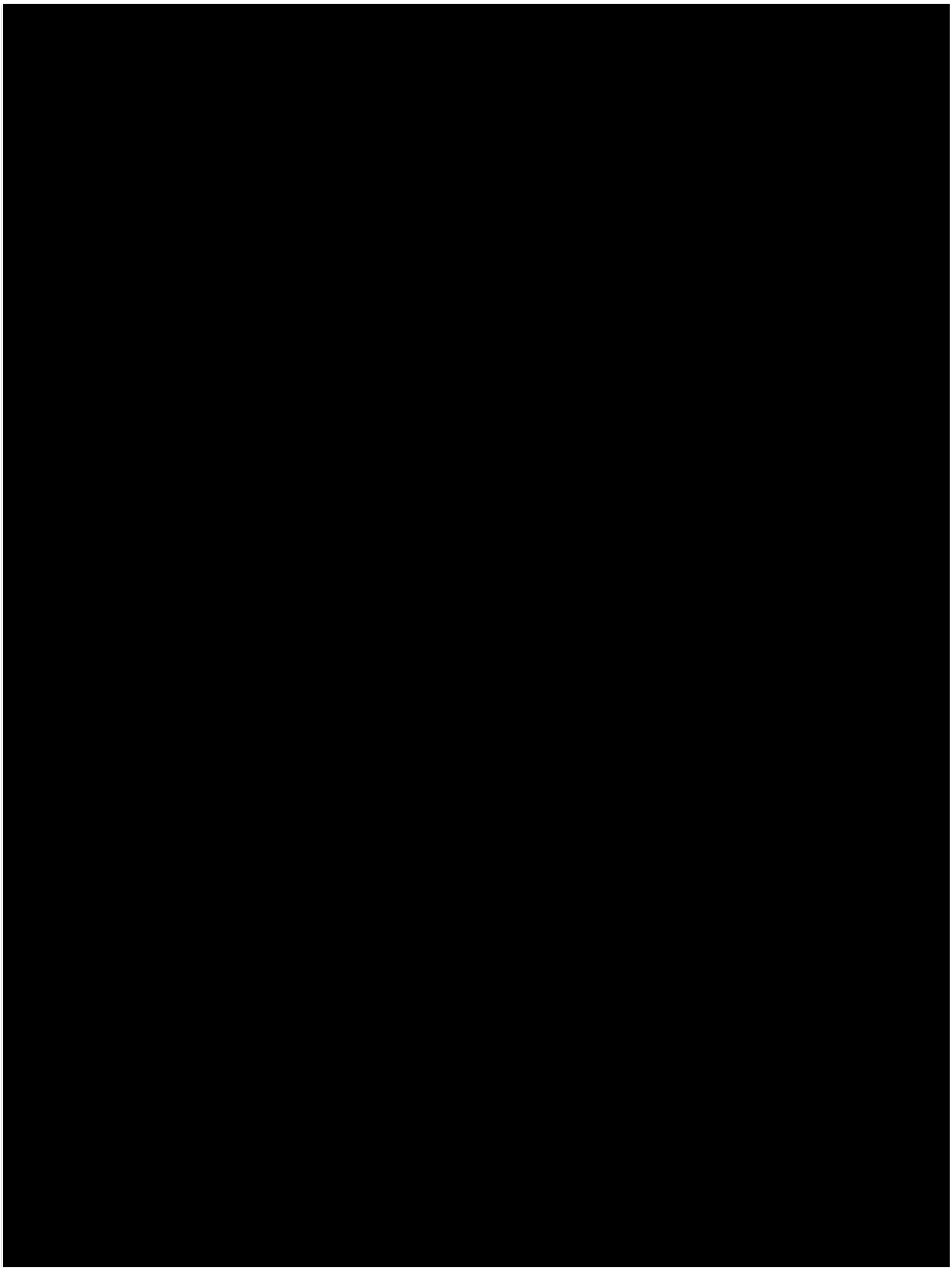


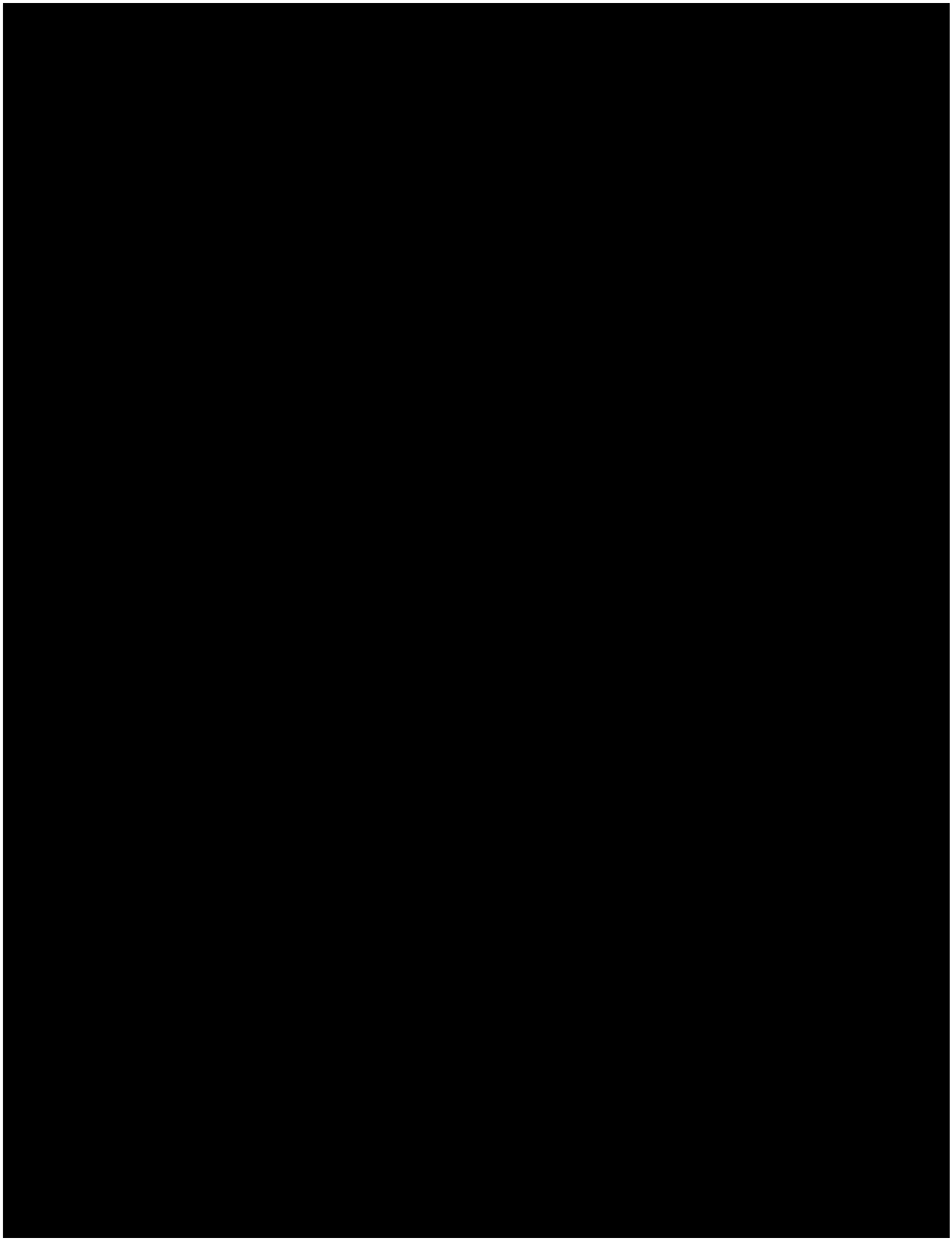












## 17.4 Hanifin & Rajka Diagnostic Criteria

To provide a clear diagnosis of AD fulfilling the diagnostic criteria of Hanifin and Rajka[13] that affects ≥ 5% of TBSA, please reference the criteria below:

**Must have three or more of the following basic features:**

(1) Pruritus
(2) Typical morphology and distribution
- Flexural lichenification in adults
- Facial and extensor eruptions in infants and children

(3) Chronic or chronically relapsing dermatitis
(4) Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

**Must have three or more of the following minor features:**

(1) Xerosis
(2) Ichthyosis/palmar hyperlinearity, keratosis pilaris
(3) Immediate (type I) skin test reaction
(4) Elevated serum IgE
(5) Early age of onset
(6) Tendency toward cutaneous infections (especially *staph*. *aureus* and *herpes simplex*), impaired cellmediated immunity
(7) Tendency toward non-specific hand or foot dermatitis
(8) Nipple eczema
(9) Cheilitis
(10) Recurrent conjunctivitis
(11) Dennie-Morgan infraorbital 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) Periofollicular accentuation
(21) Food intolerance
(22) Course influenced by environmental and emotional factors
(23) White dermographism, delayed blanch

## 17.5 Analytes to be Assessed for Blood and Urine Collections

The central laboratory will be testing blood and urine samples collected as outlined in Table 1, "Study Design and Schedule of Assessments" (pages 22-23) for the following analytes:

Chemistry Panel:

- Total Bilirubin
- Direct Bilirubin
- Indirect Bilirubin (calculation)
- Alkaline Phosphatase
- ALT (SGPT)
- AST (SGOT)
- GGT
- LDH
- Urea Nitrogen
- Creatinine
- Glucose
- Uric Acid
- Phosphorus
- Total Protein
- Albumin
- Globulin (calculation)
- Triglycerides
- Cholesterol
- CK

Electrolyte Panel:

- Sodium
- Potassium
- Bicarbonate
- Chloride
- Magnesium

Hematology & Differential Panel:

- Hemoglobin
- Hematocrit
- RBC
- MCH
- MCHC
- RBC morphology and MCV
- WBC
- Neutrophils (absolute, %)
- Lymphocytes (absolute, %)
- Monocytes (absolute, %)

- Eosinophils (absolute, %)
- Basophils (absolute, %)
- Platelets

Urine Macro & Micro Panel:

- Color & Clarity
- Specific Gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Nitrite
- Leukocyte Esterase
- Microscopic