Clinical Study Protocol

Study Title:	A Phase 3 Efficacy and Safety Study of Tapinarof for the Treatment of Moderate to Severe Atopic Dermatitis in Children and Adults
Sponsor:	Dermavant Sciences, Inc. 3300 Paramount Parkway, Suite 150 Morrisville, NC, USA 27560
Compound Name:	tapinarof
Protocol Number:	DMVT-505-3101
Indication:	Atopic Dermatitis
Development Phase:	3
IND Number:	104601
Current Version:	4.0
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Sponsor Signature Page

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This protocol has been approved by a representative of Dermavant Sciences, Inc. The following signature documents this approval.

Medical Monitor / Sponsor Information Page

Investigator Statement

Study Title:	A Phase 3 Efficacy and Safety Study of Tapinarof for the Treatment of Moderate to Severe Atopic Dermatitis in Children and Adults
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- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations and comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

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Table of Abbreviations

Term	Full Description
AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
AhR	aryl hydrocarbon receptor
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Anti-HBc	anti-hepatitis B core antigen
Anti-HBs	anti-hepatitis B surface antigen
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BSA	body surface area
%BSA	percent of total body surface area
BUN	blood urea nitrogen
CBP	child-bearing potential
[redacted]	[redacted]
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
Dermavant	Dermavant Sciences, Inc.
[redacted]	[redacted]
[redacted]	[redacted]
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
ET	early termination
FSH	Follicle-stimulating hormone
FU	follow-up
[redacted]	[redacted]
HBsAg	hepatitis B surface antigen
[redacted]	[redacted]
ICF	informed consent form
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
[redacted]	[redacted]
IRB	Institutional Review Board
ITT	Intent-to-Treat
LOCF	last observation carried forward
LTS	Local Tolerability Scale
MCH	mean corpuscular hemoglobin

Term	Full Description
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MI	Multiple Imputations
NA	not applicable
[redacted]	[redacted]
OL-LTE	Open-Label, Long-Term Extension study
P/C	phone contact
PGA	Physician's Global Assessment
PK	Pharmacokinetic(s)
[redacted]	[redacted]
PP	per protocol
PP-NRS	Peak Pruritus-Numeric Rating Scale
QD	once daily
RBC	red blood cell(s)
SAE	serious adverse event
SD	standard deviation
[redacted]	[redacted]
TEAE	treatment emergent adverse event
TF	Treatment Failure
ULN	upper limit of normal
US	United States
V	visit
vIGA-AD™	validated Investigator Global Assessment for Atopic Dermatitis
WBC	white blood cell(s)
WOCBP	women of child-bearing potential
[redacted]	[redacted]

Synopsis

Name of Sponsor/Company:					
Dermavant Sciences, Inc.					
Name of Investigational Product:					
DMVT-505 (tapinarof cream, 1%)					
Name of Active Ingredient:					
Tapinarof					
Protocol Number:	DMVT-505-3101	**Phase:**	3	**Country:**	United States (US) and Canada
Title of Study:					
A Phase 3 Efficacy and Safety Study of Tapinarof for the Treatment of Moderate to Severe Atopic Dermatitis in Children and Adults					
Study Sites(s):					
Up to approximately 60 sites in the US and Canada					
Objectives:					
Primary:					
• To evaluate the efficacy of tapinarof cream, 1% once daily (QD) compared with vehicle control in subjects with atopic dermatitis (AD)					
Secondary:					
• To further characterize the efficacy of tapinarof cream, 1% QD compared with vehicle control over time • To evaluate the safety and tolerability of tapinarof cream, 1% QD in subjects with AD • To describe the effect of tapinarof cream, 1% QD on AD symptom severity and the associated impact on daily activities and attitudes in subjects with AD • To evaluate plasma concentrations of tapinarof in subjects with AD					
Methodology:					
This is a double-blind, randomized, vehicle-controlled, Phase 3, multicenter study to evaluate the efficacy and safety of topical tapinarof cream, 1% compared with vehicle control cream in subjects ages 2 years and above with AD. Following a 30-day screening period, eligible subjects will be randomized at a 2:1 ratio to receive QD treatment with tapinarof cream, 1% or vehicle cream. Subjects will return to the clinic at Weeks 1, 2, 4, and 8 for efficacy and safety assessments. Subjects will be contacted by phone at Weeks 3 and 6 to assess AEs and concomitant medications, to review study drug administration instructions, and to confirm subject's continued participation in this study. Study drug will be dispensed and applied during the clinic visits and will be administered at home between clinic visits as instructed by site personnel. Subjects or their caregivers will be instructed to apply study drug QD to all affected areas, including newly appearing lesions and lesions/areas that improve during the study. Subjects or caregivers will apply sufficient study drug to cover completely each lesion with a thin layer of study drug and will record the time of study drug application and daily itch score (Peak Pruritus-Numeric Rating Scale [PP-NRS]) in a daily diary provided by the study site. (Note that subjects are allowed, but not required, to treat scalp lesions with study drug; however, efficacy analyses will not include assessment of AD in this area.) Subjects or caregivers will be advised to maintain the approximate dosing time chosen at the beginning of the study for their full study participation. At the phone contacts at Weeks 3 and 6, subjects should be reminded to complete their daily diary and bring it with them to the next clinic visit. Study drug application instructions will be reviewed at all post-randomization clinic visits and during any planned study phone calls. On clinic visit days, subjects will be instructed/reminded how to apply study drug (except during the final treatment/end-of-study visits). During the clinic visits, subjects or caregivers will apply the daily dose of study drug while on-site under the supervision of site personnel. The time of the dose application and assessments will depend on the time of the clinic visit. Therefore, the timing of the clinic visit may lead to a change in the subject's chosen dosing time for that day. At the end of the 8 weeks of treatment in this study, subjects will have the option to enroll in an Open-Label, Long-Term Extension (OL-LTE) study for an additional 48 weeks of treatment. Subjects who choose not to participate in the OL-LTE study or who fail to qualify for participation in the OL-LTE study will complete a Follow-up Visit (Week 9 visit) approximately 1 week after the end of treatment in this study. Subjects who withdraw from the study before Week 8 will complete an Early Termination Visit and are not eligible for the OL-LTE study.					

Number of Subjects:

Approximately 400 subjects ages 2 years and above will be enrolled in the study, randomized at a 2:1 ratio to receive tapinarof cream, 1% (approximately 267 subjects) or vehicle cream (approximately 133 subjects). Subjects will be stratified so that a minimum of 10% will have severe disease (validated Investigator Global Assessment in Atopic Dermatitis [vIGA-AD™] = 4) and the remainder will have moderate disease (vIGA AD™ = 3). A minimum of approximately 15% of subjects will be enrolled into each of the following age groups: 2-6 years, 7-11 years, 12-17 years, 18 years and above. Adults 18 years and above will comprise a maximum of 20% of enrolled subjects.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Each subject must meet all the following criteria to be eligible to participate in the study:

1. Male and female subjects ages 2 years and above with clinical diagnosis of AD by Hanifin and Rajka criteria.
2. Subjects with AD covering ≥ 5% and ≤ 35% of the body surface area (BSA). Scalp should be excluded from the BSA calculation to determine eligibility during Screening and at Baseline, and for all efficacy assessments.

   NOTE: Subjects with disease only on palms and soles are not eligible.
3. A vIGA-AD™ score of ≥ 3 at Screening and Baseline (pre-randomization).
4. An Eczema Area and Severity Index (EASI) score of ≥ 6 at Screening and Baseline (pre-randomization).
5. AD present for at least 6 months for ages 6 years old and above or 3 months for ages 2 to 5 years old, confirmed by prior medical documentation and/or according to the subject/caregiver report.
6. Female subjects of childbearing potential who are engaging in sexual activity that could lead to pregnancy should use one of the following acceptable birth control methods while on study and for 4 weeks after the last exposure to study drug.
   - Acceptable contraception methods include intrauterine device, hormonal contraceptives, barrier method (e.g., condom or diaphragm), or surgical sterilization of male partner (vasectomy)
   - Subjects who claim abstinence as their method of contraception are allowed provided they agree to use a barrier method (e.g., condom or diaphragm) should they become sexually active from Screening to 4 weeks after the last dose of study drug

   Non-child-bearing potential is defined as:
   - premenarchal
   - pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or hysteroscopic sterilization
   - postmenopausal female with a cessation of menses for at least 12 months without an alternative medical cause; a blood sample with follicle stimulating hormone > 40 mIU/mL is confirmatory in questionable cases
7. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1).
8. Subject, subject's parent(s), or legal representative must be capable of giving written informed consent/assent, which includes compliance with the requirements and restrictions listed in the consent/assent form; written informed consent must be obtained prior to any study related procedures.

Exclusion Criteria:

A subject who meets any of the following criteria will be excluded and considered ineligible for participation in the study:

1. Concurrent conditions:
   a. Immunocompromised (e.g., lymphoma, acquired immunodeficiency syndrome) or history or evidence of active or latent tuberculosis or human immunodeficiency virus antibody as documented by medical history and/or according to the subject/caregiver report..
   b. Chronic or acute systemic infection requiring treatment with antiparasitics or antiprotozoals, within 4 weeks prior to the Baseline visit.
   c. Chronic or acute systemic bacterial infection requiring treatment with systemic antibiotics within one week prior to the Baseline visit.

d. Chronic or acute superficial fungal infection requiring treatment with systemic antifungals within one week prior to the Baseline visit.

e. Acute active bacterial, fungal, or viral (herpes simplex, herpes zoster, chicken pox) skin infection within 1 week prior to the Baseline visit; the condition should be completely resolved one week prior to Baseline Visit.

f. Significant dermatologic or inflammatory condition other than AD that, in the Investigator's opinion, would make it difficult to interpret data or assessments during the study. For example, subjects with an active skin condition such as Kaposi's varicelliform eruption, scabies, molluscum contagiosum, impetigo, psoriasis, severe acne, connective tissue disorder, or Netherton's syndrome, or any other concurrent active disease.

g. Concurrent skin lesions in the treatment area or pruritus due to conditions other than AD that, in the opinion of the Investigator, would either interfere with study evaluations or affect the safety of the subject.

2. Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.0 x the upper limit of normal (ULN).
3. Screening total bilirubin > 1.5x ULN; total bilirubin > 1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%.
4. Current or chronic history of liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones), presence of hepatitis B surface antigen (HBsAg), or positive hepatitis C antibody test result, or presence of anti-hepatitis B core antigen (anti-HBc). Subjects having a negative HBsAg and a positive anti-HBc may enroll if they have a positive anti-hepatitis B surface antigen demonstrating natural immunity. Subjects with a history of hepatitis C virus infection who were medically cured and have an undetectable viral load are eligible to enroll. Subjects with a history of stable non-alcoholic fatty liver disease without evidence of active inflammation (elevated ALT/AST ≥ 2.0x ULN) or cirrhosis are eligible to enroll.
5. Current or a history of cancer within 5 years except for adequately treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix (surgical excision or electrodessication and curettage).
6. Subjects who would not be considered suitable for topical therapy (e.g., those with extensive disease involvement over a large BSA who would be candidates for systemic therapy).
7. Use of any prohibited medication or procedure within the indicated period before the Baseline visit.

   NOTE: Prohibited concomitant medications, therapy, etc. during the defined period are as listed in the bullets below. If a subject requires any of these medications throughout the study period, he/she may be excluded from or discontinued from the study, at the discretion of the Investigator and Medical Monitor.

   a. From 4 months prior to Baseline until the completion of the Follow-up visit or study discontinuation:
      - DUPIXENT® (dupilumab) injection.
      - Any monoclonal antibody product that becomes approved for AD during the course of the trial.

   b. From 28 days prior to Baseline until the completion of the Follow-up visit or discontinuation:
      - Oral, injectable, and suppository preparations of corticosteroids. Eye drops and nasal preparations are allowed. Inhaled preparations are allowed when used for a stable condition and stable dose for ≥ 28 days before Screening and are continued at the same dose throughout the study.
      - Oral preparations and injections of immunosuppressants (cyclosporine, methotrexate, azathioprine, tacrolimus, Janus kinase inhibitors, etc.).
      - Excessive sun exposure, tanning booth, other ultraviolet light source and phototherapy including psoralen and ultraviolet A therapy or is unwilling to minimize natural and artificial sunlight exposure.
      - Treatment with antivirals with the exception of short-term treatment for acute upper respiratory viral infections (i.e., influenza) or viral suppressive therapy for a history of recurrent herpes labialis or genital herpes.

   c. From 14 days prior to Baseline until the completion of the Follow-up visit or discontinuation:
      - EUCRISA® (crisaborole) and any other PDE4 inhibitor.
      - Tacrolimus ointment and pimecrolimus cream.
      - Topical corticosteroids that are classified as medium or high potency (e.g., fluocinonide, triamcinolone acetonide) or super-high potency (e.g., clobetasol propionate). Eye drops and nasal preparations are allowed.

- Coal tar products (on the body). If subject chooses to treat scalp with study drug, then coal tar products are prohibited for use on the scalp.
- Over the counter or herbal medicines for AD (topical and oral preparations). If subjects are using emollients, they may continue to use the same emollient on nonlesional skin during the study. Emollients containing salicylic acid are prohibited during the study.

d. From 7 days prior to Baseline until the completion of the Follow-up visit or discontinuation:

- Topical corticosteroids that are classified as low potency (e.g., desonide, hydrocortisone).
- Oral, injectable, or intravenous antibiotics or antifungal medications.
- Topical doxepin, topical gentamicin, or topical neomycin sulfate.
  NOTE: Oral doxepin is allowed for treatment of depression if subject has been on a stable dose (4 weeks) at Screening.
- Topical products containing urea, except for the treatment of follicular events.
- Antihistamines/antiallergics (oral, topical and injections): diphenhydramine, chlorpheniramine maleate, hydroxyzine.
  NOTE: The following antihistamines are allowed from Screening throughout the treatment period: loratadine, fexofenadine hydrochloride, cetirizine hydrochloride. Subjects are allowed to switch from non-allowed antihistamines to allowed antihistamines during Screening but must be on a stable dose for 7 days prior to Baseline.

e. The subject has received an investigational product within the following time period prior to the first dosing day in the current study: Minimum of 30 days or 5 half-lives of the investigational product (whichever is longer).

8. A history of or ongoing serious illness or medical, physical, or psychiatric condition(s) that, in the Investigator's opinion, may interfere with the subject's participation in the study, interpretation of results, safety of the subject or ability to understand and give informed consent.
9. Pregnant females as determined by positive serum (Screening) or urine (Baseline) human chorionic gonadotropin test.
10. Lactating females.
11. History of sensitivity to the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
12. Previous known participation in a clinical study with tapinarof (previously known as GSK2894512 and WBI-1001).

Investigational Product, Dosage and Mode of Administration:

Tapinarof cream, 1% [redacted] is to be administered by the subject/caregiver QD via topical application of a thin layer to affected areas.

Reference Therapy, Dosage and Mode of Administration:

Vehicle cream [redacted] is to be administered by the subject/caregiver QD via topical application of a thin layer to affected areas.

Duration of Treatment:

- Subjects randomized to tapinarof cream, 1% will receive tapinarof for 8 weeks
- Subjects randomized to vehicle cream will receive vehicle for 8 weeks

The total study duration for subjects who complete this Phase 3 study and who fail to qualify for participation in the OL-LTE study, or who qualify to participate in the OL-LTE study but elect not to enroll in that study is up to 13 weeks in total (including up to 30 days screening, 8 weeks treatment, and a 1-week follow-up period).

Criteria for Evaluation:	
Efficacy Assessments:	• vIGA-AD™ • EASI • Percentage of total body surface area (%BSA) affected
Functional Outcomes and Quality of Life Assessments:	• PP-NRS, for completion by subjects ages ≥ 12 years and for completion by caregivers of subjects ages < 12 years • [redacted] • [redacted] • [redacted]
Pharmacokinetic Assessments:	• Plasma concentrations of tapinarof
Safety Assessments:	• Adverse events (AEs) • Vital signs • Physical examinations • Clinical laboratory tests • Electrocardiograms (ECGs) • Investigator-assessed Local Tolerability Scale (LTS) • Subject (or caregiver)-assessed LTS
Study Endpoints:	
Primary:	
• Proportion of subjects who have a vIGA-AD™ score of clear or almost clear (0 or 1) and at least a 2-grade reduction from Baseline at Week 8.	
Secondary:	
• Proportion of subjects with ≥ 75% improvement in EASI from Baseline at Week 8 • Mean change in %BSA affected from Baseline at Week 8 • Proportion of subjects with ≥ 90% improvement in EASI from Baseline at Week 8 • Proportion of subjects ≥ 12 years old with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4-point reduction in the PP-NRS from Baseline at Week 8	
Exploratory:	
[redacted]	

[redacted]

Safety:

- Incidence, frequency, and duration of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Change from Baseline in laboratory values
- Change from Baseline in ECG parameters
- Change from Baseline in vital signs
- Mean Investigator-assessed LTS scores by visit (overall and sensitive areas)
- Mean subject (or caregiver)-assessed LTS scores by visit

Pharmacokinetic:

- Plasma concentrations of tapinarof at Weeks 4 and 8

Statistical Methods:

Determination of Sample Size:

It is estimated that the proportion of subjects who will achieve a vIGA-AD™ score of 0 or 1 and at least a 2-grade reduction from Baseline at Week 8 will be 45% for subjects receiving tapinarof compared with 25% for subjects receiving vehicle control, based upon the phase 2 results.

With 400 subjects randomized in a 2:1 ratio (267 subjects receiving tapinarof, and 133 subjects receiving vehicle control), this will provide 97.2% power for statistical significance (2-sided $p < 0.05$).

Efficacy Analyses:

Analyses of the primary and secondary efficacy endpoints will be based upon the Intent-to-Treat population, which is defined as all randomized subjects.

The primary efficacy endpoint will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by Baseline vIGA-AD™ score and age group. Missing values will be handled using the Multiple Imputation approach.

Dichotomized secondary efficacy endpoints will also be analyzed using a CMH test stratified by Baseline vIGA-AD™ score and age group. Continuous secondary efficacy endpoints will be analyzed using an analysis of covariance model including Baseline vIGA-AD™ score and age group as covariates and the Baseline value of the secondary endpoint as a continuous covariate. Time to achieve an vIGA-AD™ score of 0 or 1 and at least a 2-grade reduction from Baseline will be analyzed using the Kaplan Meier method.

Safety Analyses:

Analyses of the safety endpoints will be based upon the Safety population, which is defined as all randomized subjects who receive at least 1 application of study drug.

Treatment groups will not be statistically compared in terms of the safety endpoints.

AEs will be summarized by treatment group as incidence rates of any AEs, TEAEs, AEs of special interest, treatment-related TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to study discontinuation and SAEs.

Changes in laboratory parameters, vital signs, and ECG parameters will be summarized by treatment group using shift tables and descriptively for quantitative measures by visit and treatment group.

Changes in LTS scores will be summarized by treatment group.

Functional Outcomes and Quality of Life Analysis:
Change from Baseline in [redacted] Peak Pruritus-NRS scores will be analyzed using an ANCOVA model with treatment as a main effect, and baseline as a covariate.
Pharmacokinetic Analyses:
Plasma concentration data will be listed and summarized by study visit.

Schedule of Assessments

Table 1: Schedule of Assessments

Procedures and Assessment	Screening	Baseline	Double-Blind Vehicle-Controlled Treatment Phase						FU[a]	ET[b]
	V1	V2	V3	V4	P/C[c]	V5	P/C[c]	V6	V7	NA
	Day -30 to Day -1	Day 1	Week 1 Day 8 (±2 d)	Week 2 Day 15 (±2 d)	Week 3 Day 22 (±2 d)	Week 4 Day 29 (±2 d)	Week 6 Day 43 (±2 d)	Week 8 Day 57 (±2 d)	Week 9 Day 64 (±2 d)	NA
Informed consent	X									
Demographics	X									
Fitzpatrick skin type	X									
Medical history[d]	X	X[e]								
Assess/confirm eligibility	X	X								
Serum/urine pregnancy test (WOCBP)[f]	X	X[g]				X		X		X
Brief physical examination[h]	X	X				X		X	X	X
Vital signs[i]	X	X	X	X		X		X	X	X
ECG[j]		X				X		X		X
Blood sample for clinical laboratory tests[k]	X	X[l]				X		X	X[m]	X
Urinalysis	X	X[n]				X		X	X[m]	X
PK sample[o]						X		X		
Subject randomization		X								
Photograph representative of disease area[p]		X		X		X		X		
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Investigator Assessed										
vIGA-AD™ score[q]	X	X	X	X		X		X	X	X
%BSA affected[q]	X	X	X	X		X		X	X	X
EASI[q]	X	X	X	X		X		X	X	X
LTS[r]		X	X	X		X		X		X
Completed by Subject or Caregiver										
[redacted]	[redacted]									
[redacted]										

Procedures and Assessment	Screening	Baseline	Double-Blind Vehicle-Controlled Treatment Phase						FU[a]	ET[b]
	V1	V2	V3	V4	P/C[c]	V5	P/C[c]	V6	V7	NA
	Day -30 to Day -1	Day 1	Week 1 Day 8 (±2 d)	Week 2 Day 15 (±2 d)	Week 3 Day 22 (±2 d)	Week 4 Day 29 (±2 d)	Week 6 Day 43 (±2 d)	Week 8 Day 57 (±2 d)	Week 9 Day 64 (±2 d)	NA
PP-NRS (pre-dose)[s]		X	X	X		X		X	X	X
[redacted]										
[redacted]										
LTS[r]		X	X	X		X		X		X
Dispense (D)/collect (C) diary[t]		D	C/D	C/D		C/D		C		C
Review subject diaries for treatment compliance			X	X		X		X		X
Dispense (D)/Collect (C) study drug		D	C/D	C/D		C/D		C		C
Review instructions for study drug application[u]		X	X	X	X	X	X			
Study drug application under supervision[v]		X	X	X		X				
Enrollment (optional) in OL-LTE study								X		

a. The Follow-up Visit will be performed for any subject who completes Visit 6/Week 8 but fails to qualify for participation in the OL-LTE study or qualifies to participate in the OL-LTE study but elects not to enroll in that study. A follow-up visit is not required for a subject who early terminates.

b. Subjects who withdraw from the study before Visit 6 (Week 8) will complete an Early Termination Visit. A follow-up visit is not required for a subject who early terminates.

c. Phone calls to assess AEs and concomitant medications, to review study drug application procedures, and to confirm subject's continued participation in the study. Subjects should be reminded to complete the diary and bring it with them to the next clinic visit.

d. Medical history will include year of AD diagnosis, CV family history, allergic conditions, and risk factors (including height, weight, medical conditions) and family history of liver disease. As part of the subject's medical history, all systemic (oral and injectable) medications used by the subject for treatment of AD prior to 30 days before the Screening visit will be collected.

e. Review medical history at Baseline and record any changes.

f. Serum pregnancy test to be performed at the Screening visit only and urine pregnancy test to be performed at subsequent clinic visits when pregnancy testing is performed.

g. Urine pregnancy test to be performed before randomization.

h. Physical examination will include height and weight (BMI will be calculated in the CRF) at the Screening visit; a brief physical examination will be performed at other visits.

i. Vital signs will include blood pressure, pulse rate, and body temperature and should be measured after the subject is seated for at least 5 minutes. Vital signs will be measured before blood collection for clinical laboratory assessments and PK analysis (where applicable).

j. ECGs will be collected in a subset of subjects and will be collected prior to study drug administration in clinic. Informed consent/assent will be required.

k. Includes serum chemistry and liver chemistry tests, and hematology.

l. Blood sample collection for clinical laboratory tests is not required at the Baseline Visit if it has been ≤14 days since samples were collected at Screening and the results of those clinical laboratory tests were not clinically significant.

m. If needed, laboratory testing at the Follow-up visit for ongoing AEs or abnormal laboratory values.

n. Urine sample collection for urinalysis is not required at the Baseline Visit if it has been ≤14 days since samples were collected at Screening and the results of those analyses were not clinically significant.

o. Blood sample for PK will be collected in a subset of subjects. Sample to be collected prior to study drug application in clinic. Informed consent/assent will be required.

p. Photography will be performed in a subgroup of subjects at selected study sites. Informed consent/assent and photographic release will be required.

q. The vIGA-AD™ assessment should be performed before the %BSA and EASI assessments. The subject's scalp should be excluded from the vIGA-AD™, %BSA, and EASI calculations.

r. The LTS assessment consists of an Investigator-assessed and a subject (or caregiver)-assessed component. Both the Investigator-assessed LTS and subject (or caregiver)-assessed LTS should be completed within 2 hours post-dose at Weeks 1, 2 and 4. At Week 8 and the ET visit, when study drug is not applied, the LTS should be completed when other assessments are completed. If the subject (or caregiver) is applying study drug to "sensitive areas" (face, neck, skin folds, axilla, inframammary, anal crux, and/or genitalia), the Investigator will also complete a separate LTS assessment for each sensitive area where study drug is being applied.

s. Subjects (or Caregivers) should perform the PP-NRS assessment daily and record the results in their diary. When subjects dose in the clinic on study visit days, subjects will not complete the diary at home; application time and PP-NRS will be recorded in the clinic.

t. Subjects will be instructed on when and how to complete diaries.

u. Subjects will be instructed to apply study drug QD at the approximate same time each day, based on subject preference.

v. At clinic visits, study drug will be applied after safety and efficacy assessments have been conducted (except for LTS at Weeks 1, 2 and 4).

AD = atopic dermatitis; AE = adverse event (s); BMI = body mass index; %BSA = percent of total BSA; C = collect; [redacted]; CRF = case report form; CV = cardiovascular; d = day(s); D = dispense; [redacted]; ET = early termination; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; FU = follow-up; [redacted]; LTS = Local Tolerability Scale; NA = not applicable; OL-LTE = Open-Label, Long-Term Extension Study; P/C = phone contact; PK = pharmacokinetic; [redacted]; PP-NRS = Peak Pruritus-Numeric Rating Scale; QD = once daily; V = Visit; WOCBP = women of child-bearing potential; vIGA-AD™ = Validated Investigator Global Assessment in Atopic Dermatitis.

1 Introduction

1.1 Background Information and Study Rationale

1.1.1 Background Information

Atopic dermatitis (AD) (also called atopic eczema) is an intensely pruritic, chronic, relapsing, inflammatory skin disease [Bieber, 2008]. The characteristic signs and symptoms of AD include sensations of pruritis and burning, xerosis, erythematous papules and plaques, exudation, crusting, and lichenification. Quality of life is affected through sleep deprivation due to the intense and constant itching, as well as the stigma associated with having a visible skin disease [Carroll, 2005; Lewis-Jones, 2006]. Up to 30% of children may be affected by AD at some point, and 2% to 10% of adults have AD [Bieber, 2008]. Currently there is no curative therapy. Stabilizing the disease and reducing the number and severity of flares are the primary goals of treatment. Topical treatments directed at skin inflammation are a key factor in disease management, as is symptomatic relief of itching. Although multiple topical treatment options are available, there remains a need for a topical treatment that combines a high level of efficacy with an acceptable safety profile that permits application to a large body surface area (BSA) without restrictions on duration of treatment.

1.1.2 Study Rationale

This pivotal Phase 3 study is being conducted as part of a clinical development program to evaluate the efficacy and safety of tapinarof cream, 1% for the topical treatment of AD in adults and children ages 2 years and above. The results of this study are intended to support product registration in the United States and Canada.

1.2 Rationale for Study Design, Dose, and Control Groups

This study is an 8-week double-blind, vehicle-controlled treatment study in which subjects will be randomized to receive tapinarof cream, 1% or vehicle cream QD for 8 weeks. The study will be conducted at multiple study sites in more than one country to enhance the possibility of inclusion of a wider range of population groups and to increase generalizability of the results.

This randomized, double-blind, vehicle-controlled study design will minimize the potential for subjective bias related to possible identification of which subjects are receiving active treatment and will minimize selection and allocation bias by balancing potential prognostic factors. A vehicle control group is included to provide a

control for comparison and to ensure study sensitivity for characterization of the safety and efficacy profile of tapinarof cream, 1%.

[redacted]

1.3 Potential Risks and Benefits

To assess any potential impact on subject eligibility with regard to safety, the Investigator must refer to the current version of the tapinarof Investigator's Brochure for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug being used in this study.

[redacted]

[redacted]

1.3.2 Benefit Assessment

Subjects may experience improvements in their AD during the course of the study and may benefit from the additional safety assessments conducted as part of the study (e.g., physical examination, laboratory tests). Subjects in the study will also contribute to the process of developing a novel anti-inflammatory agent for the topical treatment of AD.

1.3.3 Overall Benefit Risk

Taking into account the measures taken to minimize risk to subjects in this study, the potential risks identified in association with tapinarof are justified by the anticipated benefits that may be afforded to subjects with AD.

2 Objectives and Endpoints

The objectives and associated endpoints of the study are as follows:

Objectives	Associated Endpoint
Primary	
• To evaluate the efficacy of tapinarof cream, 1% QD compared with vehicle control in subjects with AD	• Proportion of subjects who have a validated Investigator Global Assessment in Atopic Dermatitis (vIGA-AD™) score of clear or almost clear (0 or 1) and at least a 2-grade reduction from Baseline at Week 8.
Secondary/Exploratory	**Secondary:**
• To further characterize the efficacy of tapinarof cream, 1% QD compared with vehicle control over time	• Proportion of subjects with ≥ 75% improvement in EASI from Baseline at Week 8 • Mean change in %BSA affected from Baseline at Week 8 • Proportion of subjects with ≥ 90% improvement in EASI from Baseline at Week 8 • Proportion of subjects ≥ 12 years old with a Baseline Peak Pruritus-Numeric Rating Scale (PP-NRS) score ≥ 4 who achieve ≥ 4-point reduction in the PP-NRS from Baseline at Week 8 **Exploratory:** [redacted]
• To evaluate the safety and tolerability of tapinarof cream, 1% QD in subjects with AD	• Incidence, frequency, and duration of TEAEs and serious adverse events (SAEs) • Change from Baseline in laboratory values • Change from Baseline in ECG parameters • Change from Baseline in vital signs • Mean Investigator-assessed local tolerability scale (LTS) scores by visit (overall and sensitive areas) • Mean subject (or caregiver)-assessed LTS scores by visit
• To describe the effect of tapinarof cream, 1% QD on AD symptom severity and the associated impact on daily activities and attitudes in subjects with AD	• [redacted] • [redacted] • [redacted]

Objectives	Associated Endpoint
	• [redacted] • [redacted]
• To evaluate plasma concentrations of tapinarof in subjects with AD	• Plasma concentration of tapinarof at Weeks 4 and 8

3 Study Design

3.1 Overall Design

This is a double-blind, randomized, vehicle-controlled, Phase 3, multicenter study to evaluate the efficacy and safety of topical tapinarof cream, 1% compared with vehicle cream in children and adult subjects with AD.

Following a 30-day screening period, eligible subjects will be randomized at a 2:1 ratio to receive QD treatment with tapinarof cream, 1% or vehicle cream for 8 weeks. Subjects will return to the clinic at Weeks 1, 2, 4, and 8 for efficacy and safety assessments. Additionally, subjects will be contacted by phone at Weeks 3 and 6 to assess AEs and concomitant medications, to review study drug administration instructions, and to confirm subject's continued participation in this study.

Study drug will be dispensed and applied during the clinic visits and will be administered at home between clinic visits as instructed by site personnel. Subjects or their caregivers will be instructed to apply study drug QD to all affected areas, including newly appearing lesions and lesions/areas that improve during the study. Subjects or their caregivers will apply sufficient study drug to cover completely each lesion with a thin layer of study drug and will record the time of study drug application and daily itch score (PP-NRS) in a daily diary provided by the study site. Subjects are allowed, but not required, to treat scalp lesions with study drug; however, efficacy analyses will not include assessment of AD in this area. Subjects and/or caregivers will be advised to maintain the approximate dosing time chosen at the beginning of the study for their full study participation. Nonmedicated emollients that do not contain salicylic acid may be used on nonlesional skin but the subject (or caregiver) should wait at least 30 minutes after applying study drug before applying nonmedicated emollients; emollients should not be applied to lesional skin during treatment. The same emollient should be used throughout the subject's participation in the study. At the phone contacts at Weeks 3 and 6, subjects or caregivers should be reminded to complete their daily diary and bring it with them to the next clinic visit.

Study drug application instructions will be reviewed at all post-randomization clinic visits and during any planned study phone calls. On clinic visit days, subjects and/or caregivers will be instructed/reminded on how to apply study drug (except during the final treatment/end-of-study visits). During the clinic visits, subjects or their caregivers will apply the daily dose of study drug while on-site under the supervision of site personnel after efficacy and safety assessments have been completed, with the exception of the LTS at some visits (as outlined in the Schedule of Assessments [Table 1]). The time of the dose application and assessments will depend on the time of the clinic visit. Therefore, the timing of the clinic visit may lead to a change in the subject's chosen dosing time for that day.

At the end of the 8 weeks of assessments in this study, subjects will have the option to enroll in an Open-Label, Long-Term Extension (OL-LTE) study for an additional 48 weeks. Subjects who complete Visit 6/Week 8 but choose not to participate in the OL-LTE study or who fail to qualify for participation in the OL-LTE study will complete a Follow-up Visit (Visit 7/Week 9 visit) approximately 1 week after the end of treatment in this study. Subjects who withdraw from the study before Visit 6/Week 8 will complete an Early Termination Visit as their final visit and are not eligible for the OL-LTE study. The subjects who complete the Early Termination Visit must not complete a Follow-Up Visit.

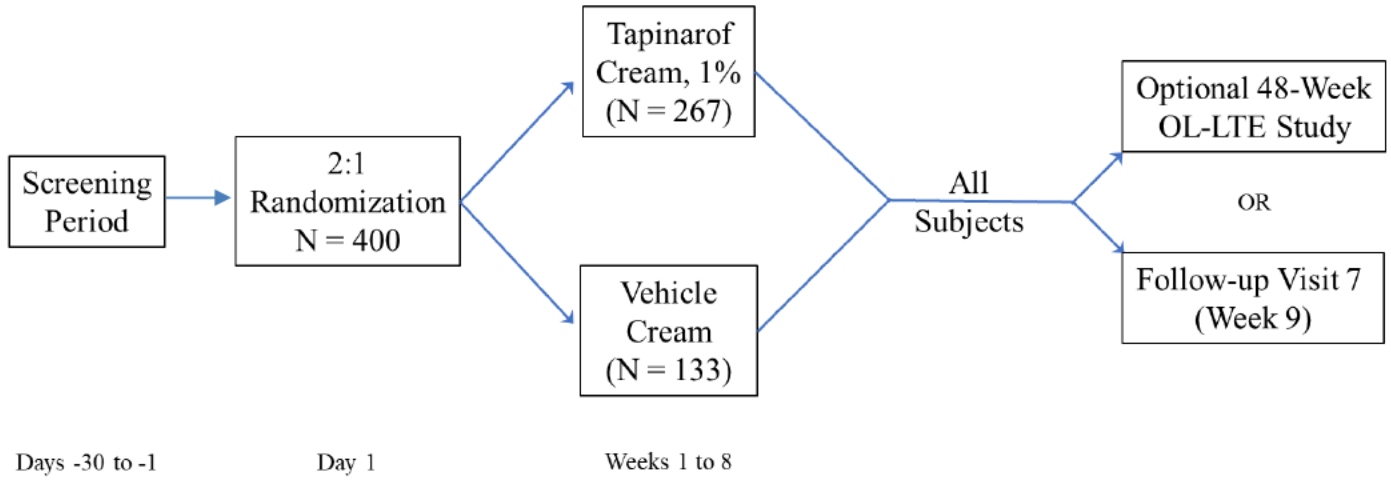
Study duration for subjects who complete this Phase 3 study and who fail to qualify for participation in the OL-LTE study, or who qualify to participate in the OL-LTE study but elect not to enroll in that study is

approximately 13 weeks in total. Study duration for subjects who complete this Phase 3 study and are eligible and decide to participate in the OL-LTE study is approximately 12 weeks in total.

Efficacy assessments will include vIGA-AD™ score, %BSA affected, EASI, PP-NRS, [redacted]. Safety assessments will include AEs, clinical laboratory tests, physical examination, vital signs, and ECGs (in a subset of subjects), and LTS. PK will be assessed in a subset of subjects at Week 4 and Week 8.

Refer to Section 6 for descriptions of study procedures and assessments and the Schedule of Assessments (Table 1) for timing of procedures and assessments. The study schema is presented in Figure 2.

Figure 2: Study Schema



OL-LTE = open label-long term extension

3.2 Treatment Groups and Duration

This 8-week, Phase 3 study is a double-blind, vehicle-controlled treatment study in which subjects will be randomized in a 2:1 ratio to receive QD treatment with either tapinarof cream, 1% or matching vehicle cream.

3.3 Definition of Study Completion and Eligibility for Open-Label, Long-Term Extension Study

In order to complete the study, a subject must complete 8 weeks of study assessments. To be considered a "study completer" in terms of treatment period, a subject must complete ≥80.0% of the intended doses. The number of intended doses is defined as the Study Day of the subject's Week 8 visit minus 1 (e.g., if the subject's Week 8 visit occurs on Day 57, their number of intended doses is 56). To be eligible for the OL-LTE study, subjects must be a "study completer." Subjects who complete the study will have the option to enroll in the Phase 3 OL-LTE study of 48 weeks in duration. Details of that study are provided in a separate clinical trial protocol.

The end of study is defined as when the last active subject has completed the 8 weeks of assessments in this study and either enrolls in the OL-LTE study OR does not enroll in the OL-LTE study and completes the Week 9 (Follow-up) Visit.

4 Study Population

4.1 Type and Number of Subjects

Approximately 400 adult and pediatric subjects ages 2 years and above with AD will be enrolled in the study at approximately 60 study sites in the US and Canada. A minimum of approximately 15% of subjects will be enrolled into each of the following age groups: 2-6 years, 7-11 years, 12-17 years, 18 years and above. Adults 18 years and above will comprise a maximum of 20% of enrolled subjects.

Protocol violations from inclusion and exclusion criteria are prohibited because ineligible study subjects can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.2 Inclusion Criteria

Each subject must meet all of the following criteria to be eligible to participate in the study:

1. Male and female subjects ages 2 years and above with clinical diagnosis of AD by Hanifin and Rajka criteria [Hanifin, 1980] (see Appendix 1).
2. Subjects with AD covering ≥ 5% and ≤ 35% of the BSA. Scalp should be excluded from the BSA calculation to determine eligibility during Screening and at Baseline, and for all efficacy assessments.

   NOTE: Subjects with disease only on palms and soles are not eligible.
3. A vIGA-AD™ score of ≥ 3 at Screening and Baseline (pre-randomization).
4. An EASI score of ≥ 6 at Screening and Baseline (pre-randomization).
5. AD present for at least 6 months for ages 6 years old and above or 3 months for ages 2 to 5 years old, confirmed by prior medical documentation and/or according to the subject/caregiver report.
6. Female subjects of childbearing potential who are engaging in sexual activity that could lead to pregnancy should use one of the following acceptable birth control methods while on study and for 4 weeks after the last exposure to study drug.

   - Acceptable contraception methods include intrauterine device, hormonal contraceptives, barrier method (e.g., condom or diaphragm), or surgical sterilization of male partner (vasectomy)
   - Subjects who claim abstinence as their method of contraception are allowed provided they agree to use a barrier method (e.g., condom or diaphragm) should they become sexually active from Screening to 4 weeks after the last dose of study drug

   Non-child-bearing potential is defined as:

   - premenarchal
   - pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or hysteroscopic sterilization
   - postmenopausal female with a cessation of menses for at least 12 months without an alternative medical cause; a blood sample with follicle stimulating hormone > 40 mIU/mL is confirmatory in questionable cases
7. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1).

8. Subject, subject's parent(s), or legal representative must be capable of giving written informed consent/assent, which includes compliance with the requirements and restrictions listed in the consent/assent form; written informed consent must be obtained prior to any study related procedures.

4.3 Exclusion Criteria

A subject who meets any of the following criteria will be excluded and considered ineligible for participation in the study:

1. Concurrent conditions:
    a. Immunocompromised (e.g., lymphoma, acquired immunodeficiency syndrome) or history or evidence of active or latent tuberculosis or human immunodeficiency virus antibody as documented by medical history and/or according to the subject/caregiver report.
    b. Chronic or acute systemic infection requiring treatment with antiparasitics, or antiprotozoals, within 4 weeks prior to the Baseline visit.
    c. Chronic or acute systemic bacterial infection requiring treatment with systemic antibiotics within one week prior to the Baseline visit.
    d. Chronic or acute superficial fungal infection requiring treatment with systemic antifungals within one week prior to the Baseline visit
    e. Acute active bacterial, fungal, or viral (herpes simplex, herpes zoster, chicken pox) skin infection within 1 week prior to the Baseline visit; the condition should be completely resolved one week prior to Baseline Visit
    f. Significant dermatologic or inflammatory condition other than AD that, in the Investigator's opinion, would make it difficult to interpret data or assessments during the study. For example, subjects with an active skin condition such as Kaposi's varicelliform eruption, scabies, molluscum contagiosum, impetigo, psoriasis, severe acne, connective tissue disorder, or Netherton's syndrome, or any other concurrent active disease.
    g. Concurrent skin lesions in the treatment area or pruritus due to conditions other than AD that, in the opinion of the Investigator, would either interfere with study evaluations or affect the safety of the subject.
2. Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.0 x the upper limit of normal (ULN).
3. Screening total bilirubin > 1.5x ULN; total bilirubin > 1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%.
4. Current or chronic history of liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones), presence of hepatitis B surface antigen (HBsAg), or positive hepatitis C antibody test result, or presence of anti-hepatitis B core antigen (anti-HBc). Subjects having a negative HBsAg and a positive anti-HBc may enroll if they have a positive anti-hepatitis B surface antigen demonstrating natural immunity. Subjects with a history of hepatitis C virus infection who were medically cured and have an undetectable viral load are eligible to enroll. Subjects with a history of stable non-alcoholic fatty liver disease without evidence of active inflammation (elevated ALT/AST ≥ 2.0 x ULN) or cirrhosis are eligible to enroll.

5. Current or a history of cancer within 5 years except for adequately treated cutaneous basal cell carcinoma, squamous cell carcinoma or carcinoma in situ of the cervix (surgical excision or electrodessication and curettage).
6. Subjects who would not be considered suitable for topical therapy (e.g., those with extensive disease involvement over a large BSA who would be candidates for systemic therapy).
7. Use of any prohibited medication or procedure within the indicated period before the Baseline visit.

   NOTE: Prohibited concomitant medications, therapy, etc. during the defined period are as listed in the bullets below. If a subject requires any of these medications throughout the study period, he/she may be excluded from or discontinued from the study, at the discretion of the Investigator and Medical Monitor.

   a. From 4 months prior to Baseline until the completion of the Follow-up visit or study discontinuation:
      - DUPIXENT® (dupilumab) injection.
      - Any monoclonal antibody product that becomes approved for AD during the course of the trial.
   b. From 28 days prior to Baseline until the completion of the Follow-up visit or discontinuation:
      - Oral, injectable, and suppository preparations of corticosteroids. Eye drops and nasal preparations are allowed. Inhaled preparations are allowed when used for a stable condition and stable dose for > 28 days before Screening and are continued at the same dose throughout the study.
      - Oral preparations and injections of immunosuppressants (cyclosporine, methotrexate, azathioprine, tacrolimus, Janus kinase inhibitors, etc.).
      - Excessive sun exposure, tanning booth, other ultraviolet light source and phototherapy including psoralen and ultraviolet A therapy or is unwilling to minimize natural and artificial sunlight exposure.
      - Treatment with antivirals with the exception of short-term treatment for acute upper respiratory viral infections (i.e., influenza) or viral suppressive therapy for a history of recurrent herpes labialis or genital herpes.
   c. From 14 days prior to Baseline until the completion of the Follow-up visit or discontinuation:
      - EUCRISA® (crisaborole) and any other PDE4 inhibitor.
      - Tacrolimus ointment and pimecrolimus cream.
      - Topical corticosteroids that are classified as medium or high potency (e.g., fluocinonide, triamcinolone acetonide) or super-high potency (e.g., clobetasol propionate). Eye drops and nasal preparations are allowed.
      - Coal tar products (on the body). If subject chooses to treat scalp with study drug, then coal tar products are prohibited for use on the scalp.
      - Over the counter or herbal medicines for AD (topical and oral preparations). If subjects are using emollients, they may continue to use the same emollient on nonlesional skin during the study. Emollients containing salicylic acid are prohibited during the study.
   d. From 7 days prior to Baseline until the completion of the Follow-up visit or discontinuation:

- Topical corticosteroids that are classified as low potency (e.g., desonide, hydrocortisone).
- Oral, injectable, or intravenous antibiotics or antifungal medications.
- Topical doxepin, topical gentamicin, or topical neomycin sulfate.

  NOTE: Oral doxepin is allowed for treatment of depression if subject has been on a stable dose (4 weeks) at Screening.
- Topical products containing urea, except for the treatment of follicular events
- Antihistamines/antiallergics (oral, topical and injections): diphenhydramine, chlorpheniramine maleate, hydroxyzine.

  NOTE: The following antihistamines are allowed from Screening throughout the treatment period: loratadine, fexofenadine hydrochloride, cetirizine hydrochloride. Subjects are allowed to switch from non-allowed antihistamines to allowed antihistamines during Screening but must be on a stable dose for 7 days prior to Baseline.

e. The subject has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days or 5 half-lives of the investigational product (whichever is longer).

8. A history of or ongoing serious illness or medical, physical, or psychiatric condition(s) that, in the Investigator's opinion, may interfere with the subject's participation in the study, interpretation of results, or ability to understand and give informed consent.
9. Pregnant females as determined by positive serum (Screening) or urine (Baseline) human chorionic gonadotropin test.
10. Lactating females.
11. History of sensitivity to the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
12. Previous known participation in a clinical study with tapinarof (previously known as GSK2894512 and WBI-1001).

4.4 Lifestyle Restrictions

Subjects must avoid ultraviolet light, phototherapy, and excessive sun exposure throughout the study. When prolonged exposure cannot be avoided, use of sunscreen products (except on AD lesions) and protective apparel are recommended.

4.5 Screening/Baseline Failures

To determine subject eligibility at Screening and Baseline, a single repeat of tests or procedures may be allowed during the screening period at the discretion of the Investigator; the Medical Monitor should be consulted if needed.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized within the screening time period. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs/SAEs.

A subject who screen fails may be allowed to re-screen one time at the discretion of the Investigator; the Medical Monitor should be consulted if needed.

4.6 Withdrawal Criteria

A subject may voluntarily discontinue treatment and/or withdraw from participation in this study at any time at his/her own request or may be discontinued from study treatment at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. Subjects withdrawn from the study will not be replaced.

4.6.1 Reasons for Withdrawal from the Study

Study drug will be discontinued and the subject withdrawn from the study for any of the following reasons:

- Subject has an AE that is considered to be related to study drug or procedures AND is severe enough to warrant treatment discontinuation, as determined by the Investigator (Section 8.1).
- Pregnancy
- Any Grade 3 or 4 AE, based on Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) criteria, considered causally related to study drug (Section 8.2.2)

Study drug may be discontinued and the subject withdrawn from the study for any of the following reasons:

- Subject requires concurrent prohibited medication during the study (Section 5.6.2). Nonmedicated emollients that do not contain salicylic acid may be used on nonlesional skin but the subject (or caregiver) should wait at least 30 minutes after applying study drug before applying nonmedicated emollients; emollients should not be applied to lesional skin during treatment. The same emollient should be used throughout the subject's participation in the study.

  NOTE: If, in the opinion of the Investigator and the study Medical Monitor, such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the subject, then the subject may continue to receive study drug. If the subject is permanently discontinued from study drug, they may remain in the study for safety assessments as needed, at the discretion of the Investigator and Medical Monitor, but they are not eligible to enroll in the OL-LTE.
- Subject noncompliance
- Investigator noncompliance
- Discontinuation of the study at the request of the Sponsor, regulatory agency, or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

If a subject meets a withdrawal criterion during treatment, an Early Termination visit will be required (Section 7.9).

4.6.2 Withdrawal Procedures

The primary reason for the discontinuation of study drug and/or withdrawal from study must be recorded in the source document and on the case report form (CRF). If a subject is prematurely discontinued from study drug, the Investigator must make every effort to perform an Early Termination Visit (Section 7.9) and document the primary reason for withdrawal.

4.7 Lost to Follow-Up

A subject is considered lost to follow-up if he/she repeatedly fails to return to the study site for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject or caregiver and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject or caregiver (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject or caregiver continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up. In this case, the discontinuation date will be listed as the date the certified letter was mailed to the subject.

5 Study Treatment

5.1 Study Drug

5.1.1 Description, Packaging, and Labeling

The descriptions of the study drugs, tapinarof cream, 1% and the vehicle cream, are presented in Table 2.

Table 2: Tapinarof and Vehicle Cream

[redacted]

All labels for tapinarof cream, 1% and vehicle cream to be distributed in the participating countries will meet all applicable requirements of those countries.

5.1.2 Storage

All study drugs must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff. The study drug storage temperature range will be provided in the study reference manual.

5.1.3 Handling and Disposal

Under normal conditions of handling and administration, study drug is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or the Sponsor study contact.

Arrangements will be made for used and unused drug supplies to be returned to the Sponsor or Sponsor designee, or for destruction on site following acceptable, documented procedures. Further guidance and information for final disposition of unused study drug will be provided.

5.1.4 Preparation

No special preparation of study drug is required.

5.1.5 Administration of Study Drug

Study drug will be dispensed to subjects or their caregivers at the clinical site in appropriately labeled tubes.

Subjects or caregivers will take the tubes home and self-administer study drug (or have caregiver apply if necessary) to affected areas QD, except on clinic visit days when study drug is applied under supervision at the site.

Subjects will be instructed to apply study drug as follows:

- QD application to affected areas; subjects or their caregivers are advised to choose the application time they prefer and to apply the study drug at that approximate time each day of study participation. Subjects should avoid dosing around midnight to avoid potentially dosing twice in one calendar day.
- If a subject misses a daily dose, it will be recorded as a protocol deviation. The subject should continue dosing the next day and should not apply more than once daily to make up for the missed dose on the previous day. If a dose is missed, the missed dose and the reason for the missed dose should be recorded in the daily diary as such. Itch rating can still be recorded in the diary even if a daily dose was missed.
- Study drug should be applied to dry, clean skin.
- Study drug may be applied to skin around the eye but avoid direct contact with the eye – study drug is not for ophthalmic use.
- Wash hands after application, unless treating lesions on the hands.
- Study drug should be applied to all lesions, including newly appearing lesions and lesions that have improved or resolved during the study. A body diagram identifying locations of lesions may be provided to the subject and/or caregiver.
- Subjects are allowed, but not required, to treat scalp lesions with study drug; however, efficacy analyses will not include assessment of AD in this area.
- If there is residual cream visible on the disease-affected lesional skin, then the subject or caregiver should be instructed to continue to lightly rub the cream into the skin until it is no longer visible.
- If study drug is applied to the subject by another person, that person should thoroughly wash his/her hands after application.
- When dosing at home subjects or caregiver should record the time of study drug application in the daily diary. Itch rating should also be recorded in the diary.
- On clinic visit days, study drug should be applied in the clinic under the supervision of site personnel and after safety and efficacy assessments have been completed (except for subject and Investigator LTS at Weeks 1, 2 and 4).

  NOTE: The time of the dose and assessments on clinic visit days will depend on the time of the clinic visit. Therefore, the timing of the clinic visit may differ from the subject's chosen dosing time. The intention is to allow flexibility to accommodate subjects' schedules.
- Nonmedicated emollients that do not contain salicylic acid may be used on nonlesional skin but the subject (or caregiver) should wait at least 30 minutes after applying study drug before applying nonmedicated emollients; emollients should not be applied to lesional skin during treatment. The same emollient should be used throughout the subject's participation in the study.

Subjects and/or caregivers will be instructed/reminded on how to apply study drug at each clinic visit (except during the final treatment visit).

5.1.6 [redacted]

[redacted]

[redacted]

5.2 Randomization/Treatment Assignment

For the double-blind, vehicle-controlled phase of the study, subjects will be randomized at a ratio of 2:1 to receive tapinarof cream, 1% or vehicle cream as follows:

Randomization in Double-Blind, Vehicle-Controlled Phase	
Regimen	**Number of Subjects**
Tapinarof cream, 1% QD for 8 weeks	Approximately 267 Subjects
Vehicle cream QD for 8 weeks	Approximately 133 Subjects

QD = once daily

Randomization will be stratified by Baseline vIGA-AD™ score so that subjects with severe AD (vIGA-AD™ score of 4) will be limited to approximately 10% each of the total randomized population, and the majority of the enrolled subjects (approximately 90%) will have a vIGA-AD™ score of 3, signifying moderate disease.

Randomization will also be stratified by age so that a minimum of approximately 15% of subjects will be enrolled into each of the following age groups: 2-6 years, 7-11 years, 12-17 years, 18 years and above. Adults 18 years and above will comprise a maximum of 20% of enrolled subjects.

The randomization lists will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. Access to the codes will be controlled and documented.

5.3 Blinding

The Investigator, study site staff, subject, and Sponsor will be blinded to treatment assignment.

The study blind should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the study drug the subject received. The following conditions will apply for breaking the blind:

- The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study drug is essential for the appropriate clinical management or welfare of the subject as judged by the Investigator.
- Investigators will contact the Medical Monitor, who will have direct access to the system for unblinding an individual study subject.
- The Investigator should discuss options with the Medical Monitor or appropriate study personnel before making the decision to unblind the subject's treatment assignment.

- If the Sponsor personnel are not contacted before the unblinding, the Investigator must notify the Sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF.
- A subject will be withdrawn if the subject's treatment code is unblinded by the Investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the source documents and CRF.
- The Sponsor or their designee may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to Investigators in accordance with local regulations.

5.4 Compliance with Study Drug Administration

At Baseline, study staff will provide the subject or caregiver with detailed instructions concerning protocol requirements and use of study drug. Additionally, subjects or caregivers will be asked to complete a daily diary with the time of each application of study drug, except on study visit days. At each post-Baseline study visit, study staff will review use of study drug, as applicable, with the subject or caregiver. Subject compliance will be assessed via study diary completion.

When subjects are dosed at the site, they and/or their caregiver will apply the study drug under supervision of the study staff. The date and time of each dose administered in the clinic will be recorded in the source documents. The study drug and study subject identification should be confirmed at the time of dosing by a member of the study site staff other than the person dispensing the study drug.

At the time of dispensing study drug to each subject, site personnel will weigh the tubes to be dispensed with the cap on and will record the weight of all tubes dispensed at each visit in the drug accountability logs. Subjects and/or caregivers will be instructed to bring all used and unused tubes with them to each study visit. Site personnel will weigh the returned tubes (used and unused) with the cap on and record the weight in the drug accountability logs. If a tube has been lost, discarded, or forgotten by the subject, then the site personnel will make a notation of this on the drug accountability logs. Forgotten tubes should be returned by the subject at the next study visit. Tubes of study medication dispensed at the most recent prior visit which remain unopened (the foil cap on the tube remains fully intact/undisturbed) may be re-dispensed to study subjects at the current visit. Unopened tubes may only be re-dispensed once. Opened, partially used tubes or tubes with foil overlay removed are not to be re-dispensed to study subjects. If there is any question as to re-dispensation, sites should issue new tubes of study medication to the subject(s).

5.5 Treatment after the End of the Study

Subjects will not receive any additional treatment with the study drug from the Sponsor after completion of the study (with the exception of eligible subjects who enroll in the OL-LTE study) because the indication being studied is not life threatening or seriously debilitating and other treatment options are available.

The Investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not the Sponsor is providing specific post-study drug.

5.6 Prior and Concomitant Therapy

Any medication (including over the counter or prescription medication, vitamins and/or herbal supplements) administered to the subject up to 30 days before the Screening visit, at the time of enrollment, and during the study must be recorded in the CRF along with the reason for use. The information to be recorded must also include name of the medication (generic name, as a general rule), dose, frequency, administration routes, and dates of the first and last dose, as applicable.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

5.6.1 Permitted Medications and Nondrug Therapies

Concomitant medications for medical treatment of other conditions are allowed under the condition that the dosage and administration of these treatments is not planned to change from the Baseline visit to the completion of the treatment phase (Week 8) and that the medication is not a prohibited medication as described in the Exclusion Criteria (Section 4.3).

In the event of skin infection, topical antibacterial agents with the exception of gentamicin and neomycin sulfate can be applied to the infected area; however, study drug must not be applied to the area until the skin infection is healed.

Nonmedicated emollients that do not contain salicylic acid may be used on nonlesional skin but the subject (or caregiver) should wait at least 30 minutes after applying study drug before applying nonmedicated emollients; emollients should not be applied to lesional skin during treatment. The same emollient should be used throughout the subject's participation in the study.

NOTE: Any emollient used during the study must be recorded as a concomitant medication.

5.6.2 Prohibited Medications and Nondrug Therapies

Medications and nondrug therapies that are prohibited throughout the study duration are described in the Exclusion Criteria (Section 4.3). A list of prohibited medications, emollients and nondrug therapies may be provided as a separate document.

If a subject chooses to treat scalp with study drug, then medicated shampoos that contain coal tar, salicylic acid, or hydrocortisone are prohibited for use.

Emollients containing salicylic acid are prohibited.

6 Study Assessments and Procedures

Study procedures and assessments are summarized in the Schedule of Assessments and in Section 7. Adherence to the study design requirements, including those specified in the Schedule of Assessments (Table 1) are essential and required for study conduct. Protocol waivers or exemptions are not allowed, except for immediate safety concerns.

6.1 Demography, Medical History, and Baseline Characteristics

6.1.1 Demographics

Demographic information collected will include age, sex, race, ethnicity, and Fitzpatrick skin type.

Information on Fitzpatrick skin type can be found in Appendix 2.

6.1.2 Medical History

Medical history will be collected to ensure subjects are eligible for participation in the study (per inclusion Section 4.2 and exclusion Section 4.3 criteria).

Data collected will include year of AD diagnosis, allergic conditions, cardiovascular (CV) medical history and risk factors (including height, weight, blood pressure, medical conditions, and family history of premature CV disease), and family history of liver disease.

As part of the subject's medical history, all systemic (oral and injectable) medications used by the subject for treatment of AD prior to 30 days before the Screening visit will be collected.

If a subject has previously tested positive for COVID-19 or has previously received a COVID-19 vaccine, it should be documented in the subject's medical history.

6.2 Efficacy Assessments

To minimize inter-observer variability, Investigators and evaluators/raters will be trained on each of the required assessments during an Investigator meeting, site initiation visit, and/or utilizing online assessments before enrolling subjects at their study site. Only trained evaluators/raters are permitted to perform the efficacy assessments. To the fullest extent possible, the same Investigator (or designated evaluator/rater) will perform all efficacy assessments for an individual subject throughout the study. If it is not possible for the same evaluator/rater to continue performing assessments, it is recommended that the primary and subsequent evaluator/rater both examine and discuss their respective scoring during at least 1 visit.

6.2.1 Assessments Completed by Investigator

6.2.1.1 Validated Investigator Global Assessment of Atopic Dermatitis

The vIGA-AD™ of disease severity will be assessed at every clinic visit. The vIGA-AD™ is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity (scalp excluded) and will be determined according to the categories described in Table 3 and Appendix 3. To be eligible, subjects must have a vIGA-AD™ score of 3 or 4 at Screening and the Baseline visit (Day 1). Eli Lilly and Company developed the vIGA-AD™ scale for use in clinical trials.

Table 3: Validated Investigator Global Assessment Scale for Atopic Dermatitis

Score	Category	Definition
0	Clear	No inflammatory signs of atopic dermatitis (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 widespread in extent. Oozing or crusting may be present.

6.2.1.2 Body Surface Area Affected

The assessment of the %BSA affected is an estimate of the percentage of total involved skin with AD. For the purpose of clinical estimation, the total palmar surface of the subject's palm and digits may be assumed to be approximately equivalent to 1% BSA. The %BSA affected by AD will be evaluated from 0% to approximately 100% (scalp excluded). Details on calculation of approximate %BSA involvement in each subject are provided in Appendix 4. Percentage BSA is a static assessment made without reference to previous scores.

6.2.1.3 Eczema Area and Severity Index

The EASI will be assessed at every clinic visit. It quantifies the severity of a subject's AD based on both lesion severity and the %BSA affected [Hanifin, 2001]. The subject's scalp is excluded from this assessment. The EASI is a composite score ranging from 0 to 72 that takes into account the degree of erythema, edema/papulation, excoriation, and lichenification (each scored from 0 to 3 separately) for each of four body regions, with adjustment for the %BSA involved for each body region relative to the whole body. A detailed procedure of EASI score calculation is provided in Appendix 4. The EASI score will be calculated in the CRF based on the subject's age, the rating scores for each region, and the number of handprints involved for each region.

6.2.2 Assessments Completed by Subject or Caregiver

A summary table of assessments completed broken down by age group is provided in Appendix 5.

[redacted]

[redacted]

6.2.2.3 Peak Pruritus-Numeric Rating Scale

The PP-NRS is a scale used to quickly assess itch/pruritus severity over a 24-hour period. The subject or caregiver will utilize the scale to assess peak pruritus QD and record the results in their daily diaries. The itch rating can be done before or after study drug administration since it should reflect the past 24 hours. On clinic visit days, the PP-NRS will be assessed in the clinic. For subjects ages 2 to < 12 years, the PP-NRS will be completed by the caregiver. For subjects ages ≥ 12 years, the PP-NRS will be completed by the subject.

An example of the PP-NRS is provided in Appendix 11.

[redacted]

[redacted]

6.2.3 Optional Clinical Photography

Clinical photography may be performed in a subgroup of subjects at selected study sites. Informed consent/assent and photographic release will be required. The photographs may not be referred to by the Investigator at any subsequent study visit for the purposes of grading.

Photographs will be taken of a representative area of the subject's disease area at the time points specified in the Schedule of Assessments (Table 1). Photographs of the selected skin area will be taken in a standardized fashion (i.e., same camera, angle, background, distance).

6.3 Safety Assessments

6.3.1 Adverse Events

All AEs and SAEs will be collected from the time the subject signs the informed consent form (ICF) until the final visit/contact with the subject. Additional safety information, including the definition of an AE and the methods for recording, evaluating, and assessing causality of AEs and the procedures for completing and transmitting SAE reports are provided in Section 8.

6.3.2 Brief Physical Examination

A brief physical examination will include, at a minimum, assessments of the skin, lungs, CV system, and abdomen (liver and spleen). Assess for changes in onset of menses (female participants) or sexual activity (male or female participants). Determine if there is a need for contraception or barrier use. Height and weight will be measured at Screening only. Investigators should pay special attention to clinical signs related to previous serious illness.

6.3.3 Vital Signs

Vital signs will be measured before blood collection for clinical laboratory assessments and PK analysis (where applicable) and will include measurements of systolic and diastolic blood pressure, pulse rate, and body temperature. Subjects should be in a seated position for at least 5 minutes before vital signs measurement.

6.3.4 Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual or Laboratory Manual and the protocol Schedule of Assessments (Table 1). Laboratory requisition forms must be completed, and samples must be clearly labeled with the subject number, protocol number, site number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Study Reference Manual or the Laboratory Manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

A list of clinical laboratory tests and parameters is provided in Table 4.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the Investigator, the etiology should be identified, if possible, and the Sponsor and Medical Monitor notified.

Table 4: Laboratory Tests

Diagnostic Screening Tests		
• HBsAg • Hepatitis C antibody • Anti-HBc • Anti-HBs[a]	• Pregnancy tests: (serum at Screening and urine at other visits when performed; women of CBP only)[b] • FSH (as needed in women of non-CBP only) • At the Investigator's discretion, subjects may be screened for alcohol and illicit drug use.	
Serum Chemistry		
• BUN • Creatinine • Glucose (fasting not required) • Sodium • Potassium • Chloride	• Total carbon dioxide • Calcium • AST • ALT • Alkaline phosphatase	• Uric acid • Total bilirubin (+fractionated if required) • Total protein • Albumin
Hematology		
• Platelet count • RBC count • WBC count (absolute) • Hemoglobin • Hematocrit	• RBC Indices: • MCV • MCH • MCHC • Reticulocyte percentage	• WBC Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Urinalysis		
• Specific gravity • Microscopic examination (if blood or protein is abnormal		• Dipstick: pH, Glucose, Protein, Blood Ketones

a. Reflex test: a negative HBsAg and a positive anti-HBc may enroll if there is a positive anti-HBs demonstrating natural immunity

b. Pregnancy tests should be administered based on CBP, which may change after the start of the study (e.g. a premenarchal female subject experiences menarche or a female subject ceases to meet the criteria of CBP)

ALT = alanine aminotransferase; Anti-HBc = anti-hepatitis B core antigen; Anti-HBs = anti-hepatitis B surface antigen; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBP = child-bearing potential; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell(s); WBC = white blood cell(s).

6.3.5 Electrocardiograms

Single 12-lead ECGs will be obtained at a subset of sites in a subset of subjects at timepoints indicated in the Schedule of Assessments (Table 1) and Section 7 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Subjects should be in a supine or semi-supine position for at least 5 minutes before ECG is measured. In case of an abnormal ECG or excess artifact, the ECG may be repeated two additional times over several minutes (triplicate in total), to allow further evaluation and averaging of interval measurements as necessary. Abnormal ECGs should be characterized as clinically or non-clinically significant by the investigator. In the event of a clinically significant change from baseline in the ECG for which the etiology cannot be identified, the Medical Monitor should be contacted.

6.3.6 Local Tolerability Scale

6.3.6.1 Investigator-Assessed Local Tolerability Scale

At each specified study visit, the Investigator (or qualified evaluator) will assess the presence and overall degree of irritation at the application sites, according to a 5-point LTS. The score will ideally represent an "average" across all application sites. To the fullest extent possible, the same Investigator (or designated evaluator) will perform all tolerability assessments for an individual subject throughout the study. If the subject is applying study drug to "sensitive areas", a separate LTS will be used to assess the degree of irritation for each of these areas where study drug is applied. The sensitive areas that will be assessed are face, neck, skin folds, axilla, inframammary, anal crux, and genitalia. An example of the Investigator-assessed LTS is shown in Appendix 15. The LTS should be completed pre-dose at Baseline and within 2 hours post-dose at Weeks 1, 2 and 4. At Week 8 and the ET visit, when study drug is not being applied at that visit, the LTS should be completed when other assessments are completed. Other than at the Baseline visit, the Investigator-assessed LTS should only completed when the subject is currently receiving study drug (i.e. has applied at least one application in the last 48 hours).

6.3.6.2 Subject (or Caregiver)-Assessed Local Tolerability Scale

At each specified study visit, the subject or caregiver will separately assess the presence and degree of burning/stinging and itching at the application sites, each according to a 5-point LTS. The subject or caregiver will not score each sensitive area individually but provide one overall score that will ideally represent an "average" across all application sites. An example of the subject (or caregiver)-assessed LTS is shown in Appendix 16. The subject (or caregiver)-assessed LTS should be completed pre-dose at Baseline and within 2 hours post-dose at Weeks 1, 2 and 4. At Week 8, when study drug is not being applied at that visit, the LTS should be completed when other assessments are completed. Other than at the Baseline visit, the subject (or caregiver)-assessed LTS should only completed when the subject is currently receiving study drug (i.e. has applied at least one application in the last 48 hours). For subjects ages < 12 years, the LTS will be completed by the caregiver. For subjects ages ≥ 12 years, the LTS will be completed by the subject.

6.4 Treatment of Study Drug Overdose

For this study, accidental or intentional oral ingestion of drug product will be considered an overdose. Ingestion of a 30-gram tube of tapinarof cream, 1% would result in an oral dose of 300 mg.

The Sponsor does not recommend specific treatment for an overdose; however, in the event of an overdose, the Investigator (or treating physician) should do the following:

- Contact Medical Monitor to discuss the event
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities
- Provide general symptomatic treatment as necessary
- Document the quantity of the excess dose as well as the duration of the overdosing.
- If the Medical Monitor requests a plasma sample for PK analysis, then a blood sample for PK should be obtained within 2 days from the date of the last dose of study drug.

Decisions regarding dose interruptions or modifications following an overdose will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.5 Pharmacokinetics

Blood samples for PK analysis of tapinarof concentration will be collected at a subset of sites in a subset of subjects at timepoints indicated in the Schedule of Assessments (Table 1) and Section 7. The actual date and time of each blood sample collection will be recorded as well as the date and time of the last dose of study drug prior to sample collection. Collection, processing, storage, and shipping procedures are provided in the Study Reference Manual or the Laboratory Manual.

Concentrations of tapinarof will be determined in plasma samples using a validated bioanalytical method. Raw data will be archived at the bioanalytical site.

Informed consent/assent for collection of PK samples will be required.

6.6 Virtual Assessments

In the event that a subject cannot attend their regularly scheduled study visits in person due to a COVID-19-like situation necessitating a limit on in-person contact, the Investigator may perform safety and efficacy assessments by phone or video. Source documentation should note if the visit was performed by phone or by video. The Investigator may use the technology platform that is currently available to them. Suggested platforms include Apple FaceTime, Zoom for Healthcare, Facebook Messenger video chat, Microsoft Teams, Google Hangouts video, and Skype. Additional details of the visit should be included in source documentation, as detailed in the Study Reference Manual.

If the subject can only be contacted by phone, the following should be assessed or performed:

- AEs
- Concomitant Medications
- Reminder to complete diary
- Instruction not to discard empty tubes of study drug

If the subject has video capabilities, the following items should be assessed or performed:

- AEs
- Concomitant Medications
- vIGA-AD™ assessment (excluding subject's scalp)

- %BSA affected calculation (excluding subject's scalp)
- EASI assessment (excluding subject's scalp)
- Investigator-assessed LTS
- Subject (or caregiver)-assessed LTS
- Application of study drug by the subject
- Completion of the PP-NRS (the subject or caregiver [as applicable] can verbally indicate the answer which the study coordinator will document in the source document)
- Reminder to complete diary
- Instruction not to discard empty tubes of study drug

The reason that assessments cannot be completed during a virtual assessment (i.e., labs, vital signs, physical exams, etc.) must be noted (e.g., COVID-19) and the missed assessments will be recorded as protocol deviations.

7 Timing of Procedures and Assessments

This section lists the procedures and assessment to be performed at scheduled timepoints during the study as outlined in the Schedule of Assessments (Table 1). Information on study procedures and assessments is provided in Section 6.

- Any change in timing or any addition of a timepoint(s) for any planned study assessment must be documented in a "Note to File," which is approved by the relevant Sponsor study team member and then archived in the study Sponsor and site study files; this will NOT constitute a protocol amendment.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring or amendment of the ICF.

NOTE: Assessments and procedures should be performed pre-dose on clinic visit days except for LTS at Weeks 1, 2 and 4.

7.1 Visit 1; Screening Period (Day -30 to Day -1)

After the subject has signed the consent/assent form, potential study subjects will undergo Screening procedures and assessments to confirm eligibility to participate in the study. Screening assessments will include the following:

- Demography recording
- Fitzpatrick skin type
- Medical history recording (including all medications administered up to 30 days prior to screening, and all systemic [oral and injectable] medications used by the subject for the treatment of AD prior to 30 days before Screening)
- Serum pregnancy test (females of child-bearing potential)
- Brief physical examination (including height and weight, body mass index will be calculated in the CRF)
- Vital signs measurements
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- AE recording (from the time the ICF is signed)
- Concomitant medication recording
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)

To determine subject eligibility at Screening, a single repeat of tests or procedures may be allowed at the discretion of the Investigator. The Medical Monitor should be consulted if needed.

7.2 Visit 2; Baseline (Day 1)

On Day 1, subjects will be reassessed to confirm continued eligibility to participate in the study. All subjects who continue to meet study eligibility criteria will be randomized to treatment.

The following additional procedures and assessments will be performed at the Baseline Visit:

- Changes to medical history will be recorded
- Urine pregnancy test (females of child-bearing potential)
- Brief physical examination
- Vital signs measurement
- ECG recording (at a subset of study sites only)
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)

  NOTE: Blood sample collection for clinical laboratory tests is not required at the Baseline Visit if it has been ≤14 days since samples were collected at Screening and the results of those clinical laboratory tests were not clinically significant.
- Urinalysis

  NOTE: Urine sample collection for urinalysis is not required at the Baseline Visit if it has been ≤14 days since samples were collected at Screening and the results of those analyses were not clinically significant.
- Photography of a representative area of the subject's disease area (at a subset of study sites only)
- AE recording
- Concomitant medication recording
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- Investigator-assessed LTS (pre-dose)
- [redacted]
- [redacted]
- PP-NRS
- [redacted]
- [redacted]
- Subject (or caregiver)-assessed LTS (pre-dose)
- Dispense diary (subjects or their caregivers will be instructed on how and when to complete diary)
- Subject randomized to study treatment
- Dispense study drug
- Instruction on how to apply study drug
- Study drug application under supervision

7.3 Visit 3; Week 1 (Day 8 ±2 Days)

The following procedures and assessments will be performed at Visit 3:

- Vital signs
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- [redacted]
- [redacted]
- PP-NRS
- [redacted]
- [redacted]
- AE recording
- Concomitant medication recording
- Collect and review subject diaries for treatment compliance
- Dispense subject diaries
- Collect and dispense study drug
- Review instructions on how to apply study drug
- Study drug application under supervision
- Investigator-assessed LTS (post-dose)
- Subject (or caregiver)-assessed LTS (post-dose)

7.4 Visit 4; Week 2 (Day 15 ±2 Days)

The following procedures and assessments will be performed at Visit 4:

- Vital signs measurement
- Photography of a representative area of the subject's disease area (at a subset of study sites only)
- AE recording
- Concomitant medication recording
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- [redacted]
- [redacted]
- PP-NRS
- [redacted]
- [redacted]
- Collect and review subject diaries for treatment compliance

- Dispense subject diaries
- Collect and dispense study drug
- Review instructions on how to apply study drug
- Study drug application under supervision
- Investigator-assessed LTS (post-dose)
- Subject (or caregiver)-assessed LTS (post-dose)

7.5 Visit 5; Week 4 (Day 29 ±2 Days)

The following procedures and assessments will be performed at Visit 5:

- Urine pregnancy test (females of child-bearing potential)
- Brief physical examination
- Vital signs measurement
- ECG recording (at a subset of study sites only)
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- Blood sample collection for PK analysis (at a subset of study sites only)
- Photography of a representative area of the subject's disease area (at a subset of study sites only)
- AE recording
- Concomitant medication recording
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- [redacted]
- [redacted]
- PP-NRS
- [redacted]
- [redacted]
- Collect and review subject diaries for treatment compliance
- Dispense subject diaries
- Collect and dispense study drug
- Review instructions on how to apply study drug
- Study drug application under supervision
- Investigator-assessed LTS (post-dose)
- Subject (or caregiver)-assessed LTS (post-dose)

7.6 Visit 6; Week 8 (Day 57 ±2 Days)

The following procedures and assessments will be performed at Visit 6:

- Urine pregnancy test (females of child-bearing potential)
- Brief physical examination
- Vital signs measurement
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- Blood sample collection for PK analysis (at a subset of study sites only)
- ECG recording (at a subset of study sites only)
- Photography of a representative area of the subject's disease area (at a subset of study sites only)
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- [redacted]
- [redacted]
- PP-NRS
- [redacted]
- [redacted]
- Investigator-assessed LTS
- Subject (or caregiver)-assessed LTS
- AE recording
- Concomitant medication recording
- Collect subject diaries
- Review subject diaries for treatment compliance
- Collect study drug
- Enrollment in OL-LTE study (optional)

7.7 Phone Contact at Weeks 3 (Day 22 ±2 Days) and 6 (Day 43 ±2 Days)

Subjects or their caregivers will be contacted by phone at Weeks 3 and 6 to review study drug application instructions and to record AEs and concomitant medication use. Subjects should be reminded to complete their daily diary and bring it with them to the next clinic visit.

7.8 Follow-Up Visit 7; Week 9 (Day 64 ±2 Days)

Subjects who complete Visit 6/Week 8 but do not enroll in the OL-LTE study will return to the study site at Week 9 to complete Follow-Up assessments as follows:

- Brief physical examination

- Vital signs measurement
- If needed, blood sample collection for clinical laboratory tests
- If needed, urinalysis
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- [redacted]
- [redacted]
- PP-NRS
- [redacted]
- [redacted]
- AE recording
- Concomitant medication recording

7.9 Early Termination Visit

Subjects who withdraw early from the study will be asked to return to the study site to complete Early Termination assessments as follows:

- Urine pregnancy test (females of child-bearing potential)
- Brief physical examination
- Vital signs measurement
- Blood sample collection for clinical laboratory tests
- Urinalysis
- ECG recording (at a subset of study sites only)
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- [redacted]
- [redacted]
- PP-NRS
- [redacted]
- [redacted]
- Investigator-assessed LTS
- Subject-assessed LTS
- AE recording
- Concomitant medication recording
- Collect subject diaries

- Review subject diaries for treatment compliance
- Collect study drug

7.10 Unscheduled Visit

Subjects may have an unscheduled visit for AE follow-up, study drug dispensation, make-up for a missed visit, or other reason. The following assessments may be performed:

- Urine pregnancy test (females of child-bearing potential)
- Brief physical examination
- Vital signs measurement
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- ECG recording (at a subset of study sites only)
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- Investigator-assessed LTS
- Subject (or caregiver)-assessed LTS
- PP-NRS
- AE recording
- Concomitant medication recording
- Dispense and/or collect subject diaries
- Review subject diaries for treatment compliance
- Dispense and/or collect study drug
- Review instructions on how to apply study drug

7.11 End of Study

The end of study is defined as when the last active subject has completed the Week 9 Follow-up Visit which is 1 week after the end of treatment (if subject does not enroll in the OL-LTE study) OR the last active subject has completed the 8 weeks of treatment in this study (if subject is eligible and enrolls in the OL-LTE study).

8 Safety Monitoring and Reporting

8.1 Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

The Investigator or site staff is responsible for detecting, documenting, and reporting events that meet the definition of an AE, SAE, or AESIs. At each visit/contact, subjects should be questioned in a general way so as not to introduce bias in detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study drug or study participation, the Investigator should promptly notify the Sponsor.

A narrative will be written and included in the Clinical Study Report for all SAEs and AESIs, and for all AEs that lead to study discontinuation.

8.1.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject temporally associated with the use of a medicinal product, whether considered causally related or not related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry) or other safety assessments (e.g., vital signs measurements), including those that worsen from Baseline, and felt to be clinically significant in the medical and scientific judgment of the Investigator
- Exacerbation of a chronic or intermittent pre-existing condition (e.g., plaque psoriasis) including either an increase in frequency and/or intensity of the condition
- For skin-related AEs, it should be noted whether or not the event is in the area of active application of study drug, and/or if spreading beyond the application site.
- New conditions detected or diagnosed after study drug administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication (overdose per se will not be reported as an AE/SAE)
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

8.1.2 Definition of Serious Adverse Event

If an event is not an AE per Section 8.1.1, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc.).

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization
  - In general, signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
- Results in disability/incapacity: a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Results in a congenital anomaly/birth defect

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for

allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.1.3 Adverse Events of Special Interest

In prior clinical studies, contact dermatitis, folliculitis, and headache have been identified as AEs of particular clinical importance and will be reported as AESIs in this study whether or not the AE is considered related to study drug.

In each case study drug may be continued or discontinued, based on Investigator judgment, and may be restarted when the event resolves. In addition, the following information must be collected for each of these AESIs:

Contact Dermatitis

The study site should collect location, duration, size, associated symptoms (itching, burning, pain), severity (mild, moderate, severe), time to onset, and photograph the affected site (if possible). If the subject or caregiver contacts the study site to report significant skin irritation at or near the site of study drug application between study visits, the subject should be brought in for an unscheduled visit, if possible.

Headache

The study site should collect duration, severity (mild, moderate, severe), time to onset, and location (e.g., frontal, temporal, occipital, diffuse).

Follicular Event

The study site should collect the location, duration, size, associated signs and symptoms (itching, burning, pain, erythema), severity (mild, moderate, severe), describe morphology [scale (keratotic/cornified) or no scale (non-keratotic/non-cornified)], time to onset, and photograph the affected site (if possible). Additional information regarding management of folliculitis is provided in Section 8.2.1.2.4.

In particular, the term ‘folliculitis’ may not correctly describe the morphology of the observed local follicular events as these appear to be more consistent with a keratoses pilaris-like follicular based papule. Tapinarof upregulates components of the stratum corneum, including involucrin, hornerin, and filaggrin and increased cornification at, and subsequent mechanical occlusion of, the follicular ostia has been suggested to be a potentially on target mechanism by which these lesions may develop in some individuals treated with tapinarof cream. Additional morphologic description will help to more fully and appropriately characterize these follicular events.

Possible descriptors include, but are not limited to:

- Folliculitis
  - Non-inflammatory
  - Inflammatory
- Milia
  - Non-inflammatory
  - Inflammatory
- Keratosis pilaris

- Non-inflammatory
- Inflammatory

Additional AESIs may be identified during the evaluation of safety data for the Clinical Study Report.

8.2 Classification of Adverse Events

8.2.1 Assigning Severity Rating for Adverse Events

8.2.1.1 Criteria for Determining Adverse Event Severity

The Investigator will make an assessment of the severity of each AE and SAE according to the National Cancer Institute CTCAE, v. 5.0, 2017. For terms not specified with the CTCAE, the criteria in Table 5 should be used to determine the grade severity.

Table 5: Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

Grade	Criteria
1	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living[b]
4	Life threatening consequences; urgent intervention indicated
5	Death related to adverse event

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

CTCAE = Common Terminology Criteria for Adverse Events.

AE severity should be recorded in the appropriate section of the AE CRF and in the subject's source documents.

8.2.1.2 Toxicity Management Criteria

8.2.1.2.1 Grade 1 or Grade 2 Adverse Event

Subjects who develop a Grade 1 or Grade 2 AE may continue investigational product at the discretion of the Investigator. Subjects who choose to withdraw from study due to a Grade 1 or 2 AE should have study withdrawal/early termination evaluations completed.

8.2.1.2.2 Grade 3 Adverse Event

Subjects who develop a Grade 3 AE should be managed as follows:

- If the Investigator has compelling evidence that the Grade 3 AE has not been caused by investigational product, then dosing may continue after discussion with the Medical Monitor.
- Subjects who develop a Grade 3 AE that the Investigator considers related to investigational product should have the investigational product discontinued. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of investigational product should be followed weekly until resolution or stability of the AE and encouraged to have withdrawal study evaluations completed.

8.2.1.2.3 Grade 4 Adverse Event

Subjects who develop a Grade 4 AE should have investigational product permanently discontinued.

Subjects experiencing Grade 4 AEs requiring permanent discontinuation of investigational product should be followed weekly until resolution or stability of the AE and encouraged to have withdrawal study evaluations completed.

8.2.1.2.4 Folliculitis

Subjects using tapinarof topically may experience folliculitis. The majority of these events are mild or moderate and do not require intervention or interruption in study drug use. On close inspection, the morphology is similar to that of keratosis pilaris suggesting that the potential mechanism may be increased follicular cornification with subsequent follicular plugging. Importantly, AhR regulates the epidermal differentiation complex and tapinarof has been shown to repair the skin barrier through activation of stratum corneum components including fillagrin, hornerin and involucrin. This latter point suggests that the keratosis pilaris-like reaction may be an on-target effect associated with a therapeutic response to tapinarof cream.

While the majority of events have not required nor resulted in the need for intervention, several approaches can be employed to manage those patients with folliculitis who may be symptomatic including temporary interruption of study drug use at sites of folliculitis and/or the local application to affected areas of topical keratolytics such as 12% lactic acid lotion or 5-10% urea creams or lotions.

8.2.1.2.5 Other Management Criteria:

The Medical Monitor should be notified if any of the following occur:

- Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the subject at risk (e.g., laboratory tests or vital signs, etc.) as judged by the Investigator.

8.2.2 Assigning Causal Relationship to Study Drug

The Principal Investigator or sub-Investigator is to make the causality assessment. The reasonable possibility of the relationship of an AE to study drug is to be assessed with careful medical consideration at the time of evaluation of an AE. The following definitions are to be used for the relationship of the AE to study drug:

- **Related**: A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship plausible, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge), although information on drug withdrawal may be lacking or unclear.
- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

Any AEs /SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to study drug will be recorded from the time a subject consented to participate in the study up to and including any follow-up contact.

All AEs, whether related to study drug or not, must be fully and completely documented on the AE page of the CRF and in the subject's clinical record. In the event a subject is withdrawn from the study because of an AE, the primary reason for withdrawal (i.e., due to an AE) must be recorded on the CRF as such.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

8.3.1 Adverse Event Reporting

All AEs will be collected from the time of signed informed consent until the final visit.

Any AEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) will be collected from the time a subject consented to participate in the study up to and including any follow-up contact.

All SAEs will be recorded in the CRF and reported to the Sponsor within 24 hours via email or phone (refer to Medical Monitor / Sponsor Information Page for contact information) (see Section 8.4).

8.3.2 Follow-Up of Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and nonserious AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or if the subject is lost to follow-up.

The Investigator will assess the outcome of each AE using the following criteria:

- **Recovered/Resolved**: The event has improved or subject recuperated.
- **Recovered/Resolved with sequelae**: The subject has recuperated but retained pathological conditions resulting from the prior disease or injury.
- **Recovering/Resolving**: The event is improving.
- **Not recovered/Not resolved**: The event has not improved or subject recuperated.
- **Unknown**: The outcome of the event is not known, not observed, not recorded, or refused.
- **Fatal**: Termination of life as an outcome of the AE.

8.4 Reporting Procedures

8.4.1 Serious Adverse Event Reporting

When an Investigator determines that an AE meets the protocol definition of an SAE during the study, he/she must notify the Sponsor using an SAE Report Form **within 24 hours of the study site personnel's knowledge of the event**, regardless of the Investigator assessment of the relationship of the event to study drug. Relevant information will be entered on the AE page and on all other applicable pages of the CRF; source documentation should not be sent with the SAE Report Form unless requested.

Follow-up information received on SAEs should be emailed or faxed to the Sponsor within 1 business day of receipt (refer to Medical Monitor/ Sponsor Information Page for contact information). This information should be included on a follow-up SAE form and filed with the original SAE information.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The completed SAE Report form should be submitted via email or fax to the SAE Reporting Contact which can be found on the Medical Monitor/ Sponsor Information Page of this protocol.

Do not delay reporting a suspected SAE in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report.

8.4.2 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of SAEs (even for non-interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and are forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.5 Pregnancy Management and Reporting

Any female subject who becomes pregnant during the study will be withdrawn. Details will be collected for all pregnancies in female subjects and female partners of male subjects that begin after the start of dosing and through the Follow-up visit. Pregnancy is not automatically considered an AE.

If a pregnancy is reported, then the Investigator should complete a Pregnancy Report Form and submit via email or fax to the Pregnancy Reporting Contact for which contact information can be found on the Medical Monitor / Sponsor Information Page of this protocol, within 2 weeks of learning of the pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the study drug must be promptly reported to the Sponsor or the Sponsor's representative.

The Investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to the Sponsor or the Sponsor's representative as described above. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Sponsor or the Sponsor's representative. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported on the Pregnancy Report Form.

9 Data Management

For this study, subject data will be entered into the Sponsor-defined CRFs, transmitted electronically to the Sponsor or designee, and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable Sponsor standards and data cleaning procedures will be used to ensure the integrity of the data, e.g., errors will be corrected, and inconsistencies queried in the data.

Adverse events and relevant medical history will be coded using the most current version of the Medical Dictionary for Regulatory Activities. Concomitant medications will be coded with the most current version of World Health Organization Drug Global Dictionary.

The Investigator will retain original source documents and the Sponsor will receive CRF-required data as electronic datasets. Subject initials will not be collected or transmitted to the Sponsor.

10 Statistical Considerations and Data Analyses

This study will evaluate the efficacy and safety of tapinarof cream, 1% compared with vehicle control cream in adults and children with AD.

10.1 General Considerations

All study data will be summarized by treatment group using descriptive statistics. Categorical variables will be reported using frequency and percentage (e.g., gender, race). Continuous variables will be reported using number of subjects, mean, standard deviation (SD), median, minimum, and maximum. All efficacy and safety data will be listed by subject.

10.2 Determination of Sample Size

It is estimated that the proportion of subjects who will achieve a vIGA-AD™ score of 0 or 1 and at least a 2-grade reduction from Baseline at Week 8 will be 45% for subjects receiving tapinarof compared with 25% for subjects receiving vehicle control, based upon the Phase 2 results. With 400 subjects randomized in a 2:1 ratio (267 subjects receiving tapinarof, and 133 subjects receiving vehicle control), this will provide 97.2% power for statistical significance (2-sided $p < 0.05$). The power is calculated from a Fisher Exact sample size calculation. It is assumed that 15% of the subjects receiving tapinarof will be lost to follow-up by 8 weeks compared with 30% of the subjects receiving vehicle control. These subjects will be included in the primary analysis using the multiple imputation method.

10.3 Analysis Populations

10.3.1 Safety

All randomized subjects who receive at least 1 application of study drug will be included in the Safety population. Subjects will be analyzed as treated.

10.3.2 Intent-To-Treat

All randomized subjects will be included in the Intent-to-treat (ITT) population. Subjects will be analyzed as randomized.

10.3.3 Per-Protocol

All subjects in the ITT population who did not have any major protocol deviations or other events that may impact the interpretation of the primary efficacy endpoint will be included in the Per Protocol (PP) population.

10.3.4 Pharmacokinetic

All subjects who undergo plasma PK sampling and have evaluable concentration-time data for analysis will be included in the PK population. A sample that is below the quantification limit of the assay is considered evaluable.

10.4 Planned Analyses

All efficacy and safety measures over the course of the study will be presented. Details of planned analyses, including the handling of subjects whose visits are impacted by the COVID-19 pandemic, will be described in the Statistical Analysis Plan.

10.4.1 Disposition and Demographics

Demographic and baseline characteristics as well as medical history will be summarized using the ITT population, including frequency and percentages for categorical variables and mean, SD, median, minimum, and maximum for continuous variables.

The numbers of subjects in the different analysis populations will be summarized by treatment group, including overall categories.

10.4.2 Efficacy Analyses

All efficacy analyses will be based on the ITT population and will be repeated for the PP population only for the primary and secondary efficacy endpoints as supportive analysis.

10.4.2.1 Primary Endpoint Analyses

The primary estimand of interest is the composite estimand in a patient population offered treatment with tapinarof cream, 1% as compared to vehicle (see Table 6). Interest is focused on the treatment effect measured by the ratio of response rates at Week 8. The primary efficacy endpoint for treatment effectiveness is proportion of subjects who achieve vIGA-AD™ score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline at Week 8. Subjects who prematurely discontinue treatment due to an AE or lack of efficacy and subjects who use a prohibited medication with significant impact on efficacy evaluations prior to Week 8 will be considered treatment failure as of the start of the intercurrent event.

Table 6 Primary Estimand Attributes

Estimand Attribute	Description
Treatment	tapinarof cream, 1% compared to vehicle
Population	Intent-to-treat
Variable of interest	Proportion of subjects who achieve vIGA-AD™ score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline at Week 8
Intercurrent event handling	Subjects who prematurely discontinue treatment due to an AE or lack of efficacy and subjects who use a prohibited medication with significant impact on efficacy evaluations prior to Week 8 will be considered treatment failure. Investigator assessments will only include data collected at in-person visits.
Summary measure	Ratio of response rates at Week 8

The primary efficacy endpoint will be analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by vIGA AD™ score at Baseline (vIGA AD™ scores of 3 or 4) and by age group (2-6 years, 7-11 years, 12-17 years, 18 years and above). Handling of missing values is described in Section 10.6.

10.4.2.2 Secondary and Exploratory Efficacy Endpoint Analyses

The secondary efficacy endpoints are as follows:

- Proportion of subjects with ≥ 75% improvement in EASI from Baseline at Week 8
- Mean change in %BSA affected from Baseline at Week 8
- Proportion of subjects with ≥ 90% improvement in EASI from Baseline at Week 8

- Proportion of subjects ≥ 12 years old with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4-point reduction in the PP-NRS from Baseline at Week 8

Exploratory efficacy endpoints are as follows:

The same methods as discussed for the primary analysis of the primary endpoint will be used to analyze all dichotomized secondary endpoints. The secondary efficacy endpoints will be tested sequentially in the order listed. Testing will stop if non-significance (2-sided $p \geq 0.05$) is observed.

Post-baseline weekly PP-NRS scores will be an average of 7 daily post-baseline PP-NRS scores prior to and including the values assessed on the visit date.

Other efficacy endpoints will be analyzed using CMH test for proportions, and analysis of covariance (ANCOVA) model for continuous variables. CMH tests will be stratified by Baseline vIGA-AD™ score and age group, and ANCOVA models will include vIGA-AD™ score and age group as categorical covariates and Baseline as a continuous covariate.

All endpoints will be summarized descriptively as follows: continuous data will include the mean, SD, minimum, maximum, median, and number of observations; descriptive summary statistics for categorical data will include frequency counts and percentages.

10.4.3 Safety Analyses

The Safety Population will be used in the analysis of safety data. Data will be listed by subject and treatment and summarized by treatment. No formal statistical comparisons will be made for safety data.

The number and proportion of subjects with TEAEs will be summarized by treatment, system organ class, and preferred term for all TEAEs, all TEAEs considered by the Investigator to be related to study drug, all SAEs, all TEAEs leading to study drug discontinuation, and all TEAEs leading to study discontinuation. All AE summaries will include information for AEs that occurred after administration of the first dose of study drug until completion of the final study visit. Data listings will be provided for subjects who discontinued the study due to an AE and for subjects with an SAE.

Laboratory values will be classified as normal, low or high based on normal ranges supplied by the laboratory. Changes from Baseline in abnormality status will be summarized using shift tables. For quantitative laboratory measures, observed values and changes from Baseline will be summarized descriptively by visit and treatment group.

Observed vital sign values (systolic and diastolic blood pressure, pulse rate, and body temperature) and change from Baseline in vital signs will be summarized similarly to the laboratory values.

Observed ECG parameters and change from Baseline in ECG parameters will be summarized similarly to the laboratory values.

LTS scores will be summarized by treatment and visit for subject (or caregiver) overall assessment and Investigator overall assessment separately.

10.4.4 Analysis of Functional Outcomes and Quality of Life Endpoints

[redacted]

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

[redacted]

10.4.5 Pharmacokinetic Analyses

Data will be listed and summarized. Listings will be sorted by subject and day; summaries will be presented by study visit.

Unless stated otherwise, descriptive summaries for continuous variables will include n, mean, SD, median, minimum, and maximum. Exploratory analyses may include relationships of plasma concentrations with subject demographics or AEs.

10.5 Interim Analyses

No interim analyses will be performed.

10.6 Handling of Missing Data

Every effort will be made to collect complete data at all visits. The primary method of handling of missing data will utilize Multiple Imputations (MI). For sensitivity analysis of the primary and secondary endpoints, Last Observation Carried Forward (LOCF) and Treatment Failure (TF) will be imputed for missing data.

For the MI model, 100 imputations will be generated using PROC MI of SAS. Fully Conditional Specification model using the regression method will be used with the response (e.g., vIGA-AD™ score) at prior post-Baseline visits, Baseline strata, and treatment group as covariates. The ROUND and MINIMUM options will be utilized to ensure imputed values are non-negative integers. The results of the 100 analyses will be transformed into a normal statistic and combined into a single analysis using PROC MIANALYZE.

Additional sensitivity analyses of the primary endpoint will be performed via tipping point analysis.

11 Responsibilities

11.1 Investigator Responsibilities

11.1.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonization guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a United States Investigational New Drug Application, the Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical trial, the Investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or Food and Drug Administration relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Investigators and all sub-Investigators must provide documentation of their financial interest or arrangements with the Sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any sub-Investigator. The Investigator and sub-Investigator agree to notify the Sponsor of any change reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

11.1.2 Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator or on behalf of the Investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the Investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

11.1.3 Informed Consent/Assent

The Investigator is responsible for obtaining written informed consent/assent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The Investigator must utilize an IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent/assent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

11.1.4 Confidentiality

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject number, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The Investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The Investigator agrees that all information received from the Sponsor, including but not limited to the Investigator Brochure, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.1.5 Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) Investigator's study file, and (2) subject clinical source documents.

The Investigator's study file will contain the protocol/amendments, CRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include at least the following information for each subject:

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Participation in trial (including trial number)
- Trial discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end dates (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well)
- Record of all adverse events and other safety parameters (start and end date, and preferably including causality and intensity)
- Concomitant medication (including start and end dates, dose if relevant; dose changes should be recorded)
- Date of trial completion and reason for early discontinuation, if applicable

All clinical study documents must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no

pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The Investigator must notify the Sponsor before destroying any clinical study records.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

11.1.6 Electronic Case Report Forms

For each subject enrolled, a CRF must be completed and signed by the Investigator. This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

11.1.7 Drug Accountability

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the Sponsor and quantities dispensed to subjects, including kit or lot number, date dispensed, subject identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the Sponsor requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. If the site cannot meet the Sponsor's requirements for disposal, arrangements will be made between the site and the Sponsor or its representative for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

11.1.8 Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

11.1.9 Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

11.2 Sponsor Responsibilities

11.2.1 Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. All protocol modifications must be submitted to the IRB or IEC and regulatory authorities in accordance with local requirements. Approval must be obtained before changes can be implemented.

11.2.2 Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study and without prior written approval from Dermavant Sciences, Inc., Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Dermavant Sciences, Inc., in an abstract, manuscript, or presentation form; OR
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Dermavant Sciences, Inc. confidential information (see Section 11.1.4).

The Investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The Investigator will comply with Dermavant Sciences, Inc. request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

11.2.3 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers as required by applicable regulations. Results will be posted as required.

11.3 Joint Investigator/Sponsor Responsibilities

11.3.1 Access to Information for Monitoring

In accordance with ICH Good Clinical Practice guidelines, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

In the event of a COVID-19-like situation necessitating a limit on in-person contact, remote monitoring may be performed.

11.3.2 Access to Information for Auditing or Inspections

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Dermavant Sciences, Inc. may conduct a quality assurance audit.

Authorized representatives of Dermavant Sciences, Inc., a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Dermavant Sciences, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The Investigator should contact Dermavant Sciences, Inc. immediately if contacted by a regulatory agency about an inspection.

Representatives of regulatory authorities or of the Sponsor may conduct inspections or audits of the clinical study. If the Investigator is notified of an inspection by a regulatory authority the Investigator agrees to notify the Sponsor Medical Monitor immediately. The Investigator agrees to provide to representatives of a regulatory agency or the Sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

11.3.3 Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

12 References

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13 Appendices

Appendix 1. Hanifin and Rajka Criteria for Atopic Dermatitis Diagnosis

Major Criteria (must have at least three)

- Pruritus
- Typical morphology and distribution:
  - Adults: flexural lichenification or linearity
  - Children and infants: involvement of facial and extensor surfaces
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor Criteria (must have at least three)

- Xerosis
- Ichthyosis/keratosis pilaris/palmar hyperlinearity
- Immediate (Type 1) skin test reactivity
- Elevated serum IgE
- Early age at onset
- Tendency to skin infections (Staphylococcus aureus, herpes simplex)/impaired cellular immunity
- Tendency to nonspecific hand/foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influenced by environmental/emotional factors
- White dermographism/delayed blanch

Source: Hanifin, 1980.

Appendix 2. Fitzpatrick Skin Type Scale

Skin Type	Sunburn Tendency	Suntan Tendency
Type I	Always burns easily	Never tan
Type II	Always burns easily	Tans slightly
Type III	Burns moderately	Tans gradually
Type IV	Burns minimally	Tans moderately
Type V	Rarely burns	Tans profusely
Type VI	Never burns	Tans profusely

Appendix 3. Validated Investigator Global Assessment Scale for Atopic Dermatitis

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions (excluding lesions on the scalp) at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (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 widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".

2. Excoriations should not be considered when assessing disease severity.

Appendix 4. Calculation of Percent Body Surface Area Affected and Eczema Area Severity Index

Calculation of %BSA Affected

NOTE: At Screening, Baseline and for all efficacy assessments, lesions on the scalp will not be included in the calculation of %BSA affected as these areas will not be included in the efficacy analyses.

Measurement of involved BSA is estimated by the handprint method: the total palmar surface of the subject's palm and digits is approximately 1% of their total BSA.

Estimate the involved regional area by determining the number of "full" handprints plus the number of handprints covered if several smaller lesions are "pushed together."

For subjects ages 8 years and above the maximum involvement by region is as follows:

- Head and neck = 10% of overall BSA (10 handprints);
  1 hand-sized lesion ~ 10% of head and neck area
- Arms/Upper extremities = 20% of overall BSA (20 handprints);
  1 hand-sized lesion ~ 5% of the upper extremities
- Trunk (including axillae and groin) = 30% of overall BSA (30 handprints);
  1 hand-sized lesion ~ 3.33% of the trunk
  Legs/Lower extremities (including buttocks) = 40% of overall BSA (40 handprints);
  1 hand-sized lesion ~ 2.5% of the lower extremities

For subjects ages <8 years the maximum involvement by region is as follows:

- Head and neck = 20% of overall BSA (20 handprints);
  1 hand-sized lesion ~ 5% of head and neck area
- Arms/Upper extremities = 20% of overall BSA (20 handprints);
  1 hand-sized lesion ~ 5% of the upper extremities
- Trunk (including axillae and groin) = 30% of overall BSA (30 handprints);
  1 hand-sized lesion ~ 3.33% of the trunk
- Legs/Lower extremities (including buttocks) = 30% of overall BSA (30 handprints);
  1 hand-sized lesion ~ 3.33% of the lower extremities

Table 7. Calculation of Percent Body Surface Area Affected

Body Region	Number of Handprints for Each Region
Head and neck	
Arms/upper extremities	
Trunk	
Legs/lower extremities	
TOTAL Involved %BSA – sum of handprints for each region	

Note: Shaded cells will be calculated in the CRF.

%BSA = percent body surface area; CRF = case report form

Calculation of EASI score (scalp excluded)

Four anatomic sites – head, upper extremities, trunk, and lower extremities – are assessed for erythema, edema/papulation, excoriation and lichenification as seen on the day of the examination. The severity of each sign is assessed using a 4-point scale, half points may be used (e.g. 0.5, 1.5, 2.5):

0 = None (Absent)
1 = Mild
2 = Moderate
3 = Severe

The area affected by AD within a given anatomic site is estimated as a percentage of the total area of that anatomic site, based on the %BSA calculation, and assigned a numerical value according to the degree of AD involvement. For the purpose of assigning a numerical value for each anatomic site, %BSA ranges will be used as follows:

0 = no (0%) involvement
1 = > 0% to < 9.50% involvement
2 = ≥ 9.50% to < 29.50% involvement
3 = ≥ 29.50% to < 49.50% involvement
4 = ≥ 49.50% to < 69.50% involvement
5 = ≥ 69.50% to < 89.50% involvement
6 = ≥ 89.50% to 100% involvement

The EASI score will be calculated in the CRF based on the subject's age, the rating scores for each region, and the number of handprints involved for each region.

Table 8. Calculation of Eczema Area and Severity Index Score for Ages 8 Years and Above

Characteristic of lesions	Rating Score	Body region			
		Head and Neck	Arms / Upper Extremities	Trunk	Legs / Lower Extremities
Erythema	0 = None (Absent) 1 = Mild 2 = Moderate 3 = Severe				
Edema/Papulation					
Lichenification					
Excoriation					
Add together each of the 4 scores for each of the body regions to give 4 separate subtotals					
Subtotals		A1 =	A2 =	A3 =	A4 =
From the BSA calculation in Table 6, score each body region using the Regional %BSA Involvement column to covert that percentage into a value from 0-6					
Number of Handprints					
Multiplier for body region		10	5	3.33	2.5
Percentage for each Region		%	%	%	%
Area of involvement for each body region affected Score between 0 and 6 for each region	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%				
		B1 =	B2 =	B3 =	B4 =
For each body region, multiply subtotal A1, A2, A3, and A4 by the degree of body involvement (B1, B2, B3, and B4) and multiplier to give 4 subtotals (C1, C2, C3, C4)					
		C1 = A1 x B1 x 0.1	C2 = A2 x B2 x 0.2	C3 = A3 x B3 x 0.3	C4 = A4 x B4 x 0.4
		C1 =	C2 =	C3 =	C4 =
The subject's EASI score is the sum of C1+C2+C3+C4				EASI =	

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Note: Shaded cells are either fixed values or will be calculated in the CRF. Multiplier is a fixed number representing fraction of total body area. The number of handprints will be imputed from data entered for the calculation of %BSA affected.

%BSA = percent body surface area; BSA = body surface area; CRF = case report form; EASI = Eczema Area and Severity Index

Table 9. Calculation of Eczema Area and Severity Index Score for Ages < 8 Years

Characteristic of lesions	Rating Score	Body region			
		Head and Neck	Arms / Upper Extremities	Trunk	Legs / Lower Extremities
Erythema	0 = None (Absent) 1 = Mild 2 = Moderate 3 = Severe				
Edema/Papulation					
Lichenification					
Excoriation					
Add together each of the 4 scores for each of the body regions to give 4 separate subtotals					
Subtotals		A1 =	A2 =	A3 =	A4 =
From the BSA calculation in Table 7, score each body region using the Regional %BSA Involvement column to covert that percentage into a value from 0-6					
Number of Handprints					
Multiplier for body region		5	5	3.33	3.33
Percentage for each Region		%	%	%	%
Area of involvement for each body region affected Score between 0 and 6 for each region	0 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%				
		B1 =	B2 =	B3 =	B4 =
For each body region, multiply subtotal A1, A2, A3, and A4 by the degree of body involvement (B1, B2, B3, and B4) and multiplier to give 4 subtotals (C1, C2, C3, C4)					
		C1 = A1 x B1 x 0.2	C2 = A2 x B2 x 0.2	C3 = A3 x B3 x 0.3	C4 = A4 x B4 x 0.3
		C1 =	C2 =	C3 =	C4 =
The subject's EASI score is the sum of C1+C2+C3+C4				EASI =	

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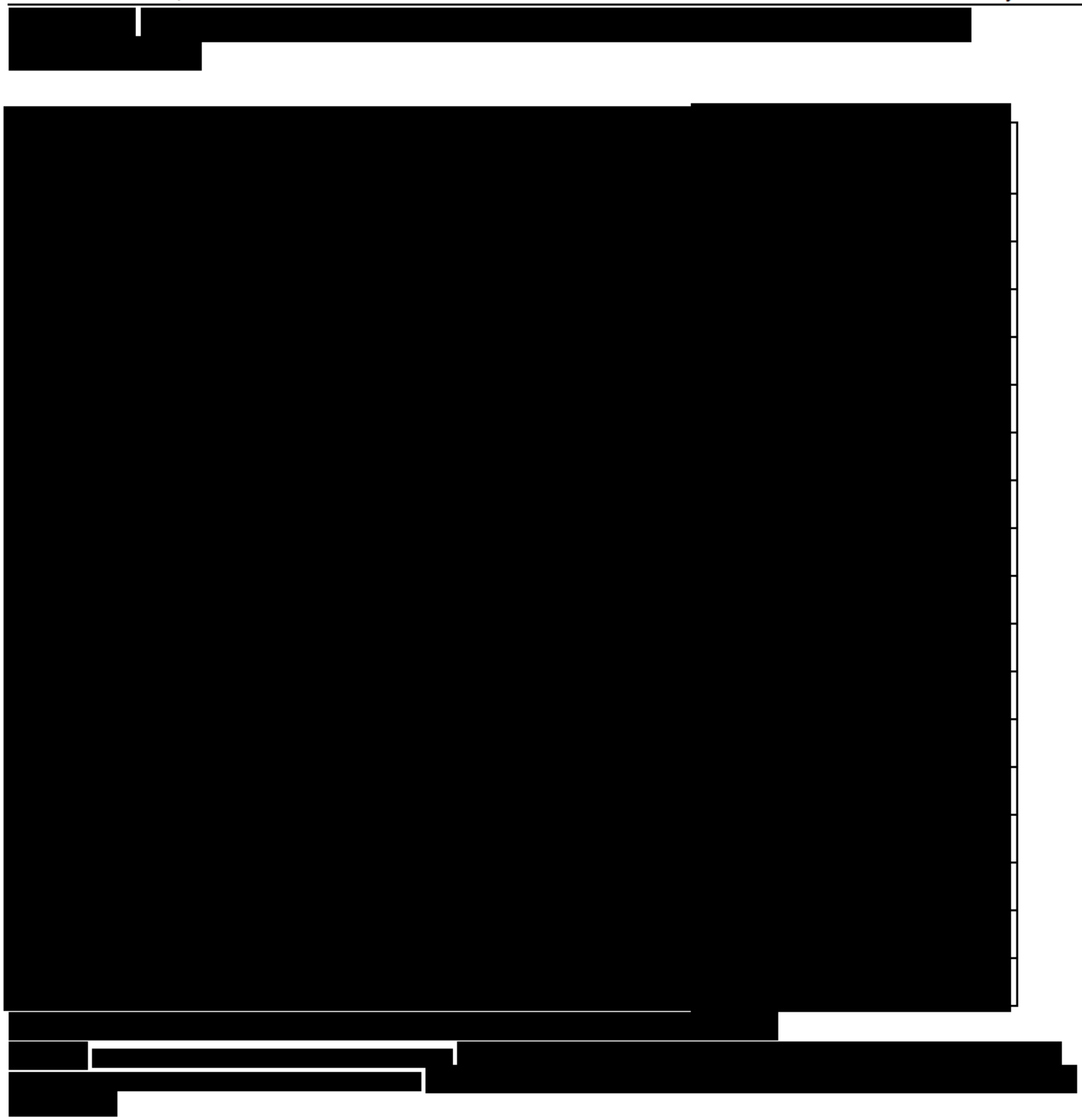
Note: Shaded cells are either fixed values or will be calculated in the CRF. Multiplier is a fixed number representing fraction of total body area. The number of handprints will be imputed from data entered for the calculation of %BSA affected.

%BSA = percent body surface area; BSA = body surface area; CRF = case report form; EASI = Eczema Area and Severity Index

The EASI score is obtained by using one of the below formulas, based on the subject's age:

- For children age 8 years and older:
  $EASI = 0.1\ (E_h + I_h + Ex_h + L_h)\ A_h + 0.2\ (E_u + I_u + Ex_u + L_u)\ A_u + 0.3\ (E_t + I_t + Ex_t + L_t)\ A_t + 0.4\ (E_l + I_l + Ex_l + L_l)\ A_l$
- For children under the age of 8 years:
  $EASI = 0.2\ (E_h + I_h + Ex_h + L_h)\ A_h + 0.2\ (E_u + I_u + Ex_u + L_u)\ A_u + 0.3\ (E_t + I_t + Ex_t + L_t)\ A_t + 0.3\ (E_l + I_l + Ex_l + L_l)\ A_l$

Where E, I, Ex, L and A denote erythema, induration, excoriation, lichenification and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively.



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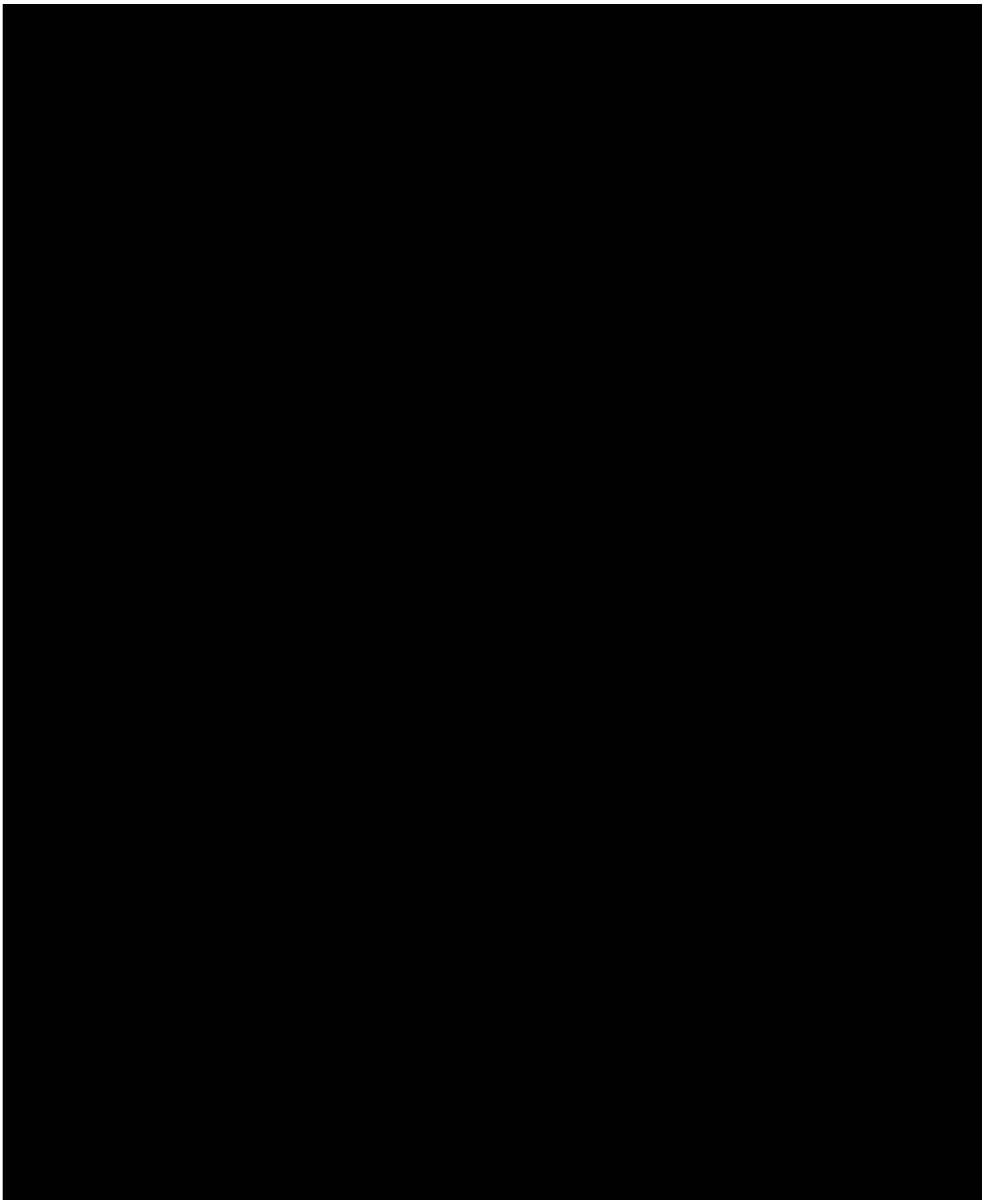

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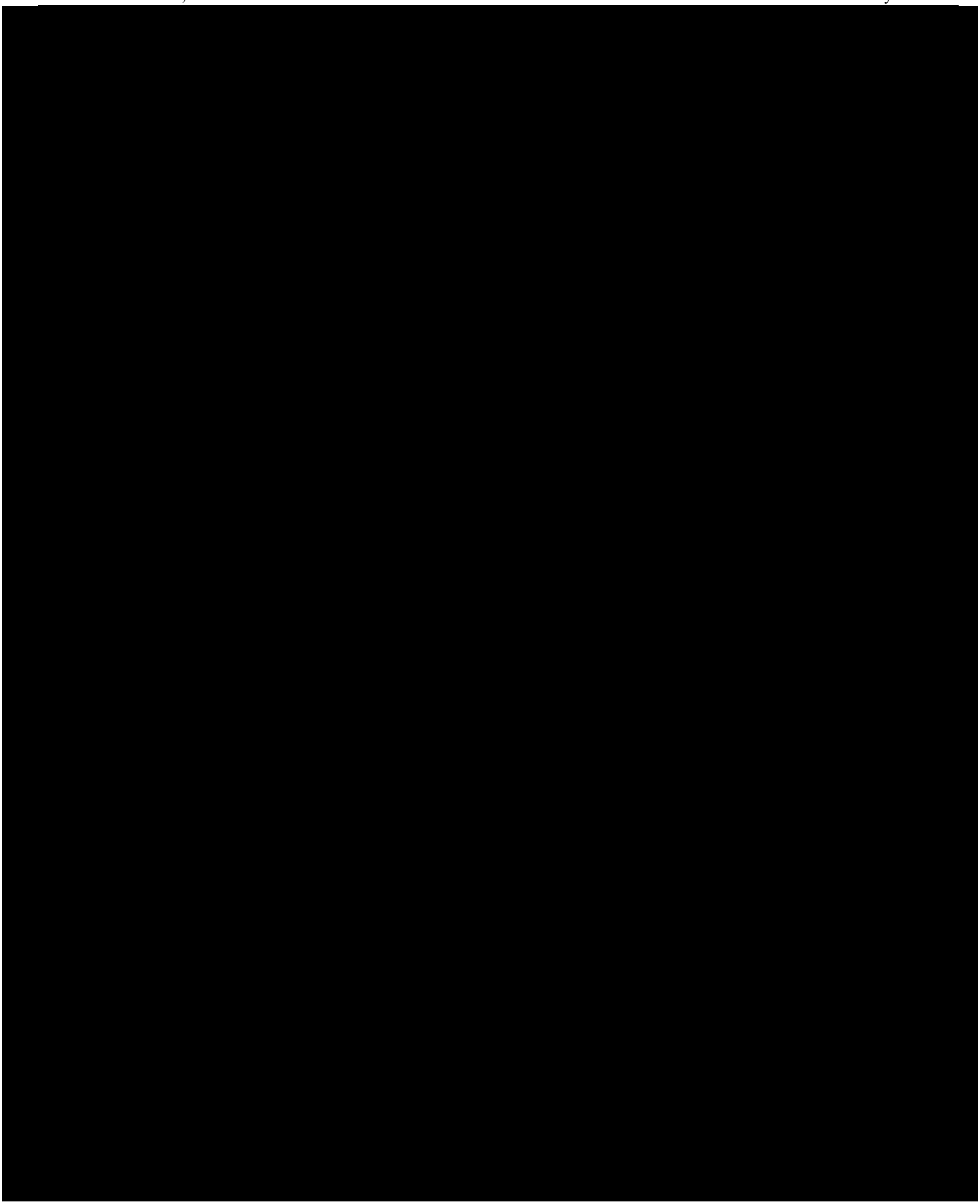

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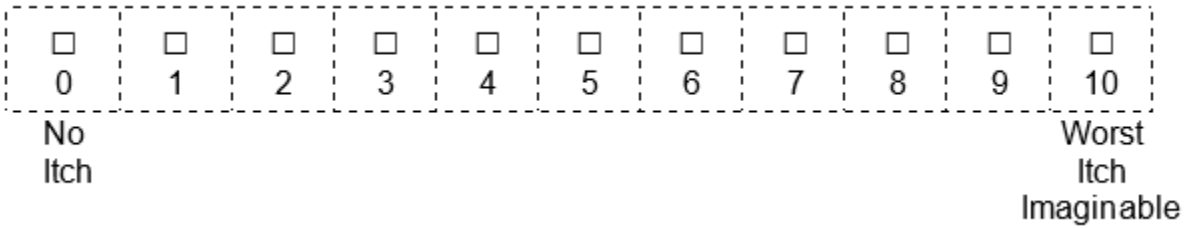
Appendix 11. Peak Pruritus-Numeric Rating Scale

The PP-NRS is a scale used to quickly assess itch/pruritus severity over a 24-hour period which will be used daily to assess peak pruritus.

For subjects ages 2 to < 12 years, the PP-NRS will be completed by the caregiver. For subjects ages ≥ 12 years, the PP-NRS will be completed by the subject.

PP-NRS

On a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?



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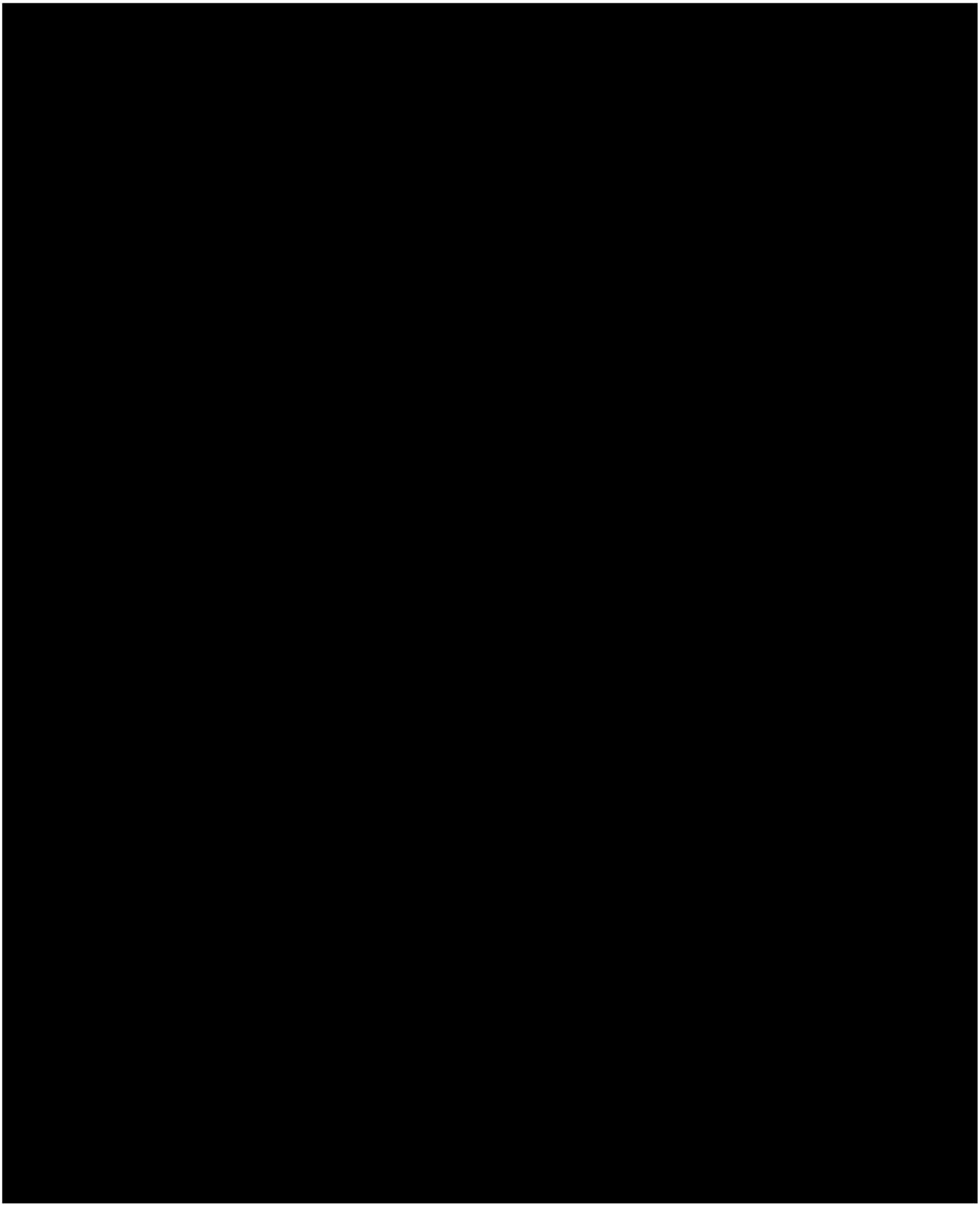

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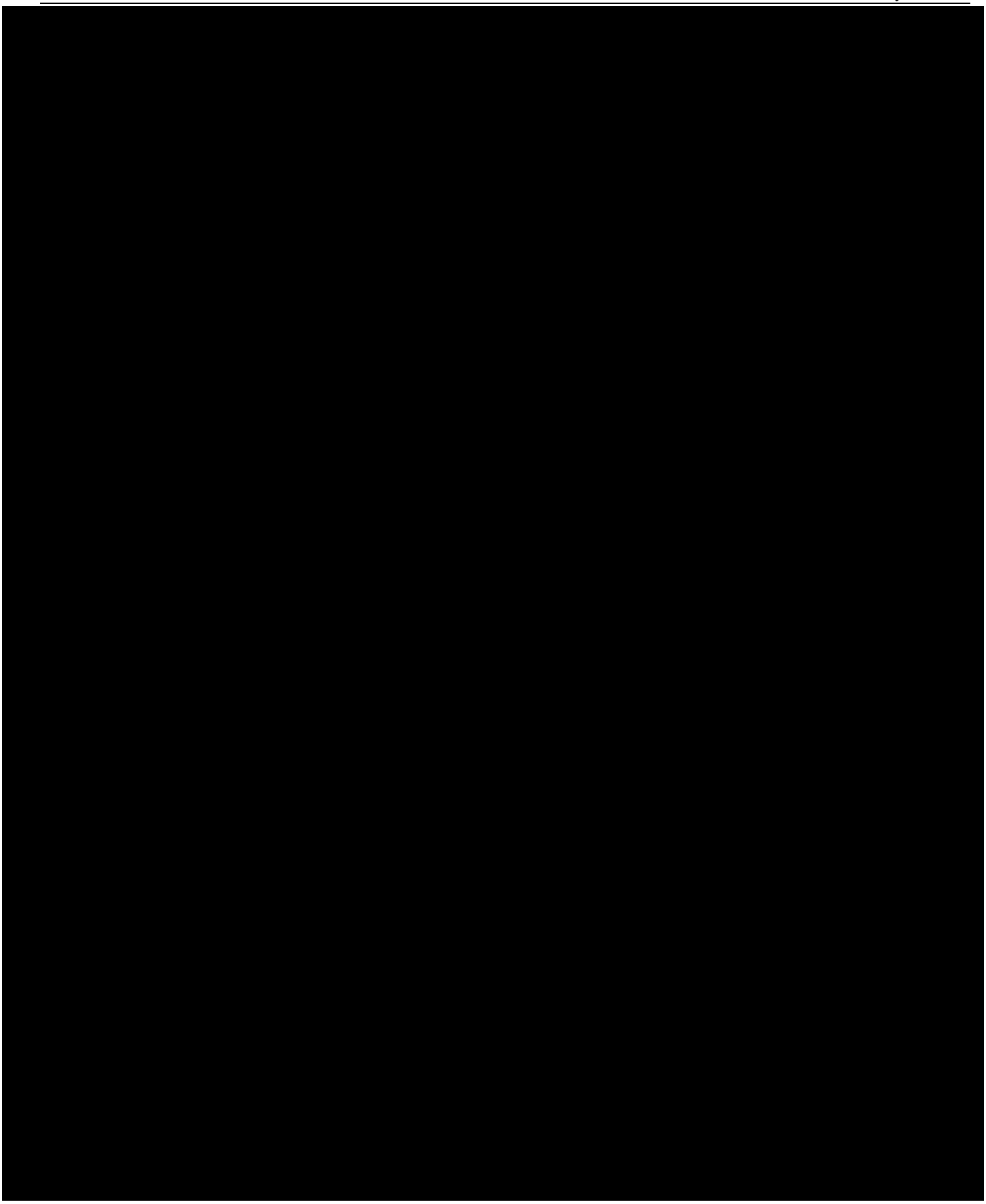

Appendix 15. Investigator-Assessed Local Tolerability Scale

At each specified study visit, the Investigator (or qualified evaluator) will assess the presence and overall degree of irritation at the application sites, according to the 5-point LTS below. The score will ideally represent an "average" across all application sites. To the fullest extent possible, the same Investigator (or designated evaluator) will perform all tolerability assessments for an individual subject throughout the study.

If the subject is applying study drug to "sensitive areas", a separate LTS will be used to assess the degree of irritation for each of these areas where study drug is applied. The sensitive areas that will be assessed are face, neck, skin folds, axilla, inframammary, anal crux, and genitalia.

Investigator Local Tolerability Scale – Dryness, Erythema, and Peeling

Score	Severity	Description
0	No irritation	No evidence of local irritation/intolerance
1	Mild	Minimal erythema and/or edema, slight glazed appearance
2	Moderate	Definite erythema and/or edema with peeling and/or cracking but does not require treatment modification
3	Severe	Erythema, edema glazing with fissures, few vesicles or papules
4	Very Severe	Strong reaction spreading beyond the treated area, bullous reaction, erosions

Appendix 16. Subject (or Caregiver)-Assessed Local Tolerability Scale

At each specified study visit, the subject or caregiver will separately assess the presence and degree of burning/stinging and itching at the application sites, each according to a 5-point LTS. The subject or caregiver will not score each sensitive area individually but provide one overall score that will ideally represent an "average" across all application sites. For subjects ages < 12 years, the LTS will be completed by the caregiver. For subjects ages ≥ 12 years, the LTS will be completed by the subject.

Subject (Or Caregiver) Local Tolerability Scale – Burning/Stinging

Score	Severity	Description
0	None	Normal, no discomfort
1	Slight	An awareness, but no discomfort and no intervention required
2	Mild	A noticeable discomfort that causes intermittent awareness
3	Moderate	A noticeable discomfort that causes intermittent awareness and interferes occasionally with normal daily activities
4	Strong/Severe	A definite continuous discomfort that interferes with normal daily activities

Subject (Or Caregiver) Local Tolerability Scale – Itching

Score	Severity	Description
0	None	Normal, no discomfort
1	Slight	An awareness, but no discomfort and no intervention required
2	Mild	A noticeable discomfort that causes intermittent awareness
3	Moderate	A noticeable discomfort that causes intermittent awareness and interferes occasionally with normal daily activities
4	Strong/Severe	A definite continuous discomfort that interferes with normal daily activities