Clinical Study Protocol

Study Title:	Open Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Pediatric Subjects with Extensive Atopic Dermatitis
Sponsor:	Dermavant Sciences, Inc. 3300 Paramount Parkway, Suite 150 Morrisville, NC, USA 27560
Compound Name:	Tapinarof (DMVT-505)
Protocol Number:	DMVT-505-2104
Indication:	Atopic Dermatitis
Development Phase:	2
IND Number:	104601
Current Version:	4.0
Original Protocol Approved/Effective Date	3/25/2021
Amendment 1 Approved/Effective Date:	

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.

[redacted]

25 Aug 2021
Date

This electronic signature is legally binding equivalent of traditional handwritten signatures and is captured in the audit trail of the document.

Medical Monitor / Sponsor Information Page

Role	Name	Daytime Phone Number and Email Address	After-hours Phone/Cell/Pager Number
Primary Medical Monitor	[redacted]	[redacted]	[redacted]
Secondary Medical Monitor	[redacted]	[redacted]	[redacted]
Serious Adverse Event (SAE)/ Pregnancy Reporting Contact Information	North America Safety Mailbox	[redacted]	N/A

Study Sponsor

This study is sponsored by Dermavant Sciences, Inc.

Sponsor Registered Address and Regulatory Contact

Dermavant Sciences, Inc.
3300 Paramount Parkway, Suite 150
Morrisville, NC 27560
USA

Investigator Statement

Study Title: Open Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Pediatric Subjects with Extensive Atopic Dermatitis

- 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.

Principal Investigator Name	Signature
Date	Site

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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
Anti-HBc	anti-hepatitis B core antigen
Anti-HBs	anti-hepatitis B surface antigen
AST	aspartate aminotransferase
$AUC_{0\text{-last}}$	area under the plasma concentration versus time curve from time zero to the last quantifiable concentration
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
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
Dermavant	Dermavant Sciences, Inc.
EASI	Eczema Area and Severity Index
ET	early termination
FU	follow-up
GSK	GlaxoSmithKline
HBsAg	hepatitis B surface antigen
ICF	informed consent form
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IL	Interleukin
IRB	Institutional Review Board
LTS	Local Tolerability Scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
NA	not applicable
Nrf2	nuclear factor erythroid 2-related factor 2
P/C	phone contact

Term	Full Description
PGA	Physician's Global Assessment
PK	Pharmacokinetic(s)
PP-NRS	Peak Pruritus-Numeric Rating Scale
QD	once daily
RBC	red blood cell(s)
SAE	serious adverse event
SD	standard deviation
TAMA	therapeutic AhR-modulating agent
TEAEs	treatment emergent adverse events
t_{last}	time of last quantifiable concentration
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
V	visit
vIGA-AD™	validated Investigator Global Assessment for Atopic Dermatitis™
WBC	white blood cell(s)
[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-505-2104	**Phase:**	2	**Country:**	United States and Canada
Title of Study:					
Open Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Pediatric Subjects with Extensive Atopic Dermatitis					
Study Center(s):					
Approximately 12 sites in the United States and Canada					
Objectives:					
Primary:					
• To evaluate the safety and tolerability of tapinarof cream, 1% once daily in pediatric subjects ages 2 to 17 years old with extensive atopic dermatitis (AD) • To evaluate the pharmacokinetics (PK) of tapinarof cream, 1% once daily in pediatric subjects ages 2 to 17 years old with extensive AD					
Secondary:					
• To assess the efficacy of tapinarof cream, 1% once daily in pediatric subjects ages 2 to 17 years old with extensive AD					
Methodology:					
This is a Phase 2a, multicenter, open-label, safety, tolerability and PK study in subjects ages 2 to 17 years with AD. The study will consist of three phases: Screening (up to 30 days), Treatment (27 days), and Follow-up (approximately 7 days). At Day 1 (Baseline), eligible subjects and/or their caregiver(s) will be instructed on how to apply tapinarof cream, 1% while under the supervision of site personnel in the clinic and have collection of PK samples to assess systemic absorption. During the treatment period, subjects and/or their caregiver(s) will apply tapinarof cream, 1% to affected areas once a day for 28 days, 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 will return to the clinic on Days 8 and 28 for study assessments. On clinic visit days, subjects and/or their caregiver(s) will apply study drug under the supervision of site personnel. Additionally, subjects will be contacted by phone at Day 15 to assess adverse events (AEs) and concomitant medications, to review study drug administration instructions, and to confirm subject's continued participation in this study. At the end of the 27 days of treatment in this study, a final PK sample will be collected and subjects will have the option to enroll in a separate open label long-term safety study for an additional 48 weeks of treatment. Subjects who choose not to participate in the open-label long-term safety study or who fail to qualify for participation in the open-label long-term safety study will complete a Follow-up visit (Day 35) approximately 7 days after the end of treatment in this study. Subjects who withdraw from the study before Day 28 will complete an Early Termination Visit and are not eligible for the open-label long-term safety study. A follow-up visit will not be completed for a subject who completes an Early Termination visit. Subjects across the age range will be enrolled simultaneously. The blood sample collected at Screening will serve as the pre-dose plasma concentration. PK sampling will occur on Day 1 at 1, 3, and 5 hours post-dose. A single PK sample will be collected on Day 28. After 9 subjects have been enrolled (25% of the study), the PK data will be evaluated with the potential to eliminate the 5-hour post-dose sampling time point on Day 1.					

Number of Subjects:

Approximately 36 subjects ages 2 to 17 years old will be enrolled in the study with approximately 12 subjects, and a minimum of 10 subjects, enrolled into each of the three following age cohorts: 2-6 years old, 7-11 years old, 12-17 years old.

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 to 17 years old with clinical diagnosis of AD by Hanifin and Rajka criteria.
2. Subjects with AD covering ≥25% of the body surface area (BSA) for subjects ages 12-17 years old, or ≥35% of the BSA for subjects ages 2-11 years old. Scalp should be excluded from the BSA calculation to determine eligibility during Screening and at Baseline, and for all efficacy assessments.
3. A Validated Investigator Global Assessment in Atopic Dermatitis (vIGA-AD™) score of 3 or greater at Screening and Baseline (pre-dosing).
4. AD present for at least 6 months for subjects ages 6-17 years old or 3 months for subjects ages 2 to 5years old, confirmed by prior medical documentation and/or according to the subject and/or caregiver(s).
5. 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
6. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1).
7. Subject, subject's parent(s), or legal representative must be capable of giving written informed consent, 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 medical history of positive human immunodeficiency virus antibody at Screening.
    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 one 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 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:
      - DUPIXENTt® (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 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).

Investigational Product, Dosage and Mode of Administration:

Tapinarof cream, 1% is a white to off-white cream containing 1% weight/weight (10 mg/gram) tapinarof, supplied in 30 gram tubes, and is to be administered by the subject and/or caregiver(s) once daily via topical application of a thin layer to affected areas.

Reference Therapy, Dosage and Mode of Administration:

n/a

Duration of Treatment:

Study duration for subjects who complete this Phase 2a study and do not enroll in the open-label long-term safety study is approximately 9 weeks in total (including approximately 30 days for Screening, 27 days of treatment, and a 1 week follow-up period).

Criteria for Evaluation:	
Pharmacokinetic Assessments:	• Plasma concentrations of tapinarof
Safety Assessments:	• AEs • Vital signs • Physical examinations • Clinical laboratory tests • Investigator-assessed Local Tolerability Scale (LTS)
Efficacy Assessments:	• vIGA-AD™ • Eczema Area Severity Index (EASI) • Percentage of total body surface area (%BSA) affected • PP-NRS for completion by subjects ages ≥ 12 years and for completion by caregivers of subjects ages < 12 years

Study Endpoints:

Primary:

- 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 vital signs
- Mean Investigator-assessed LTS scores by visit (overall and sensitive areas)
- Tapinarof plasma PK parameters on Day 1, if data permit, including:
    - area under the plasma concentration versus time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-last}}$)
    - maximum plasma concentration (C_{max})
    - time to maximum plasma concentration (t_{max})
    - time of last quantifiable concentration (t_{last})
- Tapinarof plasma concentration on Day 28

Secondary:

- Change in vIGA-AD™ score from Baseline at each study visit
- Proportion of subjects who have a vIGA-AD™ score of clear or almost clear (0 or 1) at each study visit
- Proportion of subjects with ≥50% improvement in EASI score from Baseline at each study visit
- Proportion of subjects with ≥75% improvement in EASI score from Baseline at each study visit
- Proportion of subjects with ≥90% improvement in EASI score from Baseline at each study visit
- Mean change and percent change in EASI score from Baseline at each study visit
- Mean change and percent change in %BSA affected from Baseline at each study visit
- Mean change and percent change in BSA x vIGA-AD™ values from Baseline at each study visit
- Proportion of subjects with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4-point reduction in the PP NRS from Baseline at each study visit
- Proportion of subjects ≥ 12 years old with a Baseline PP-NRS score ≥4 who achieve a ≥4-point reduction in PP-NRS score from Baseline at each study visit
- Proportion of subjects 2 to < 12 years old with a Baseline PP-NRS score ≥4 who achieve a ≥4-point reduction in PP-NRS score from Baseline at each study visit
- Mean change in PP-NRS score from Baseline to Day 28 at each study visit by age group

Statistical Methods:

Safety Analyses:

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

- AEs will be summarized 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 and vital signs will be summarized using shift tables and descriptively for quantitative measures by visit.
- LTS scores will be summarized by visit.

Pharmacokinetics:

- Plasma concentration data will be listed and summarized by study visit. PK parameters will be presented in tabular and/or graphical format and summarized descriptively if data permit

Efficacy Analyses:

- Analyses of efficacy endpoints will be based upon the Safety population. Proportions will be summarized using frequency counts and percentages, and mean changes and percent changes will be summarized using descriptive statistics (mean, median, standard deviation, minimum and maximum).

Schedule of Assessments

Table 1: Schedule of Assessments

Procedures and Assessment	Screening	Treatment Phase				FU[a]	ET[b]
	V1	V2	V3	P/C	V4	V5	NA
	Day -30 to Day -1	Baseline, Day 1	Day 8 (±1 day)	Day 15 (±2 days)	Day 28 (±2 days)	Day 35 (±3 days)	NA
Informed consent	X						
Inclusion and exclusion criteria	X	X					
Demography	X						
Fitzpatrick skin type	X						
Brief physical exam[c]	X	X	X		X	X	X
Medical history[d]	X	X[e]					
Pregnancy test (females of child-bearing potential)[f]	X	X[g]			X		X
Blood sample for clinical laboratory assessments[h]	X				X	X[i]	X
Urinalysis	X				X	X[i]	X
Vital signs[j]	X	X	X		X	X	X
Study drug Dispensation / Collection[k]		D	C/D		C		C
Review instructions for study drug application[l]		X	X	X			
Dispense/collect subject diary of study drug application		D	C/D		C		C
Tapinarof cream administration in-clinic under site supervision[m]		X	X				
PK samples[n]	X	X			X		
AE/SAE review	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X
vIGA-AD™ score[o]	X	X	X		X	X	X
%BSA affected[p]	X	X	X		X	X	X
EASI[p]		X	X		X	X	X
LTS assessment by Investigator[q]		X	X		X		
PP-NRS (assessed pre-dose at visit, as applicable)[r]		X	X		X		
Enrollment (optional) in open-label long-term safety study					X		

a. The Follow-up Visit will be performed for any subject who fails to qualify for participation in the open-label long-term safety study or qualifies to participate in the open-label long-term safety study but elects not to enroll in that study. A follow-up visit will be not completed for a subject who terminates early.

b. Subjects who withdraw from the study before Day 28 (Visit 4) will complete an Early Termination Visit.

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

d. Medical history will include month and year of AD diagnosis. 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. Record any changes to medical history and document changes in source and EDC.

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 being performed.

g. Urine pregnancy test to be performed before dosing.

h. Clinical laboratory assessments include serum chemistry and liver chemistry tests, and hematology.

i. If needed for ongoing AE or laboratory abnormality from previous visit.

j. Vital signs will include systolic and diastolic 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.

k. Site personnel will weigh the tubes to be dispensed and will record the weight of all tubes dispensed at each visit in the drug accountability logs. Site personnel will weigh the returned tubes (used and unused) 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.

l. Subjects and/or caregivers will be instructed to apply study drug once daily at the approximate same time each day, based on subject and/or caregiver(s) preference.

m. At all clinic visits, study drug will be applied after all safety and efficacy assessments have been conducted.

n. The blood sample collected at Screening will serve as the pre-dose plasma concentration. PK sampling will occur on Day 1 at 1, 3, and 5 hours post-dose. A single PK sample will be collected on Day 28.

o. The vIGA-AD™ assessment should be performed before the %BSA and EASI assessments.

p. The subject's scalp should be excluded from the %BSA and EASI calculation.

q. The LTS assessment should be conducted pre-dose.

r. PP-NRS daily itch diaries will be dispensed at Day 1 (Baseline) and Day 8 and collected on Day 28.

%BSA = percent of total body surface area; AD = atopic dermatitis; AE = adverse event (s); BMI = body mass index; BP = blood pressure; C = study drug collection; CRF = case report form; D = study drug dispensation; ET = early termination; EASI = Eczema Area and Severity Index; Hep = hepatitis; HIV = human immunodeficiency virus; HR = heart rate; LTS = Local Tolerability Scale; NA = not applicable; P/C = phone call; PK = pharmacokinetic; SAE = serious adverse event; vIGA-ADTM = 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 still 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.

Tapinarof (DMVT-505), formerly known as GSK2894512 and WBI-1001, is a fully synthetic naturally derived stilbene that is being developed by Dermavant Sciences, Inc. (Dermavant) as a novel anti-inflammatory agent for the topical treatment of AD and plaque psoriasis. The compound (number WBI-1001) was initially developed by Welichem Biotech Inc. (Welichem; Burnaby, British Columbia, Canada) and then was acquired by GlaxoSmithKline (GSK) on 31 July 2012 for further development in the rest of the world except China. Dermavant acquired the drug from GSK on 20 August 2018 for continued development. Development of tapinarof cream in Japan is being jointly pursued with Japan Tobacco Inc. (JT), with a Phase 3 program in PSO and AD scheduled to commence in late 2021. In China, the compound was independently developed by Beijing Wenfeng Tianji Pharmaceutical Technology Co. (BWTP) (Shenzhen Celestial) under the name benvitimod (active ingredient corresponds to tapinarof). BWTP was granted authorization to market benvitimod cream (a different formulation and excipient profile compared to tapinarof cream) as Symbiox® in China in July 2019.

Tapinarof cream, 1% is a white to off-white, oil-in-water emulsion intended for topical application to AD and psoriatic skin lesions, which has a novel mechanism of action. Tapinarof is a nonsteroidal, small molecule therapeutic aryl hydrocarbon receptor (AhR) modulating agent (TAMA) which exerts its therapeutic effects via agonism of AhR, a cytosolic ligand dependent transcription factor. Upon ligand binding, AhR translocates to the nucleus and dimerizes with AhR nuclear translocator (ARNT) forming an AhR ARNT heterodimer [Smith, 2017]. The AhR-ARNT heterodimer modulates gene transcription through direct and indirect interaction with DNA. By activation of this AhR signaling pathway, tapinarof has the potential to downregulate the expression of pro-inflammatory cytokines, including interleukin (IL)-4, IL-5, IL-6, IL-13, IL-17A and F, and eotaxin, and upregulate the expression of several skin barrier proteins, including filaggrin, hornerin, and involucrin. In addition, AhR also activates the antioxidative transcription factor nuclear factor-erythroid 2-related factor-2 (Nrf2), upregulating the expression of antioxidative enzymes [Smith, 2017; Furue 2019]. By targeting AhR, tapinarof has a biological profile that differs from that of currently available products, offering patients a truly novel therapeutic treatment option.

Two Phase 2b, 12-week, randomized, double-blind, vehicle-controlled, 6-arm, parallel group, dose-finding studies with topically applied tapinarof cream were conducted by GSK; 1 study each in subjects with AD or psoriasis. These 2 studies evaluated the safety and efficacy of tapinarof cream (Formulation F) at 2 concentrations (0.5% or 1% weight/weight [w/w]) and 2 application frequencies (once daily [QD] or twice daily [BID]) in 247 adult and adolescent subjects with AD and in 227 adult subjects with plaque psoriasis. In both studies, tapinarof showed a clear therapeutic effect compared with vehicle, with the 1% w/w concentration treatment groups demonstrating a higher proportion of subjects with treatment success compared with the 0.5% w/w concentration groups (applied QD and BID in the AD study). In both indications, the tapinarof 1% dosing groups showed a faster onset of action than the 0.5% dosing groups, and QD application had similar efficacy to BID application. In both Phase 2b studies, tapinarof showed an acceptable safety profile. Treatment-emergent adverse events (TEAEs) were reported with a higher frequency in the tapinarof groups than in the vehicle groups. The most frequent TEAEs (≥ 5% in any arm or in total) were nasopharyngitis, folliculitis, dermatitis contact, atopic dermatitis, upper respiratory tract infection, headache, vomiting, acne, application site dermatitis, miliaria, dermatitis allergic, and impetigo. The majority of TEAEs were mild or moderate in severity. In each study, the tapinarof 1% QD treatment group had a lower frequency of TEAEs than the tapinarof 1% BID treatment group.

Tapinarof has been evaluated in two identical Phase 3, 12-week, randomized, double-blind, vehicle-controlled trials in adult subjects with plaque psoriasis. These studies evaluated the safety and efficacy of tapinarof cream, 1% once a day versus vehicle cream once a day in a combined 1025 subjects randomized 2:1 tapinarof to vehicle. In both trials, tapinarof demonstrated superiority against vehicle on the primary endpoint, a Physician Global Assessment (PGA) score of 0 (clear) or 1 (almost clear) with a 2-point improvement at Week 12. In addition, tapinarof was highly statistically significant compared to vehicle on all secondary endpoints which included proportion of subjects achieving a 75% improvement in the Psoriasis Area and Severity Index, a PGA score of 0 or 1, change in percent body surface area (%BSA), and proportion of subjects achieving a 90% improvement in PASI at Week 12. TEAEs were reported with a higher frequency in the tapinarof group than in the vehicle group. The most frequent TEAEs (≥ 5% in any arm or in total) were folliculitis, nasopharyngitis, and contact dermatitis. The majority of TEAEs were mild or moderate in severity. In addition, a 40-week open label extension study was conducted which confirmed the safety profile observed in 12-week studies with no new safety signals emerging.

1.1.2 Study Rationale

This Phase 2a maximal use study is being conducted as part of a clinical development program to evaluate the safety and systemic exposure of tapinarof cream, 1% for the topical treatment of AD in subjects ages 2 to 17 years. Maximal use trials enroll subjects with the disease under study and who generally have more severe disease or with a large BSA of affected skin who might be more susceptible to systemic AEs. The purpose of these studies is to evaluate systemic exposure under conditions that would maximize the potential for drug absorption with the intended use of the product [Bashaw, 2014]. The results of this study are intended to support product registration in the United States and Canada.

1.2 Rationale for Study Design and Dose

The dose of tapinarof in this trial will be the 1% cream administered QD, the same as that studied in the Phase 3 pivotal trials in plaque psoriasis and in the maximal use study in plaque psoriasis. This is also the dose that

was selected for the Phase 3 pivotal trials in AD based on the efficacy and safety data from Study 203121 [Peppers, 2019]. In study 203121, applications of tapinarof cream at concentrations of 0.5% and 1% applied once or QD were evaluated. The groups treated with a 1% concentration showed higher efficacy and resulted in a quicker onset of effect than did the groups treated with a 0.5% concentration. Efficacy responses began as early as Week 2 and continued through Week 12. The proportion of subjects with ≥ 75% improvement in Eczema Area Severity Index (EASI) was also higher for the 1% BID (60%) and 1% QD (51%) compared to vehicle (25-26%). Overall, both concentrations demonstrated an acceptable safety profile when applied once or BID with the 1% QD arm having a lower number of reported TEAEs compared to the 1% BID arm (54% vs 70%, respectively). QD application was selected as efficacy was similar between 1% BID and 1% QD regimens and provided a better safety profile. In addition, QD application may improve treatment adherence compared with more frequent dosing administrations.

Extrapolation of tapinarof safety, efficacy, and dosing regimen from adults to adolescents, and to children is appropriate on the grounds of similarity of skin development, pharmacokinetics (PK), formulation composition, and clinical endpoints. The tapinarof cream formulation does not contain excipients that would preclude its use in pediatric patients. Furthermore, the skin of infants would be expected to have similar barrier function to adults. Infants born at 30 and 32 weeks gestational age were found to have a fully functional stratum corneum comparable with that of adults [Kalia, 1998]. Another study demonstrated that the way the stratum corneum stores and transports water becomes adult-like after the first year of life [Nikolovski, 2008]. In GSK study 203121, the safety, efficacy, and plasma concentrations of tapinarof were similar between adults and adolescents. Therefore, there is no evidence to suggest that safety, efficacy, or dosing regimen in the pediatric population down to age 2 will be different from that in adults. Thus, product strength and dosing frequency is the same for all subjects in the study, regardless of age.

An open-label study is appropriate as the main objective of a maximal use study is to assess pharmacokinetics and safety. Since systemic absorption is likely to be greatest early in the study when the skin has the most lesions, short -term treatment is adequate to assess the study objectives. This study includes an open label treatment phase in which subjects will receive tapinarof cream, 1% QD for 27 days. Tapinarof has a unique PK profile whereby the highest plasma concentrations are observed in the first week of the treatment period followed by a subsequent decline to undetectable or near undetectable levels after multiple weeks of dosing. Accumulation of drug after multiple dosing has not been observed in any clinical study with tapinarof to date. The 27-day treatment phase was selected to ensure steady state is achieved and to provide a treatment duration that allows for evaluation of safety in this population with extensive disease that has not been evaluated to date.

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, adverse events (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. Furthermore, subjects participating in this trial will be offered enrollment in a long-term safety study (DMVT-505-3103), if eligibility requirements are met, where they will have continued access to tapinarof for an additional 48 weeks.

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 safety and tolerability of tapinarof cream, 1% QD in pediatric subjects ages 2 to 17 years old with extensive AD	• Incidence, frequency and duration of TEAEs and serious adverse events (SAEs) • Change from Baseline in laboratory values • Change from Baseline in vital signs • Mean Investigator-assessed local tolerability scores (LTS) scores by visit (overall and sensitive areas)
• To evaluate the PK of tapinarof cream, 1% QD in pediatric subjects ages 2 to 17 years old with extensive AD	• Tapinarof plasma PK parameters on Day 1, if data permit, including: ○ area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration ($AUC_{0\text{-last}}$) ○ maximum plasma concentration (C_{max}) ○ time to maximum plasma concentration (t_{max}) ○ time of last quantifiable concentration (t_{last}) • Tapinarof plasma concentration on Day 28
Secondary	**Secondary:**
• To assess the efficacy of tapinarof cream, 1% QD in pediatric subjects ages 2 to 17 years old with extensive AD	• Change in Validated Investigator Global Assessment in Atopic Dermatitis (vIGA-AD™) score from Baseline at each study visit • Proportion of subjects who have a vIGA-AD™ score of clear or almost clear (0 or 1) at each study visit • Proportion of subjects with ≥50% improvement in EASI score from Baseline at each study visit • Proportion of subjects with ≥75% improvement in EASI score from Baseline at each study visit • Proportion of subjects with ≥90% improvement in EASI score from Baseline at each study visit • Mean change and percent change in EASI score from Baseline at each study visit • Mean change and percent change in %BSA affected from Baseline at each study visit • Mean change and percent change in BSA x vIGA-AD™ values from Baseline at each study visit • Proportion of subjects with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4-point reduction in the PP NRS from Baseline at each study visit • Proportion of subjects ≥ 12 years old with a Baseline PP-NRS score ≥4 who achieve a ≥4-point reduction in PP-NRS score from Baseline at each study visit • Proportion of subjects 2 to < 12 years old with a Baseline PP-NRS score ≥4 who achieve a ≥4-point reduction in PP-NRS score from Baseline at each study visit • Mean change in PP-NRS score from Baseline to Day 28 by age group

3 Study Design

3.1 Overall Design

This is a Phase 2a, multicenter, open-label, safety, tolerability and PK study in pediatric subjects with AD. The study will consist of three phases: Screening (up to 30 days), Treatment (27 days), and Follow-up (approximately 7 days).

At Day 1 (Baseline), eligible subjects and/or their caregiver(s) will be instructed on how to apply tapinarof cream, 1% while under the supervision of site personnel in the clinic and have collection of PK samples to assess systemic absorption. During the treatment period, subjects and/or their caregiver(s) will apply tapinarof cream, 1% to affected areas once a day for 27 days, 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 will return to the clinic on Days 8 and 28 for study assessments. On clinic visit days, subjects and/or their caregiver(s) will apply study drug under the supervision of site personnel and instructed/reminded on how to apply study drug (except during the final treatment/end-of-study visits). Additionally, subjects will be contacted by phone at Day 15 to assess AEs and concomitant medications, to review study drug administration instructions, confirm subject's continued participation in this study, and reminded to complete their daily diary and bring it with them to the next clinic visit.

Study drug will be dispensed and applied to subjects during the clinic visits and will be administered at home between clinic visits as instructed by site personnel. 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; emollients should not be applied to lesional skin during treatment. The same emollient should be used throughout the subject's participation in the study.

Study drug application instructions will be reviewed at all post-baseline clinic visits and during the planned study phone call. 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.

On Day 28 of this study, a final PK sample will be collected and subjects will have the option to enroll in a separate open-label long-term safety study for an additional 48 weeks. Subjects who choose not to participate in the open-label long-term safety study or who fail to qualify for participation in the open-label long-term safety study will complete a Follow-up Visit (Day 35) approximately 7 days after the end of treatment in this study. Subjects who withdraw from the study before Day 28 will complete an Early Termination Visit as their final visit and are not eligible for the open-label long-term study. Subjects that complete an Early Termination visit will not complete a Follow-up visit.

Study duration for subjects who complete this study and who fail to qualify for participation in the open-label long-term safety study, or who qualify to participate in the open-label long-term safety study but elect not to enroll in that study is approximately 9 weeks in total. Study duration for subjects who complete this study

and are eligible and decide to participate in the open-label long-term safety study is approximately 8 weeks in total.

Efficacy assessments will include v-IGA-AD™ score, %BSA affected, EASI, and PP-NRS. Safety assessments will include AEs, clinical laboratory tests, physical examination, vital signs, and LTS.

Pharmacokinetics will be assessed at Days 1 and 28. The screening blood sample will be used for baseline PK if the subject is enrolled. Blood samples for PK should not be collected from any anatomic site where study drug has been applied in order to minimize potential contamination.

Refer to Section 6 for descriptions of study procedures and assessments and Section 7 and the Schedule of Assessments (Table 1) for timing of procedures and assessments

3.2 Treatment Groups and Duration

All subjects will receive tapinarof cream, 1% QD for 27 days, at an appropriate dose in accordance with the size of the affected area. Subjects or their caregivers will be instructed to apply a thin layer to the affected areas.

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

In order to complete the study, a subject must complete 4 weeks of 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 Day 28 visit minus 1 (e.g., if the subject's Day 28 visit occurs exactly on Day 28 then their number of intended doses is 27).

To be eligible for the open-label, long-term safety study, subjects must be a "study completer". Subjects who complete the study will have the option to enroll into the Phase 3 open-label long term safety study of 48 weeks in duration. Details of that study are provided in a separate clinical trial protocol.

The end of the study is defined as when the last subject has completed the 4 weeks of assessments and either enrolls in the long-term safety study or does not enroll and completes the Follow-up visit.

4 Study Population

4.1 Type and Number of Subjects

Approximately 36 subjects ages 2 to 17 years old will be enrolled in the study with approximately 12 subjects, and a minimum of 10 subjects, enrolled into each of the three following age cohorts: 2-6 years old, 7-11 years old, 12-17 years old. Subjects across the age range will be enrolled simultaneously.

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 to 17 years with a clinical diagnosis of AD by Hanifin and Rajka criteria [Hanifin, 1980] (see Appendix 1).
2. Subjects with AD covering ≥25% of the BSA for subjects ages 12-17 years old, or ≥35% of the BSA for subjects ages 2-11 years old, suitable for topical therapy. Scalp should be excluded from the BSA calculation to determine eligibility during Screening and at Baseline, and for all efficacy assessments.
3. A vIGA-AD™ score of 3 or greater at Screening and Baseline (pre-dosing).
4. AD present for at least 6 months for subjects ages 6-17 years old or 3 months for subjects ages 2 to 5 years old, confirmed by prior medical documentation and/or according to the subject and/or caregiver(s).
5. 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
6. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1).
7. Subject, subject's parent(s), or legal representative must be capable of giving written informed consent, 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 medical history of positive human immunodeficiency virus antibody at Screening.
    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 one 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 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 atopic dermatitis (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 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 enrolled. 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 will be 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 National 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. Nonmedicated emollients that do not contain salicylic acid may be used on nonlesional skin; 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 open-label, long-term safety study.
- 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 7.7).

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 7.7) 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 and/or caregiver(s) 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 and-or caregiver(s) (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 and/or caregiver(s) 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 description of the study drug, tapinarof cream, 1%, is presented in Table 2.

Table 2: Tapinarof Cream

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	

[redacted]

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

5.1.2 Storage

All study drug 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 and/or their caregivers at the clinical site in appropriately labeled tubes.

Subjects and/or caregivers will take the tubes home and self-administer study drug (or have caregiver(s) 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 QD 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
- On Day 1, study drug application should be avoided at the site of phlebotomy for PK blood draws.
- 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 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 and/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 and/or caregivers should record the time of study drug application in the daily diary. Itch rating should also be recorded in the diary.
- 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.
- On clinic visit days, study drug should be applied in the clinic under the supervision of site personnel.

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.

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

[redacted]

5.2 Randomization/Treatment Assignment

All subjects will receive tapinarof cream, 1% QD for 27 days.

5.3 Blinding

This will be an open label study.

5.4 Compliance with Study Drug Administration

At Baseline, study staff will provide the subject and/or caregiver with detailed instructions concerning protocol requirements and use of study drug. Additionally, subjects and/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. Subject compliance will be assessed via study diary completion.

When subjects are dosed at the site, they and/or their caregivers 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. In clinic doses are not recorded in the subject's daily diary. 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 open-label, long-term safety 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 poststudy care of the subject's medical condition, whether or not the Sponsor is providing specific poststudy 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 (Day 28) 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 6. 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 month and year of AD diagnosis, allergic conditions, and cardiovascular (CV) medical history 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 disease 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

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 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 at least 3 or 4 at Screening and the Baseline visit (Day 1). Eli Lilly and Company (Lilly) developed the vIGA-AD™ scale for use in clinical trials. For more information on the vIGA-AD™ please refer to Appendix 3 and the website http://www.eczemacouncil.org/research/investigator-global-assessment-scale/

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.

6.2.2 Eczema Area and Severity Index

The EASI will be assessed at every clinic visit beginning with the Baseline visit. It quantifies the severity of a subject's AD based on both lesion severity and the %BSA affected (Hanifin, 2001). 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 % 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.

6.2.3 Assessments Completed by Subject

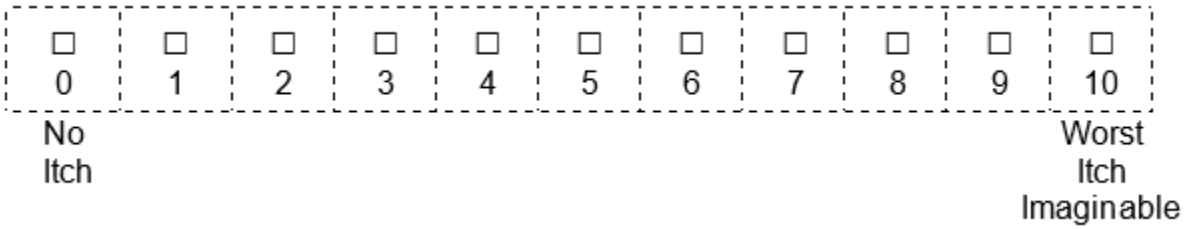
6.2.3.1 Peak Pruritus Numeric Rating Scale

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 and not recorded in the diary. For subjects ages 2 to < 12 years, the PP-NRS will be completed by the parent or caregiver. For subjects ages ≥ 12 years, the PP-NRS will be completed by the subject.

An example of the PP-NRS is provided below.

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?



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, cardiovascular 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] • 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) • Reticulocyte count • 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 they have 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; 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 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 being applied. The sensitive areas that will be assessed are face, neck, skin folds, axilla, inframammary, anal crux, and genitalia. An example of the LTS is shown in Appendix 5. The LTS should be completed pre-dose at Baseline/Day 1, Day 8, and Day 28 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).

6.4 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 cream, 1% will be collected at timepoints indicated in the Schedule of Assessments (Table 1) and Section 7. Blood samples for PK should not be collected from any anatomic site where study drug has been applied in order to minimize potential contamination. 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 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. From the plasma concentration time data on Day 1, the following primary PK parameters will be determined: $AUC_{0\text{-last}}$, C_{max}, t_{max}, and t_{last}.

An analysis of the PK data will be performed after 25% of the subjects (n=9) have completed the study to re-assess the PK sampling scheme with the potential to eliminate the 5-hour post-dose blood draw. If required, changes to the protocol will be made through a protocol amendment

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 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 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 or caregiver 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 (excluding subject's scalp)
- LTS (Investigator assessment)
- Application of study drug by the subject
- Completion of the PP-NRS itch scale – The subject 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 assessments 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 scheme or amendment of the ICF.

NOTE: Assessments and procedures should be performed pre dose on clinic visit days.

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
- Brief physical examination (including height and weight [BMI will be calculated in the CRF])
- Medical history recording (including all medications 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)
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- Vital signs measurements
- Blood sample collection for PK analysis (if the subject is eligible)
- AE recording (from the time the ICF is signed)
- Concomitant medication recording (including emollients)
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (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 enrolled and receive treatment.

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

- Brief physical exam
- Changes to medical history
- Urine pregnancy test (females of child-bearing potential)
- Vital signs measurement
- Dispense study drug
- Provide instructions on how to apply study drug
- Dispense study drug subject diary and PP-NRS diary
- Study drug application under supervision
- Blood sample collection for PK analysis
- AE recording
- Concomitant medication recording
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- LTS assessment by Investigator
- Assessment of itch (PP-NRS)

7.3 Visit 3; Week 1 (Day 8 ±2 Days)

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

- Brief physical exam
- Vital signs measurement
- Collect and dispense study drug
- Review instructions on how to apply study drug
- Collect study drug subject diary and PP-NRS diary and review for compliance
- Dispense study drug subject diary and PP-NRS diary
- Study drug application under supervision
- AE recording

- Concomitant medication recording
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- LTS assessment by Investigator
- Assessment of itch (PP-NRS)

7.4 Phone Contact at Day 15 ±2 Days

Subjects or their caregivers will be contacted by phone at Day 15 to review instructions on how to apply study drug 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.

7.5 Visit 4; Day 28 ±2 Days

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

- Brief physical exam
- Urine pregnancy test (females of child-bearing potential)
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- Vital signs measurement
- Collect study drug
- Collect study drug subject diary and PP-NRS diary and review for compliance
- Blood sample collection for PK analysis
- AE recording
- Concomitant medication recording
- vIGA-ADTM score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- LTS assessment by Investigator
- Assessment of itch (PP-NRS)
- Enrollment in open-label, long-term safety study (optional)

7.6 Visit 5; Follow-Up (Day 35 ±3 Days)

Subjects who do not enroll in the open-label long-term safety study will return to the study site 7-10 days after Day 28 to complete follow-up assessments as follows:

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

7.7 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:

- Brief physical examination
- Urine pregnancy test (females of child-bearing potential)
- Blood sample collection for clinical laboratory tests
- Urinalysis
- Vital signs measurement
- Collect study drug
- Collect study drug subject diary and PP-NRS diary and review for compliance
- AE recording
- Concomitant medication recording
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)

7.8 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 as needed:

- Brief physical examination

- Urine pregnancy test (females of child-bearing potential)
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- Vital signs measurement
- Dispense and / or collect study drug
- Review instructions on how to apply study drug
- AE recording
- Concomitant medication recording
- Dispense and / or collect subject diaries
- vIGA-AD™ score (excluding subject's scalp)
- %BSA affected calculation (excluding subject's scalp)
- EASI (excluding subject's scalp)
- Assessment of itch (PP-NRS)
- Review subject diaries for treatment compliance

7.9 End of Study

The end of study is defined as when the last active subject has completed the Follow up Visit (if subject does not enroll in the separate open-label, long-term safety study) OR the last active subject has completed the 27 days of treatment in this study (if subject is eligible and enrolls in the separate open-label, long-term safety 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 adverse events of special interest (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.

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 should be collected for each of these AESIs:

Contact Dermatitis

The study site should collect location, time to onset, duration, size, associated symptoms (itching, burning, pain), severity (mild, moderate, severe), concomitant medications used to treat, action taken with study drug and photograph the affected site (if possible). If the subject 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 time to onset, duration, severity (mild, moderate, severe), 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 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 if these events are mild and moderate and do not require intervention or interruption in study drug use. On close inspection, the morphology is similar to that of keratoses 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, 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 adverse event 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 the 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 until 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 safety, tolerability, PK, and efficacy of tapinarof cream, 1% in pediatric subjects with AD.

10.1 General Considerations

All study data will be summarized overall and by age group (2-6 years old, 7-11 years old, and 12-17 years old) 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

There is no formal statistical hypothesis planned and the sample size is mainly based on feasibility and an estimated number of subjects needed to address the objectives of the study.

10.3 Analysis Populations

10.3.1 Safety

All 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 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 (BQL) of the assay is considered evaluable.

10.4 Planned Analyses

All safety, tolerability, PK, and efficacy measures over the course of the study will be presented. Details of planned analyses will be described in the Statistical Analysis Plan (SAP).

10.4.1 Disposition and Demographics

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

10.4.2 Safety Analyses

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

The number and proportion of subjects with TEAEs will be summarized by system organ class, and preferred term for all TEAEs, all TEAEs considered by the Investigator to be related to study drug, all SAEs, and all TEAEs leading to study drug discontinuation.

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.

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.

LTS scores will be summarized by visit.

10.4.3 Pharmacokinetic Analyses

The PK analysis set will be used in the analysis of PK data. Data will be listed and summarized. Listings will be sorted by subject, day, and time; summaries will be presented by day and time.

Unless stated otherwise, descriptive summaries for continuous variables will include n, mean, SD, median, minimum, and maximum. If data permit, PK parameters ($AUC_{0\text{-}last}$, C_{max}, t_{max}, and t_{last}) will be derived using non compartmental methods based on the actual sampling times recorded in the study.

10.4.4 Efficacy Analyses

All efficacy analyses will be based on the Safety population. The efficacy endpoints are as follows:

- Change in vIGA-AD™ score from Baseline at each study visit
- Proportion of subjects who have a vIGA-AD™ score of clear or almost clear (0 or 1) at each study visit
- Proportion of subjects with ≥50% improvement in EASI score from Baseline at each study visit
- Proportion of subjects with ≥75% improvement in EASI score from Baseline at each study visit
- Proportion of subjects with ≥90% improvement in EASI score from Baseline at each study visit
- Mean change and percent change in EASI score from Baseline at each study visit
- Mean change and percent change in %BSA affected from Baseline at each study visit
- Mean change and percent change in BSA x vIGA-AD™ values from Baseline at each study visit
- Proportion of subjects with a Baseline PP-NRS score ≥ 4 who achieve ≥ 4-point reduction in the PP NRS from Baseline at each study visit
- Proportion of subjects ≥ 12 years old with a Baseline PP-NRS score ≥4 who achieve a ≥4 point reduction from Baseline at each study visit
- Proportion of subjects 2 to < 12 years old with a Baseline PP-NRS score ≥4 who achieve a ≥4 point reduction from Baseline at each study visit
- Mean change in PP-NRS score from Baseline at each study visit by age group

10.5 Interim Analyses

No formal interim analyses will be performed, however the study team may review PK and safety data on an ongoing basis. This includes an analysis of the PK data after 25% of the subjects (n=9) have completed the study to re-assess the PK sampling scheme with the potential to eliminate the 5-hour post-dose blood draw. If required, changes to the protocol will be made through a protocol amendment.

10.6 Handling of Missing Data

No imputations will be made for missing values. Summaries will be based on observed data only.

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, ie, 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 Case Report Forms

For each subject enrolled, a case report form (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 adverse event, 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 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 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.

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13 Appendices

Appendix 1: 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

From 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 vIGA AD™ score is selected using the descriptors below that best describe the overall appearance of the lesions 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 6. 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 7. 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; EASI = Eczema Area and Severity Index

Table 8. 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; EASI = Eczema Area and Severity Index

Appendix 5: Local Tolerability Scale Assessment

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 scale 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 treatment to "sensitive areas" (e.g., genitals, face, neck, and skin folds), then also assess the degree of irritation for these areas.

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 6: The Protocol Amendment Summary of Changes Table

Protocol Section	Description of Change	Rationale
Medical Monitor/Sponsor Information Page	Sponsor contact information was deleted. Secondary MM was added.	Sponsor contact information may change during the study, therefore it will be provided separately. Secondary MM was inadvertently not included in the original protocol.
Synopsis **Section 4.3 Exclusion Criteria**	Oral doxepin is allowed if the drug is being taken for depression and the subject is on a stable dose.	Regimen does not impact assessment of AD.
Synopsis **Section 2 Objectives and Endpoints** **Section 10.4.4 Efficacy Analyses**	The secondary endpoint: "BSA x vIGA-AD™ values and change from Baseline at each study visit" Was changed to "Mean change and percent change in BSA x vIGA-AD™ values from Baseline at each study visit"	To accurately reflect what will be analyzed.
Schedule of Assessments **Section 5.1.1 Description, Packaging, and Labeling**	References to "Double Blind Vehicle Controlled" and "Vehicle Cream removed.	Inadvertently included in the original protocol.
Background	Background information was updated to describe development and marketing of the molecule, known as tapinarof or benvitimod, globally.	Updated information included.
Section 1.3.1.3 Reproductive and Developmental Toxicity	"highly effective method of contraception" was changed to "acceptable method of contraception"	To align with inclusion/exclusion criteria
Section 1.3.1.3 Reproductive and Developmental Toxicity **Section 6.3.2 Brief Physical Examination** **Section 6.3.4 Clinical Safety Laboratory Assessments**	Throughout the protocol text was updated and/or added to address that CBP of adolescents, as well as adults, may change during the study warranting changes in contraception requirements and pregnancy testing.	To ensure safety in all WOCBP.
Section 6.2.1.2 Body Surface Area Affected **Appendix 4**	Details on the calculation of approximate % BSA were updated throughout the protocol.	The updated text accurately reflects how BSA affected will be calculated.
Section 6.2.2 Eczema Area and Severity Index **Appendix 4**	Language in the PP-NRS was updated to align verbatim with the copyrighted tool. Copyright information below PP-NRS.	Copyrighted version will be used during the study. Copyright information was inadvertently omitted in original protocol.

Protocol Section	Description of Change	Rationale
Section 8.1.3 Adverse Events of Special Interest	Description for reporting folliculitis (AESI) was updated to reflect how data will be collected. "…associated symptoms (itching, burning, pain)…" was changed to "…associated signs and symptoms (itching, burning, pain, erythema)…" Language was changed from 'indicate whether pustular' to 'describe morphology [scale (keratotic/cornified) or no scale (non-keratotic/non-cornified)]. 'Infectious/Non-infectious' was removed from possible descriptors.	The updated text aligns with how data will be collected in the CRF and reflects evolving understanding of this AESI.
Appendix 4	Instructions for %BSA calculation were updated to accurately reflect how %BSA will be calculated.	Description in the original protocol did not accurately represent how calculations will be done.
Appendix 4	Copyright information was added below EASI calculation tables.	Copyright information was inadvertently omitted in original protocol.
Throughout the protocol	Edits were made to remove reference to randomization. Minor grammatical/formatting updates were made	Clarification