CLINICAL STUDY PROTOCOL

Title	Open-Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Adults with Extensive Plaque Psoriasis
Sponsor	Dermavant Sciences GmbH [redacted]
Compound Name	Tapinarof (DMVT-505)
Protocol Number	DMVT-505-2002
Indication	Plaque Psoriasis
Development Phase	2a
IND #	104601
Version/Effective Date:	Original Protocol – Version 1.0 26-April-2019

SPONSOR SIGNATURE PAGE

Study Title: Open-Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Adults with Extensive Plaque Psoriasis

Protocol Number: DMVT-505-2002

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

[redacted]

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/Serious Adverse Event Contact Information

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number
[redacted]			

Study Sponsor

This study is sponsored by Dermavant Sciences, GmbH.

Dermavant Sciences GmbH Registered Address

Dermavant Sciences GmbH
[redacted]

United States Agent and Regulatory Contact

Dermavant Sciences, Inc.
[redacted]

INVESTIGATOR STATEMENT

Study Title: Open-Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Adults with Extensive Plaque Psoriasis

- 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 (Printed)	Signature
Date	Site

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Description
%BSA	percent body surface area
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
AST	aspartate aminotransferase
AUC0-τ	area under the plasma concentration vs time curve in one dosing interval
BMI	body mass index
BP	blood pressure
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
Cmax	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
Dermavant	Dermavant Sciences GmbH
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FSH	follicle-stimulating hormone
[redacted]	[redacted]
HBC	hepatitis C virus
HBsAg	hepatitis B surface antigen
Hep	hepatitis
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Term	Description
IV	intravenous
LS	least squares
LTS	Local Tolerability Scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PK	pharmacokinetic(s)
PND	postnatal day
QTcF	QT interval corrected with Fridericia's formula
RBC	red blood cell(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
TEAE	treatment-emergent adverse event
tmax	time of maximum plasma concentration
t1/2	elimination half life
ULN	upper limit of normal
US; USA	United States (of America)
UV	ultraviolet
WBC	white blood cell(s)
WOCBP	women of childbearing potential

SYNOPSIS

Name of Sponsor/Company: Dermavant Sciences GmbH		
Name of Study Drug: DMVT-505 (tapinarof cream, 1%)		
Name of Active Ingredient: Tapinarof		
Protocol Number: DMVT-505-2002	**Phase**: 2a	**Country:** United States (US)
Title of Study: Open-Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Adults with Extensive Plaque Psoriasis		
Study Center(s): Approximately 6 centers in the US		
Objectives: **Primary:** • To evaluate the safety and tolerability of tapinarof cream, 1% in adult subjects with extensive plaque psoriasis • To evaluate the pharmacokinetics (PK) of tapinarof cream, 1% in adult subjects with extensive plaque psoriasis **Secondary:** • To exclude clinically relevant effects of tapinarof cream, 1% on QT interval corrected by Fridericia's formula (QTcF) • To assess the efficacy of tapinarof cream, 1% in adult subjects with extensive plaque psoriasis [redacted]		
Methodology: This is a Phase 2a, multicenter, open-label, safety, tolerability and PK study. The study will consist of three phases: Screening (up to 34 days), Treatment (29 days), and Follow-up (7-10 days). At Day 1 (Baseline), eligible subjects will be instructed on how to apply tapinarof cream, 1% while under the supervision of site personnel in the clinic. During the treatment period, subjects will apply tapinarof cream, 1% to affected areas once a day for 29 days. Subjects will return to the clinic on Days 2, 15, 29, and 30 for study assessments and will receive a phone call on Days 8 and 22. Subjects will return to the clinic for a follow-up visit 7-10 days after the Day 29 visit. On clinic visit days, subjects will apply study drug under the supervision of site personnel, after assessments have been completed. Full PK profiles and Holter monitoring will be collected on Days 1 and 29 (with corresponding 24-hour time points collected on Days 2 and 30, respectively). Limited PK sampling will be performed on Day 15. Pre-treatment, time-matched Holter monitoring will be conducted on Day -1 and the morning of Day 1.		
Number of Subjects: Approximately 20 subjects ages 18 to 75 years will be enrolled in the study.		

Diagnosis and Main Criteria for Inclusion:

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 18 to 75 years with confirmed clinical diagnosis of chronic psoriasis and stable disease for at least 6 months prior to the study;
2. Body surface area (BSA) involvement ≥ 20% (the subject's scalp, palms, and soles should be excluded from the percent BSA [%BSA] calculations to determine eligibility at Screening);
3. A Physician Global Assessment (PGA) score of ≥ 3 at Screening;
4. Women of childbearing potential (WOCBP) and male subjects who are engaging in sexual activity that could lead to pregnancy must use at least 1 of the following adequate birth control methods while on study and for 4 weeks after the last exposure to study drug. Acceptable contraception methods are:
   - Male or male partner with vasectomy, OR
   - Male condom AND partner use of one of the contraceptive options below:
     - Spermicide;
     - Contraceptive subdermal implant that meets effectiveness criteria including a < 1% rate of failure per year, as stated in the product label;
     - Intrauterine device or intrauterine system that meets effectiveness criteria including a < 1% rate of failure per year, as stated in the product label;
     - Oral contraceptive, either combined or progestogen alone;
     - Injectable progestogen;
     - Contraceptive vaginal ring;
     - Percutaneous contraceptive patches.

   Note: Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Baseline.

   These allowed methods of contraception are only effective when used consistently, correctly, and in accordance with the product label. The Investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

   Non-childbearing potential is defined as premenarchal; or pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries) or hysterectomy; or hysteroscopic sterilization; or postmenopausal females defined as a cessation of menses for at least 12 months without an alternative medical cause. In questionable cases a blood sample with simultaneous follicle-stimulating hormone (FSH) > 40 mIU/mL is confirmatory. Documented verbal history from the subject is acceptable.

   Subjects who are abstinent are eligible, but they must agree to use one of the birth control methods listed above if they start engaging in sexual activity that could lead to pregnancy during the study.

   WOCBP must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Day 1).
5. Presence of venous access for multiple blood draws on an area that is devoid of psoriasis.
6. Capable of giving written informed consent, as applicable, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF); written informed consent must be obtained prior to performing 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. Psoriasis other than plaque variant;
2. Any sign of infection of any of the psoriatic plaques;
3. Concurrent conditions or history of other diseases:
   a. Immunocompromised (e.g., lymphoma, acquired immunodeficiency syndrome) or medical history of positive human immunodeficiency virus (HIV) antibody at Screening;
   b. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to the Baseline visit;
   c. Acute active bacterial, fungal, or viral (herpes simplex, herpes zoster, or chicken pox) skin infection within 1 week prior to the Baseline visit;
   d. Significant dermatologic or inflammatory condition other than plaque psoriasis that, in the Investigator's opinion, would make it difficult to interpret data or assessments during the study.
4. Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq$ 2 x the upper limit of normal (ULN);
5. Screening total bilirubin > ULN; total bilirubin > ULN and $\leq$ 1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%;
6. A QTcF > 470 msec;
7. 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 a positive anti -hepatitis B core antigen (anti-HBc) result;
8. Ultraviolet (UV) light therapy or prolonged exposure to natural or artificial sources of UV radiation (e.g., phototherapy, tanning beds/booths, or therapeutic sunbathing) within 4 weeks prior to the Baseline visit and/or plans to have such exposures during the study which could potentially impact the subject's psoriasis (as determined by the Investigator);
9. Use of any prohibited medication 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.

   - Minimum of 5 half-lives for biologic agents: e.g., 12 months for rituximab; 8 months for ustekinumab; 5 months for secukinumab; 12 weeks for golimumab; 10 weeks for ixekizumab; 8 weeks for infliximab, adalimumab, or alefacept; and 4 weeks for etanercept;
   - 4 weeks for systemic treatments: cyclosporin, interferon, methotrexate, apremilast, tofacitinib, mycophenolate, thioguanine, hydroxyurea, sirolimus, azathioprine, other systemic immunosuppressive or immunomodulating agents, fumaric acid derivatives, Vitamin D and analogs, retinoids (e.g., acitretin, isotretinoin), psolarens, corticosteroids, or adrenocorticotropic hormone analogs;
   - 2 weeks for immunizations with a live viral component;
   - 2 weeks for drugs known to possibly worsen psoriasis, such as beta-blockers (e.g., propranolol), lithium, iodides, angiotensin-converting enzyme inhibitors, and indomethacin, unless on a stable dose for > 12 weeks;
   - With the exception of emollients, 2 weeks for topical treatments including corticosteroids, immunomodulators, anthralin (dithranol), Vitamin D derivatives (e.g., calcipotriene, calcipotriol), retinoids (e.g., tazarotene), or coal tar.

10. 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 and ability to understand and give informed consent;
11. Pregnant females as determined by positive serum (Screening) or urine (Baseline) human chorionic gonadotropin test at Screening or prior to dosing;
12. Lactating females;
13. History of sensitivity to the study drug, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates the subject's participation in the study;
14. The subject has received an investigational drug within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives, or twice the duration of the biological effect of the investigational drug (whichever is known to be longer);
15. Current or a history of cancer within 5 years except for fully excised skin basal cell carcinoma, squamous cell carcinoma or carcinoma in situ of the cervix;
16. Subjects with active infection that required oral, intramuscular, or intravenous (IV) administration of antibiotics, antifungal, or antiviral agents within 7 days of the Baseline visit;
17. Concurrent skin lesions in the treatment area that, in the opinion of the Investigator, would either interfere with study evaluations or affect the safety of the subject;
18. Subjects with advanced disease or abnormal laboratory test values that could affect the safety of the subject or the implementation of this study;
19. Previous known participation in a clinical study with tapinarof; Evidence of significant hepatic, renal, respiratory, endocrine, hematologic, neurologic, psychiatric, or cardiovascular (CV) system abnormalities or laboratory abnormality that will affect the health of the subject or interfere with interpretation of the results.

Study Drug, Dosage and Mode of Administration:

Tapinarof cream, 1% is a white to off-white cream containing 10 mg/gram tapinarof, supplied in 30 gram tubes, and is to be self-administered once daily via topical application of a thin layer to affected areas.

Duration of Treatment: Study duration for subjects who complete this Phase 2a study is approximately 10 weeks in total (including approximately 34 days for Screening, 29 days of treatment, and a 7-10 day follow-up period).

Study Endpoints:

Primary: Frequency and severity of adverse events (AEs; local and systemic)

- Laboratory and [redacted] values
- Vital signs
- ECGs
- Mean Local Tolerability Scale scores by visit
- Tapinarof and tapinarof sulfate (metabolite) plasma PK parameters on Day 1 and Day 29, if data permit, including:
  - area under the plasma concentration versus time curve in one dosing interval ($AUC_{0-\tau}$)
  - maximum plasma concentration (C_{max})
  - time to maximum plasma concentration (t_{max})
  - elimination half-life ($t_{1/2}$)

Secondary:

- Analysis of change from Baseline in QTcF (ΔQTcF) at each post-treatment time point on the sampling day with the higher C_{max} (Day 1 or Day 29)
- Concentration-QTc analysis investigating the relationship between tapinarof plasma concentration and ΔQTcF, if data permit
- Mean change from Baseline to Day 29 in PGA, PASI, and %BSA

[redacted]

Statistical Methods:

Safety and PK data will be presented in tabular and/or graphical format and summarized descriptively.

For cardiodynamic ECG assessments, the primary analysis will be based on by-time point analysis to evaluate the effect of tapinarof cream, 1% on the ΔQTcF at each post-dosing time point using the Intersection Union Test. The effect of tapinarof on ΔHR, ΔPR, and ΔQRS will also be evaluated using the Intersection Union Test. An analysis of categorical outliers will also be performed for changes in HR, PR, QRS, QTcF, T-wave morphology and U-wave presence. In addition, a potential concentration-QTc analysis will be performed if a sufficient number of PK samples are measurable, i.e., above the lower limit of quantification, to provide a PK profile in most subjects. In this concentration-QTc analysis, the relationship between tapinarof plasma concentrations and ΔQTcF will be evaluated using a linear mixed-effects modeling approach.

PGA, PASI, and %BSA will be compared to Baseline values using a one sample t-test.

SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

Procedure	Screening (up to 34 days prior to Day 1)	Day -1	Treatment Period (Tapinarof Cream, 1% Once Daily)							Follow-up (7-10 days after Day 29) or ET
			Baseline Day 1	Day 2	Day 8	Day 15	Day 22	Day 29	Day 30	
	Visit 1	Visit 2	Visit 3	Visit 4	Phone Call	Visit 5	Phone Call	Visit 6	Visit 7	Visit 8
Informed consent	X									
Inclusion and exclusion criteria	X	X	X							
Demography	X									
Brief physical exam (including height, weight and BMI at Screening)	X									X
Medical history (including year of psoriasis diagnosis)	X									
Pregnancy test (WOCBP)	X		X							X
PGA, PASI, and % BSA evaluation[a]	X		X					X		
HIV, Hep B and Hep C Screen	X									
Laboratory assessments (chemistry including liver chemistries, hematology, urinalysis)	X		X					X		X
LTS assessment by Investigator			X			X		X		
Single 12-lead ECG	X									X
Continuous Holter Monitoring		X[b]	X[c]	X[d]				X[c]	X[d]	
Vital signs (pre-dose; HR, BP, and temperature)	X		X							X
Randomization			X							
Study drug Dispensation / Collection			X			X		X		
Training on drug application			X	X	X	X	X			
Dispense/collect subject diary			X			X		X		
Tapinarof cream administration in-clinic under site supervision			X	X		X		X		
Serial PK profile samples[e]			X	X		X		X	X	
[redacted]			X	X				X	X	
AE/SAE review	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X

Note: Phone calls to subjects are on Day 8 and Day 22

Abbreviations: %BSA = percent body surface area; AE = adverse event; BMI = body mass index; BP = blood pressure; ECG = electrocardiogram; ET = early termination; Hep = hepatitis; HIV = human immunodeficiency virus; LTS = local tolerability scale; PGA = Physician Global Assessment; PASI = Psoriasis Area and Severity Index; PK = pharmacokinetic; SAE = serious adverse event; WOCBP = women of childbearing potential

[a] The subject's scalp, palms, and soles should be excluded from the %BSA calculations.

[b] On Day -1, a Holter monitor will be attached for approximately 13 hours to collect pre-treatment, time-matched ECG data. 12-lead ECGs will be extracted from the continuous recording at time points corresponding to time points on Day 1 and Day 29. Subjects will rest in a supine or semi-recumbent position for at least 10 minutes before and 5 minutes after each time point for ECG extraction.

[c] On Day 1 and Day 29, a Holter monitor will be attached one hour prior to dosing and for 12 hours post-dose. 12-lead ECGs will be extracted at the same time points as PK samples, i.e., pre-dose and at 1, 2, 3, 4, 5, 8, and 12 hours post-dose. Subjects will rest in a supine or semi-recumbent position for at least 10 minutes before and 5 minutes after each time point for ECG extraction. All ECG extractions will be performed immediately before the PK sample is drawn.

[d] On Day 2 and Day 30, a Holter monitor will be attached for one hour prior to the 24-hour post-dose PK time point to allow for extraction of 12-lead ECGs corresponding to the 24-hour post-dose PK time point. Subjects will rest in a supine or semi-recumbent position for at least 10 minutes before and 5 minutes after the time point for ECG extraction. The ECG extraction will be performed immediately before the PK sample is drawn.

[e] On Day 1 and Day 2 (Visits 3 and 4) as well as Day 29 and Day 30 (Visits 6 and 7), serial PK profile samples will be collected at pre-dose and at 1, 2, 3, 4, 5, 8, 12, and 24 hours after dosing. On Day 15 (Visit 5), serial PK profile samples will be collected pre-dose and at 2 and 4 hours after dosing.

[f] [redacted]

1. INTRODUCTION

1.1. Background Information and Study Rationale

1.1.1. Background Information

Psoriasis is a common, chronic relapsing inflammatory skin disease [Parisi, 2012] with recurrent episodes of prominently erythematous and scaly patches (plaques). Approximately 2 to 3% of the global population is affected by psoriasis; those affected are predominantly adults, who are most often diagnosed between the ages of 18 to 35 years. Psoriasis disrupts daily activities such as work attendance, interpersonal relationships, recreational activities, and intimacy, thereby significantly impacting sufferers' quality of life. Furthermore, psoriasis sufferers can also have co-morbidities such as arthritis, depression, inflammatory bowel disease, and CV diseases.

Up to 80% of patients have mild to moderate plaque-type psoriasis, which is generally managed with topical treatments. The most commonly used treatments for psoriasis include topical corticosteroids and Vitamin D analogs, alone or in combination. Vitamin D analogs are moderately efficacious as monotherapy, whereas application of topical corticosteroids, particularly the very potent ones, is restricted in terms of body areas that can be treated and the duration of use due to the well-known application site and systemic adverse drug reactions [Mason, 2013]. Although numerous topical treatment options are available, there remains a need for a topical treatment that combines a high level of efficacy with an acceptable safety profile and permits application to a large body surface area (BSA) without restrictions on duration of treatment.

Tapinarof (DMVT-505), formerly known as [redacted], is a fully synthetic hydroxylated stilbene that is being developed by Dermavant Sciences GmbH (Dermavant) as a novel anti-inflammatory agent for the topical treatment of plaque psoriasis and atopic dermatitis and [redacted] The compound ([redacted] was initially developed by [redacted] for further development in the rest of the world except China. [redacted] with a unique topical formulation. Dermavant acquired the drug [redacted] for continued development.

Tapinarof cream, 1% is a white to off-white, [redacted] intended for topical application to atopic dermatitis and psoriatic skin plaques, which has a novel mechanism of action. The drug likely mediates its effects via the aryl hydrocarbon receptor (AhR) agonist and nuclear factor erythroid 2-related factor 2 (Nrf2) because the pattern of pro-inflammatory mediators inhibited by tapinarof is different from that of corticosteroids, calcineurin inhibitors, Vitamin D analogs, and other immunosuppressive agents commonly used to treat atopic dermatitis and psoriasis. Together, existing data identify tapinarof as a non-steroid, therapeutic AhR-modulating agent, which is a unique mechanism of action compared with existing therapies.

Tapinarof cream has been evaluated in nonclinical studies at concentrations up to 8% and in clinical studies at concentrations up to 2%. Three Phase 1 clinical pharmacology studies in healthy volunteers and seven Phase 1 or 2 studies in subjects with psoriasis or atopic dermatitis

have been completed. Refer to the current version of the tapinarof investigator's brochure for detailed information. Tapinarof has demonstrated an acceptable safety profile and a clear therapeutic effect, as compared to vehicle, in both psoriasis and atopic dermatitis.

Four randomized, double-blind, vehicle-controlled, clinical studies to evaluate the safety and efficacy of topically applied tapinarof cream in subjects with psoriasis or atopic dermatitis were conducted by [redacted] one 28-day and one 12-week study were completed for each indication. These studies enrolled a total of 282 adult subjects, with 235 subjects exposed to tapinarof cream, 0.5%, 1%, or 2% ([redacted]) once or twice daily for a period of 28 to 84 days. Efficacy was rapid, and statistically significant differences versus vehicle were observed as early as Day 14 for the majority of the efficacy parameters in both indications. The most frequently reported (1% to 6% of 235 subjects) dermatological adverse events (AEs), regardless of causality, were application site discoloration/hyperpigmentation, application site dermatitis, papular rash, pruritus, contact dermatitis, folliculitis, erythema, and skin burning sensation. Nasopharyngitis and headache were the most frequently reported (> 10% of subjects) nondermatological AEs overall. Overall, results of the clinical studies indicated tapinarof was highly efficacious for both psoriasis and atopic dermatitis, with a favorable safety profile.

The first clinical study with [redacted] was a Phase 1 study to evaluate the systemic exposure and pharmacokinetic (PK) parameters of tapinarof cream, 1% and 2%. This study was conducted in 11 subjects with atopic dermatitis; 5 subjects were treated with the 2% tapinarof concentration and 6 subjects were treated with the 1% concentration. Headache was the most frequently reported (100% and 60% of subjects at the 1% and 2% concentrations, respectively) nondermatological AE.

A Phase 2b, 12-week, randomized, double-blind, vehicle-controlled, 6-arm, parallel group, dose-finding study with topically applied tapinarof cream was conducted in patients with psoriasis by [redacted] This study evaluated the safety and efficacy of tapinarof cream [redacted] at 2 concentrations (0.5% or 1%) and 2 application frequencies (once daily or twice daily) in 227 adult subjects with plaque psoriasis. Tapinarof showed a clear therapeutic effect compared with vehicle, with the 1% concentration treatment groups demonstrating a higher proportion of subjects with treatment success compared with the 0.5% concentration groups (applied once daily or twice daily). Once daily application had similar efficacy to twice daily application.

Across two Phase 2b studies in psoriasis and atopic dermatitis, 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% once daily treatment group had a lower frequency of TEAEs than the tapinarof 1% twice daily treatment group.

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 (including ECG parameters) and systemic exposure of tapinarof cream, 1% for the topical treatment of plaque psoriasis in adults. 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.

1.2. Rationale for Study Design and Dose

This study includes a 29-day, open-label treatment phase in which subjects will receive tapinarof cream, 1% once daily for 29 days. Tapinarof cream has been investigated in prior studies at concentrations from 0.5% to 8.0% and at once and twice daily dosing frequencies. The 1% concentration applied once daily was chosen as the dose and dosing frequency to take forward in the clinical development program based on the data from the GSK Phase 2b clinical study in subjects with psoriasis (Study 203120). In that study, applications of tapinarof at concentrations of 0.5% and 1% applied once or twice daily were evaluated. Overall, both concentrations demonstrated an acceptable safety profile when applied once or twice daily. A once daily application regimen may reduce systemic exposure as the skin heals, thereby providing a better safety profile for a drug intended for long-term use to treat a chronic condition. Based on the efficacy and safety data from Study 203120, a regimen of 1% once daily was chosen as the tapinarof concentration and dosing frequency to be investigated in this study and intended for registration. 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 29-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, AEs, and other significant data pertaining to the study drug being used in this study.

1.3.1. Risk Assessment

1.3.1.1. Dermatological Adverse Events, Including Skin Irritation, or Allergic Reaction:

Tapinarof or its excipients may induce skin irritation. Allergic or irritant reactions in the exposed areas may present as erythema, edema, papules, or vesicles. In the event of pronounced skin reaction, spreading of the eczematous reaction beyond the original application site(s) and/or more generalized (remote) skin reactions may be observed.

In the dose-ranging study (Study 203120) in subjects with psoriasis, the most frequently reported dermatologic AEs were folliculitis and contact dermatitis. In the dose-ranging study (Study 203121) in subjects with atopic dermatitis, the most frequently reported dermatologic AEs were folliculitis and atopic dermatitis. Nonclinical dermal toxicity studies of up to 8% tapinarof for up to 13 weeks indicated local effects are primarily mild-to-moderate skin irritation that is reversible; tapinarof did not show evidence of sensitization. In initial clinical studies using a different formulation of tapinarof [redacted], AEs of skin hyperpigmentation, application site dermatitis, papular rash, pruritus, contact dermatitis, folliculitis, erythema, and skin burning sensation were reported.

1.3.1.2. Systemic Adverse Events:

Nasopharyngitis and headache were the most frequently reported nondermatological AEs in the dose-ranging study (Study 203120) in subjects with psoriasis. In the dose-ranging study (Study 203121) in subjects with atopic dermatitis, the most frequently reported nondermatological AEs were nasopharyngitis, upper respiratory tract infection, and headache. In the initial clinical studies (in psoriasis and atopic dermatitis) using a different tapinarof formulation [redacted], nasopharyngitis, and headache were the most frequently-reported nondermatological AEs. In Study 201851 with [redacted] of tapinarof cream, 1% and 2%, headache was most frequently reported during the study (reported for 100% and 60% of subjects at the 1% and 2% doses, respectively).

In a nonclinical study in minipigs using IV administration, reversible decreases in arterial blood pressure and PR interval were observed; however, in this study and repeat dermal toxicity studies, there were no effects on QT interval or HR. Repeat-dose dermal toxicity studies also showed findings related to the liver (increased weights and hepatocellular hypertrophy/regeneration) and thymus (thymic cortex depletion in adult rabbits and rats; changes in thymus weight, microscopic decreased cellularity, and changes in thymic T cell maturation in juvenile rats) with associated secondary hematological findings. Thymic findings were also noted in repeat adult and juvenile rat studies; however, there were no clinically relevant AEs/serious adverse events (SAEs) reported.

To mitigate potential systemic risks, subjects will be monitored for AEs and any abnormal vital signs, physical examination, and laboratory test results.

1.3.1.3. Reproductive and Developmental Toxicity

Results of embryo-fetal development studies in rats and rabbits indicated an increased risk for embryo-fetal developmental effects, as evidenced by an increase in post-implantation loss and incidence of fetal skeletal variations. Results of a juvenile rat study indicated adverse microscopic changes in the form of renal pelvic dilatation in both sexes, along with reversible increases in total urinary glucose and protein excretion in males at ≥ 10/15 mg/kg/day tapinarof (administered subcutaneously).

An investigative study in rats suggested an increased risk for hydronephrosis during a narrow window of postnatal sensitivity prior to postnatal day (PND) 32 (specifically PND 15 to 21). Rat renal tubule anatomic maturation and nephrogenesis occurs during this period [Cappon, 2010; Frazier, 2013; Zoetis, 2003], however tubule morphogenesis/nephrogenesis occurs entirely prenatally in humans [Cappon, 2010; Zoetis, 2003].

To mitigate these potential risks, women of childbearing potential (WOCBP) must utilize abstinence or a highly effective method of contraception consistently and correctly during the study and for 4 weeks after the end of treatment (Section 4.2). Pregnant women and subjects under 18 years of age will be excluded from the study. If a woman becomes pregnant during the study, she will immediately discontinue the study drug. Additionally, AEs will be monitored and clinical laboratory testing will be performed.

1.3.2. Benefit Assessment

Subjects may experience improvements in their psoriasis 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 psoriasis.

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 psoriasis.

2. OBJECTIVES AND ENDPOINTS

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

Objectives	Associated Endpoint
Primary	**Primary**
• To evaluate the safety and tolerability of topical tapinarof cream, 1% in adult subjects with extensive plaque psoriasis	• Frequency and severity of AEs (local and systemic) • Laboratory and biomarker values • Vital signs • ECGs • Mean Local Tolerability Scale scores by visit
• To evaluate the PK of topical tapinarof cream, 1% in adult subjects with extensive plaque psoriasis	• Tapinarof and tapinarof sulfate (metabolite) plasma PK parameters on Day 1 and Day 29, if data permit, including: o $AUC_{0-\tau}$ o C_{max} o t_{max} o $t_{1/2}$
Secondary	**Secondary**
• To exclude clinically relevant effects of tapinarof cream, 1% on QTcF	• Analysis of ΔQTcF at each post-treatment time point on the sampling day with the higher C_{max} (Day 1 or Day 29) • Concentration-QTc analysis investigating the relationship between tapinarof plasma concentration and ΔQTcF, if data permit
• To assess the efficacy of tapinarof cream, 1% in adult subjects with extensive plaque psoriasis	• Mean change from Baseline to Day 29 in PGA, PASI, and %BSA
Exploratory	**Exploratory**
[redacted]	[redacted]

3. STUDY DESIGN

3.1. Overall Design

This is a Phase 2a, multicenter, open-label study to evaluate the safety and PK of topical tapinarof cream in adults with extensive plaque psoriasis. The study will consist of three phases: Screening (up to 34 days), Treatment (29 days), and Follow-up (7-10 days).

At Day -1, eligible subjects will be enrolled into the study. During the treatment period beginning on Day 1 (Baseline), subjects will apply tapinarof cream, 1% to affected areas once a day for 29 days. Subjects will return to the clinic on Days 2, 15, 29, and 30 for study assessments and will receive a phone call on Days 8 and 22. Subjects will return to the clinic for a follow-up visit 7-10 days after the Day 29 visit. On clinic visit days, subjects will apply the study drug under the supervision of site personnel, after assessments have been completed. Full PK profiles and Holter monitoring will be collected on Day 1 and Day 29 (with corresponding 24-hour time points collected on Day 2 and Day 30, respectively). Limited PK sampling will be performed on Day 15. Pre-treatment, time-matched Holter monitoring will be conducted on Day -1 and the morning of Day 1.

Study drug will be dispensed to subjects during the clinic visits and will be administered at home between clinic visits as instructed by site personnel. Subjects will be instructed to apply study drug once daily to all affected areas, including newly appearing plaques and plaques/areas that improve during the study. Subjects 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 in a daily diary provided by the study site. Note that subjects are allowed, but not required, to treat palms, fingernails, soles, toenails, and scalp plaques with study drug. If a subject chooses to treat plaques on palms, fingernails, soles, toenails, and/or scalp, they should do so for the entirety of the treatment period from Day 1 to Day 29. Subjects will be instructed to apply study drug in the morning throughout the entirety of their participation in the study. At the phone contacts at Days 8 and 22, subjects should be reminded to complete their daily diary and bring it with them to the next clinic visit.

Study drug application instructions will be reviewed at all post-randomization clinic visits. On clinic visit days, subjects will be instructed/reminded on how to apply study drug (except during the final treatment/end-of-study visits). During the clinic visits, subjects will apply the daily dose of study drug while on-site under the supervision of site personnel, after other assessments have been completed.

Subjects who withdraw from the study before Day 30 will complete an Early Termination Visit. Study duration for subjects who complete this study is approximately 10 weeks in total. 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% for 29 days with once daily application.

A subject will be considered to have completed the study when he/she completes all required procedures/visits for the 29-day treatment phase.

4. STUDY POPULATION

4.1. Type and Number of Subjects

Approximately 20 adult subjects with extensive plaque psoriasis will be enrolled in the study at approximately 6 sites in the US.

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 18 to 75 years with confirmed clinical diagnosis of chronic psoriasis and stable disease for at least 6 months prior to the study;
2. BSA involvement ≥ 20% (the subject's scalp, palms, and soles should be excluded from the %BSA calculations to determine eligibility at Screening);
3. A PGA score of ≥ 3 at Screening;
4. WOCBP and male subjects who are engaging in sexual activity that could lead to pregnancy must use at least 1 of the following adequate birth control methods while on study and for 4 weeks after the last exposure to study drug. Acceptable contraception methods are:

    - Male or male partner with vasectomy, OR
    - Male condom AND partner use of one of the contraceptive options below:
        - Spermicide;
        - Contraceptive subdermal implant that meets effectiveness criteria including a < 1% rate of failure per year, as stated in the product label;
        - Intrauterine device or intrauterine system that meets effectiveness criteria including a < 1% rate of failure per year, as stated in the product label;
        - Oral contraceptive, either combined or progestogen alone;
        - Injectable progestogen;
        - Contraceptive vaginal ring;
        - Percutaneous contraceptive patches.

    Note: Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Baseline.

    These allowed methods of contraception are only effective when used consistently, correctly, and in accordance with the product label. The Investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

    Non-childbearing potential is defined as premenarchal; pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries) or hysterectomy; or hysteroscopic sterilization; or postmenopausal females defined as a cessation of menses for at least 12 months without an alternative medical cause. In questionable cases a blood sample with simultaneous follicle-stimulating hormone

(FSH) > 40 mIU/mL is confirmatory. Documented verbal history from the subject is acceptable.

Subjects who are abstinent are eligible, but they must agree to use one of the birth control methods listed above if they start engaging in sexual activity that could lead to pregnancy during the study.

WOCBP must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Day 1).

5. Presence of venous access for multiple blood draws on an area that is devoid of psoriasis.
6. Capable of giving written informed consent, as applicable, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF); written informed consent must be obtained prior to performing 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. Psoriasis other than plaque variant;
2. Any sign of infection of any of the psoriatic plaques;
3. Concurrent conditions or history of other diseases:
    a. Immunocompromised (e.g., lymphoma, acquired immunodeficiency syndrome) or have a history of malignant disease within 5 years prior to the Baseline visit;
    b. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to the Baseline visit;
    c. Acute active bacterial, fungal, or viral (herpes simplex, herpes zoster, or chicken pox) skin infection within 1 week prior to the Baseline visit;
    d. Significant dermatologic or inflammatory condition other than plaque psoriasis that, in the Investigator's opinion, would make it difficult to interpret data or assessments during the study.
4. Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2x upper limit of normal (ULN);
5. Screening total bilirubin > ULN; total bilirubin > ULN and ≤ 1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%;
6. QTcF interval > 470 msec;
7. 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 a positive anti-hepatitis B core antigen (anti-HBc) result;
8. Ultraviolet (UV) light therapy or prolonged exposure to natural or artificial sources of UV radiation (e.g., phototherapy, tanning beds/booths, or therapeutic sunbathing) within

4 weeks prior to the Baseline visit and/or plans to have such exposures during the study which could potentially impact the subject's psoriasis (as determined by the Investigator);

9. Use of any prohibited medication within the indicated period before the Baseline visit:

   NOTE: Prohibited concomitant medications, therapy, etc., during the defined period areas 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.

   - Minimum of 5 half-lives for biologic agents: e.g., 12 months for rituximab; 8 months for ustekinumab; 5 months for secukinumab; 12 weeks for golimumab; 10 weeks for ixekizumab; 8 weeks for infliximab, adalimumab, or alefacept; and 4 weeks for etanercept;
   - 4 weeks for systemic treatments: cyclosporin, interferon, methotrexate, apremilast, tofacitinib, mycophenolate, thioguanine, hydroxyurea, sirolimus, azathioprine, other systemic immunosuppressive or immunomodulating agents, fumaric acid derivatives, Vitamin D and analogs, retinoids (e.g., acitretin, isotretinoin), psolarens, corticosteroids, or adrenocorticotropic hormone analogs;
   - 2 weeks for immunizations with a live viral component;
   - 2 weeks for drugs known to possibly worsen psoriasis, such as beta-blockers (e.g., propranolol), lithium, iodides, angiotensin-converting enzyme inhibitors, and indomethacin, unless on a stable dose for > 12 weeks;
   - With the exception of emollients, 2 weeks for topical treatments including corticosteroids, immunomodulators, anthralin (dithranol), Vitamin D derivatives (e.g., calcipotriene, calcipotriol), retinoids (e.g., tazarotene), or coal tar.

10. 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 and ability to understand and give informed consent.
11. Pregnant females as determined by positive serum (Screening) or urine (Baseline) human chorionic gonadotropin test at Screening or prior to dosing;
12. Lactating females;
13. History of sensitivity to the study drug, or components thereof, or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates the subject's participation in the study;
14. The subject has received an investigational drug within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives, or twice the duration of the biological effect of the investigational drug (whichever is known to be longer);
15. Current or a history of cancer within 5 years except for fully excised skin basal cell carcinoma, squamous cell carcinoma or carcinoma in situ of the cervix;
16. Subjects with active infection that required oral, intramuscular, or intravenous (IV) administration of antibiotics, antifungal, or antiviral agents within 7 days of the Baseline visit;

17. Concurrent skin lesions in the treatment area that, in the opinion of the Investigator, would either interfere with study evaluations or affect the safety of the subject;
18. Subjects with advanced disease or abnormal laboratory test values that could affect the safety of the subject or the implementation of this study;
19. Previous known participation in a clinical study with tapinarof;
20. Evidence of significant hepatic, renal, respiratory, endocrine, hematologic, neurologic, psychiatric, or CV system abnormalities or laboratory abnormality that will affect the health of the subject or interfere with interpretation of the results.

4.4. Lifestyle Restrictions

Subjects must avoid UV light, phototherapy, and excessive sun exposure throughout the study. When prolonged exposure cannot be avoided, use of sunscreen products (except on psoriasis plaques) 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 at the discretion of the Investigator in consultation with the Medical Monitor.

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 SAEs.

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 drug at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. Subjects who discontinue from the study prematurely may be replaced at the discretion of the Sponsor.

4.6.1. Reasons for Withdrawal from the Study

Study drug will be discontinued 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
- Subject requires concurrent prohibited medication during the study. 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.
- Pregnancy
- Any Grade 3 or 4 AE considered causally related to study drug

Study drug may be discontinued for any of the following reasons:

- 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 7.10).

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 electronic case report form (eCRF). If a subject is prematurely discontinued from study drug, the Investigator must make every effort to perform an Early Termination Visit (Section 7.10) and document the primary reason for withdrawal.

Should a subject fail to attend a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

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 reschedule the missed visit as soon as possible and 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 (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 continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5. STUDY TREATMENT

5.1. Study Drug

5.1.1. Description, Packaging, and Labeling

The description of tapinarof cream, 1% is presented in Table 2.

Table 2: Tapinarof Cream

Study drug	Tapinarof (DMVT-505)
Physical Description:	White to off-white cream
Unit dose strength / How Supplied	1% (10 mg/gram) / 30 gram tube
Route of Administration/Duration	Topical/29 days
Dosing Instructions:	Once daily topical application of a thin layer to affected areas (Section 5.1.5)
Manufacturer	GSK

Abbreviations: GSK = GlaxoSmithKline

[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.

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.

A Material Safety Data Sheet/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from the Sponsor.

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 at the clinical site in appropriately labeled tubes.

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

Subjects will be instructed to apply study drug as follows:

- Once daily application to affected areas each morning.
- Study drug should be applied to dry, clean skin.
- Wash hands after application, unless treating plaques on the hands or fingernails.
- Study drug should be applied to all plaques, including newly appearing plaques and plaques that have improved during the study.
- Subjects are allowed, but not required, to treat palms, fingernails, toenails, and scalp plaques with study drug. If using study drug on scalp, no other treatment for scalp psoriasis is permitted during the study. If a subject chooses to treat plaques on palms, fingernails, soles, toenails, and/or scalp, they should do so for the entirety of the treatment period from Day 1 to Day 29.
- If there is residual cream visible on the disease-affected skin, then the subject 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 possible, use of disposable gloves is recommended.
- Subject should record the time of study drug application in the daily diary.
- Subjects should avoid swimming, bathing, showering, or strenuous activities for at least 2 hours after application of study drug.
- On clinic visit days, study drug should be applied in the clinic under the supervision of site personnel and after assessments have been completed.

  NOTE: The time of the dose and assessments on clinic visit days will depend on the time of the clinic visit (clinic visits should be scheduled for the morning to allow time to complete all study procedures). While the subjects should be instructed to apply study drug in the morning throughout the entirety of their participation in the study, the timing of the clinic visit may lead to a slight deviation from the subject's normal dosing time; if this occurs, it will NOT be considered a protocol deviation; the subject should resume their morning dosing time following any such clinic visit application.
- Subjects will be instructed/reminded on how to apply study drug at each clinic visit and phone call (except during the final treatment visit).

5.2. Randomization/Treatment Assignment

All subjects will receive tapinarof cream, 1% once daily for 29 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 with detailed instructions concerning protocol requirements and use of study drug. Additionally, subjects will be asked to complete a daily diary with the time of each application of study drug. At each post-Baseline study visit, study staff will review use of study drug, as applicable, with the subject.

When subjects are dosed at the site, they will apply the study drug under supervision of the study staff. The date and time of each dose administered in the clinic will be recorded in the source documents. The study drug and study subject identification will 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 and will record the weight of all tubes dispensed at each visit in the drug accountability log. Subjects will be instructed to bring all used and unused tubes of study drug with them to each study visit. Site personnel will weigh returned tubes (used and unused) and record the combined tube weight in drug accountability log. 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 log. The site personnel will remind the subject to keep all tubes of study drug dispensed and to bring all used and unused tubes to each clinic visit. These data will be used to estimate subject compliance with use of study drug. Tubes of study drug 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. 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 drug 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 because the indication being studied is not life-threatening or seriously debilitating and other treatment options are available.

The Investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

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 eCRF 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 are not planned to change during the course of the study 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 can be applied to the infected area; however, study drug must not be applied to the area until the skin infection is healed.

Subjects may use nonmedicated shampoos (must not contain corticosteroids, Vitamin D analogs, salicylic acid, or coal tar).

Nonmedicated emollients may be used on nonlesional skin; emollients should not be applied to lesional skin during treatment and should not be applied on the morning of clinic visits. 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 as follows:

- **Biologic agents:** rituximab, ustekinumab, secukinumab, golimumab, ixekizumab, infliximab, adalimumab, alefacept, etanercept (list is not exclusive, contact Medical Monitor for questions)
- **Systemic treatments**: cyclosporin, interferon, methotrexate, apremilast, tofacitinib, mycophenolate, thioguanine, hydroxyurea, sirolimus, azathioprine, other systemic immunosuppressive or immunomodulating agents, fumaric acid derivatives, Vitamin D3 and analogs, retinoids (e.g., acitretin, isotretinoin), psoralens, corticosteroids, or adrenocorticotropic hormone analogs
- **UV light**: UV light therapy or prolonged exposure to natural or artificial sources of UV radiation (e.g., phototherapy, tanning beds/booths, or therapeutic sunbathing); When prolonged exposure cannot be avoided, use of sunscreen products (except on psoriasis plaques) and protective apparel are recommended.

- **Topical treatments**: corticosteroids, immunomodulators, anthralin (dithranol), Vitamin D derivatives (e.g., calcipotriene, calcipotriol), retinoids (e.g., tazarotene), or coal tar
- **Drugs known to possibly worsen psoriasis (unless on a stable dose for >12 weeks)**: beta blockers (e.g., propranolol), lithium, iodides, angiotensin-converting enzyme inhibitors, and indomethacin
- **Immunizations:** live, attenuated vaccines (inactivated or subunit vaccines are acceptable when required)
- **Other:** Any study drugs or investigational procedures

6. STUDY ASSESSMENTS AND PROCEDURES

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

6.1. Medical History, Demography, and Baseline Characteristics

6.1.1. Medical History

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

Data collected will include year of plaque psoriasis diagnosis, CV medical history and risk factors (including height, weight, blood pressure (BP), smoking history, medical conditions, and family history of premature CV disease) and family history of liver disease.

6.1.2. Demographics

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

6.1.3. Baseline Characteristics

During Screening, single 12-lead electrocardiograms (ECGs) will be obtained using an ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT, and QTcF intervals. Subjects should be in a supine or semi-recumbent position for at least 5 minutes before ECG is measured.

Holter monitoring will be conducted for approximately 13 hours on Days -1, 1 and 29, and approximately 1 hour on Days 2 and 30 to collect pre-treatment and time-matched ECG data.

6.2. Psoriasis Disease Assessments

6.2.1. Physician Global Assessment

The PGA is a clinical tool for assessing the current state/severity of a subject's psoriasis at a given time point. It is a static 5-point morphological assessment of overall disease severity, as determined by the Investigator, using the clinical characteristics of erythema, scaling, and plaque thickness/elevation as guidelines; higher PGA scores represent more severe disease. The BSA affected is not considered in scoring of the PGA (see Section 6.2.2 for details on BSA scoring). Variations of the PGA are frequently used in clinical studies because it is a simple assessment that is more similar to the assessments actually used in clinical practice (see Appendix 1 for details). The PGA should be performed first, prior to %BSA, PASI, and Local Tolerability Scale (LTS) assessments.

6.2.2. Body Surface Area Affected

The assessment of the %BSA affected is an estimate of the percentage of total involved skin with psoriasis. For the purpose of clinical estimation, the total palmar surface of the subject's palm (including fingers) may be assumed to be approximately equivalent to 1% BSA. The %BSA affected by psoriasis will be evaluated (from 0 to 100%). Details on calculation of approximate %BSA involvement in each subject (total and individual areas) are provided in Appendix 2. %BSA is a static assessment made without reference to previous scores. Note that plaques on the scalp, palms, and soles should be excluded from the %BSA calculations used to determine eligibility.

6.2.3. Psoriasis Area and Severity Index

The PASI scoring system is a widely used standard clinical tool for assessing the severity of psoriasis that takes into account the overall severity of erythema (redness), induration (plaque thickness), and scale, and the extent of %BSA affected with psoriasis. The 3 clinical signs are each graded on a 5-point scale (0 to 4) and the %BSA affected is scored on a 7-point scale (0 to 6) for each of the 4 specified body regions (head, upper extremities, trunk, and lower extremities). The individual scores are multiplied by a weighted factor for each body region; the sum of these scores gives the overall PASI score. Higher scores indicate more severe disease. PASI is a static assessment made without reference to previous scores. Details on PASI calculation are provided in Appendix 2.

6.3. Safety Assessments

6.3.1. Adverse Events

All AEs will be collected from the time the subject signs the 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 Exam

A brief physical examination will include, at a minimum, assessments of the skin, lungs, CV system, and abdomen (liver and spleen). 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 measurement of systolic and diastolic BP, HR, and body temperature. Subjects should be in a supine or semi-recumbent 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/center 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 3.

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 notified.

Table 3: Laboratory Tests

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

Abbreviations: ALT = alanine aminotransferase; Anti-HBc= anti-hepatitis B core antigen; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle-stimulating hormone; HBC = hepatitis C virus; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell(s); WBC = white blood cell(s); WOCBP = women of childbearing potential.

6.3.5. [redacted]

[redacted]

6.3.6. Local Tolerability Scale

At each specified study visit, the Investigator (or qualified evaluator) will assess the presence and overall degree of irritation at the application sites, according to the LTS (an example of the LTS is provided in Table 4). 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 participant throughout the study. If the subject is applying study treatment to "sensitive areas" (e.g., genitals, face, neck, and skin folds), a separate LTS will be used to assess the degree of irritation for these areas.

Table 4: Grading Scale for Local Tolerability

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

6.3.7. Continuous Holter Monitoring

The 12-lead Holter and ECG equipment will be supplied and supported by ERT. All ECG data will be collected using a Global Instrumentation (Manlius, NY, USA) M12R ECG continuous 12-lead digital recorder. The continuous 12-lead digital ECG data will be stored onto secure digital memory cards. ECGs to be used in the analyses will be selected by pre-determined time points as defined in the Schedule of Assessments (Table 1) and will be read centrally by ERT.

The following principles will be followed in ERT's core laboratory:

- ECG analysts are blinded to the subject number and visit;
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader;
- The primary analysis lead is lead II. If lead II is not analyzable, then primary lead of analysis will be changed to another lead for the entire subject data set.

The following is a brief description of ECG analysis methods utilized by ERT's core laboratory:

TQT Plus ECG Extraction Technique

- Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter recordings using the 'Thorough QT Plus method,' a computer-assisted and statistical process utilized by ERT. The method enables extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (e.g., the HR and QT changes from beat-to-beat in the range of < 10%). At each protocol-specified time point, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position).

Expert-Precision QT Analysis

- Expert-precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:
    - QT or QTc values exceeding or below certain thresholds (biologically unlikely);
    - RR values exceeding or below certain thresholds (biologically unlikely);
    - Rapid changes in QT, QTc or RR from beat to beat.

- Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" are performed using COMPAS software. All low confidence beats are reviewed manually and adjudicated using pass-fail criteria. The final QC assessment is performed by a cardiologist. The beats found acceptable by manual review are included in the analysis. The median QT, QTc, and RR values from each extracted replicate are calculated, and then the mean of all available medians from a nominal time point is used as the subject's reportable value at that time point.

- Categorical T-wave morphology analysis and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each time point. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) is electronically marked.
- For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed, i.e., changes not present at Baseline. For each category of T-wave morphology and U-waves, the category will be deemed as present if observed in all replicates at the time point. For Baseline, the category will be deemed as present if observed in all replicates from all time points that constitute Baseline. The T-wave morphology categories are described as follows:

Category	Description
Normal T-wave	Any positive T-wave not meeting any criterion below
Flat T-wave	T amplitude < 1 mm (either positive or negative) including flat isoelectric line
Notched T-wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T-wave
Biphasic	T-wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive/negative and negative/positive and polyphasic T-waves included)
Normal T-wave (-)	T amplitude that is negative, without biphasic T wave or notches
Notched T-wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T-wave
U-waves	Presence of abnormal U-waves

6.4. Treatment of Study Drug Overdose

For this study, accidental or intentional oral ingestion of study drug or excessive application onto the skin (e.g., using a greater quantity, or applying more frequently than instructed) 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;
- In the event of excessive topical application, instruct the subject to wash study drug off of the skin and monitor for application-site AEs;
- 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 in the eCRF;
- 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 time points indicated in the Schedule of Assessments (Table 1) and Section 7. The actual date and time of each blood sample collection will be recorded as well as the date and time of the last dose of study drug prior to sample collection. Collection, processing, storage, and shipping procedures are provided in the Laboratory Manual.

Concentrations of tapinarof and tapinarof sulfate (metabolite) 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 Days 1 and 29, the following primary PK parameters will be determined, if data permit: $AUC_{0-\tau}$, C_{max}, t_{max}, and $t_{½}$.

Limited PK sampling will be performed on Day 15.

Once the plasma has been analyzed for tapinarof and tapinarof sulfate (metabolite), any remaining plasma may be analyzed for other metabolites.

7. TIMING OF PROCEDURES AND ASSESSMENTS

This section lists the procedures and assessments to be performed at scheduled time points 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 time point(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 (Up to 34 Days Prior to Day 1)

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

- Serum pregnancy test (WOCBP only)
- ECG recording
- Medical history recording
- Demography recording
- Brief physical exam (including weight, height, and body mass index [BMI])
- Vital signs measurements
- PGA score
- %BSA affected calculation (performed before PASI); subject's scalp, palms, and soles should be excluded from the %BSA calculations used to determine eligibility
- PASI
- Blood and urine sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- AE recording (from the time the ICF is signed)
- Concomitant medication recording (from the time ICF is signed)

To determine subject eligibility at Screening, a single repeat of tests or procedures may be allowed at the discretion of the Investigator in consultation with the Medical Monitor.

7.2. Visit 2; Day -1

On Day -1, subjects will be reassessed to confirm continued eligibility to participate in the study.

The following additional procedures and assessments will be performed at Visit 2:

- AE recording
- Concomitant medication recording
- Continuous Holter Monitoring for 13 hours

7.3. Visit 3; Day 1 (Baseline)

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

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

- Urine pregnancy test (WOCBP only)
- Vital signs measurements
- PGA score
- %BSA affected calculation (performed before PASI); subject's scalp, palms, and soles should be excluded from the %BSA calculations
- PASI
- Continuous Holter Monitoring for 13 hours (1 hour prior to dosing and 12 hours post-dose)
- Blood and urine sample collection for clinical laboratory tests
- Blood sample collection for PK analysis and [redacted]
- AE recording
- Concomitant medication recording
- Paper diary dispensed (subjects will be instructed in how and when to complete diary)
- LTS scoring
- Dispense study drug
- Instruction on how to administer study drug
- Study drug administration under supervision

7.4. Visit 4; Day 2

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

- Continuous Holter Monitoring for 1 hour (1 hour prior to PK sample collection)
- Blood sample collection for PK analysis and [redacted]
- AE recording
- Concomitant medication recording
- Instruction on how to administer study drug
- Study drug administration under supervision

7.5. Day 8 (Phone Call)

The following procedures and assessments will be performed by phone call on Day 8:

- AE recording
- Concomitant medication recording
- Instruction on how to administer study drug

7.6. Visit 5; Day 15

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

- Collect and dispense study drug
- Collect and dispense subject diary
- Blood sample collection for PK analysis
- AE recording
- Concomitant medication recording
- LTS scoring
- Instruction on how to administer study drug
- Study drug administration under supervision

7.7. Day 22 (Phone Call)

The following procedures and assessments will be performed by phone call on Day 22:

- AE recording
- Concomitant medication recording
- Instruction on how to administer study drug

7.8. Visit 6; Day 29

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

- PGA score
- %BSA affected calculation (performed before PASI); subject's scalp, palms, and soles should be excluded from the %BSA calculations
- PASI
- Continuous Holter Monitoring for 13 hours (1 hour prior to dosing and 12 hours post-dose)
- Collect subject diary
- Blood and urine sample collection for clinical laboratory tests
- Blood sample collection for PK analysis and [redacted]
- AE recording
- Concomitant medication recording
- LTS scoring
- Study drug administration under supervision
- Collect study drug

7.9. Visit 7; Day 30

The following procedures and assessments will be performed at Visit 7:

- Continuous Holter Monitoring for 1 hour (1 hour prior to PK sample collection)
- Blood sample collection for PK analysis and [redacted]
- AE recording
- Concomitant medication recording

7.10. Visit 8; Follow-Up (7-10 days After Day 29)/Early Termination

Follow-up/Early Termination assessments are as follows:

- ECG recording
- Urine pregnancy test (WOCBP only)
- Brief physical examination
- Vital signs measurements
- Blood and urine sample collection for clinical laboratory tests
- AE recording
- Concomitant medication recording

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events, Treatment-Emergent 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, TEAE, SAE, or adverse event of special interest (AESI). At each visit/contact, subjects should be questioned in a general way so as not to introduce bias in detecting AEs, TEAEs, and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE and TEAE occurrence.

Investigators are not obligated to actively seek AEs, TEAEs, 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.

8.1.1. Definition of Adverse Events

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

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 study drug.

Events meeting the definition of an AE **include**:

- Any abnormal laboratory test results (e.g., 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., atopic dermatitis) 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. 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.
- Evaluation of local tolerability at the site of topical application (e.g., burning/stinging, pruritus, and erythema).

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 Treatment-Emergent Adverse Event

A TEAE is an AE that occurs following the first application of study drug.

8.1.3. Definition of Serious Adverse Event

If an event is not an AE per Section 8.1.1 or a TEAE per Section 8.1.2, 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 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.

8.1.4. Adverse Events of Special Interest

In prior clinical studies, the following AEs 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 discontinued, based upon Investigator's judgment, and the subject may be discontinued from the study.

- Contact dermatitis: the study site should collect location, duration, size, associated symptoms (itching, burning, pain), severity (mild, moderate, or severe), and photograph the affected site (if possible). If 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 for an unscheduled visit, if possible.
- Folliculitis: the study site should collect the location, duration, size, associated symptoms (itching, burning, pain), severity (mild, moderate, or severe), indicate whether pustular, and photograph the affected site (if possible).
- Headache: site should collect duration, severity (mild, moderate, or severe), onset, and location.

For each AESI, a narrative may be written and included in 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 Common Terminology Criteria for Adverse Events (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 AE

Abbreviation: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events

[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.

AE severity should be recorded in the appropriate section of the eCRF 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 study drug at the discretion of the Investigator. Subjects who choose to withdraw from study due to a Grade 1 or 2 AE should have early termination assessments completed as outlined in Section 7.10.

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 3AE has not been caused by study drug, then dosing may continue after discussion with the Medical Monitor.
- Subjects who develop a Grade 3 AE that the Investigator considers related to study drug should have the study drug discontinued. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of study drug should be followed weekly until resolution or stability of the AE and encouraged to have early termination assessments completed as outlined in Section 7.10.

8.2.1.2.3. Grade 4 Adverse Event

Subjects who develop a Grade 4 AE should have study drug permanently discontinued.

Subjects experiencing Grade 4 AEs requiring permanent discontinuation of study drug should be followed weekly until resolution or stability of the AE and encouraged to have early termination assessments completed as outlined in Section 7.10.

8.2.1.2.4. 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 Investigator is to make the causality assessment. Causality assessment is not to be delegated; however, if delegation is unavoidable due to Investigator inaccessibility, this must be recorded as a protocol deviation. The reasonable possibility of the relationship of an AE to study drug is to be assessed with careful medical consideration at the time of evaluation of an AE. The following definitions are to be used for the relationship of the AE to study drug:

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

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

All AEs, whether related to study drug or not, must be fully and completely documented on the AE page of the eCRF 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 eCRF as such.

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

8.3.1. Adverse Event and Serious Adverse Event Reporting

All AEs will be collected from the time of signed ICF 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 recorded 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 eCRF and reported to the Sponsor within 24 hours via email or phone (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 eCRF; these pages will be submitted with the SAE Report Form.

Follow-up information received on SAEs should be emailed or faxed to the Sponsor within one business day of receipt. This information should be included on a follow-up SAE form and placed 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 an 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 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 data collection 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.

8.6. Safety Oversight

No independent Data Monitoring Committee will be used for this study; however, the Sponsor (including the Medical Monitor) will monitor safety on a periodic basis throughout the study.

9. DATA MANAGEMENT

For this study, subject data will be entered into the Sponsor defined eCRFs, 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.

AEs 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 eCRF-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 and PK of tapinarof cream, 1% in adults with plaque psoriasis.

10.1. General Considerations

All study data will be summarized 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 safety and PK data will be listed by subject.

10.2. Determination of Sample Size

This study will be conducted to evaluate the safety and PK of tapinarof cream, 1% in adult subjects with extensive plaque psoriasis. 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 Sets

10.3.1. Safety Analysis Set

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

10.3.2. PK Analysis Set

All subjects who have at least 1 application of study drug and have at least 1 evaluable PK assay result will be included in the PK analysis set. A value that is below the limit of quantification is considered evaluable.

10.3.3. QT/QTc Analysis Set

The QT/QTc analysis set will include all subjects in the safety analysis set with measurements at Baseline as well as on-treatment with at least 1 post-dose time point with a valid ΔQTcF value.

10.3.4. PK/QTc Analysis Set

The PK/QTc analysis set will include all subjects who are in both the QT/QTc and PK analysis sets with at least 1 pair of post-dose PK and QTcF data from the same time point.

10.4. Planned Analyses

All safety and PK measures over the course of the study will be presented. Details of planned analyses will be described in the statistical analysis plan (SAP) which will be finalized prior to database lock.

10.4.1. Disposition and Demographics

Demographic and Baseline characteristics as well as medical history will be summarized using the safety analysis set, including frequency and percentages for categorical variables and mean, SD, median, minimum, and maximum for continuous variables.

10.4.2. Safety Analyses

The safety analysis set will be used in the analysis of safety and [redacted] data. Data will be listed by subject and summarized. No formal statistical comparisons will be made for safety data.

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

Selected [redacted] data will be analyzed using descriptive summary statistics and will be presented by study visit/time point, including the number of non-missing observations, mean and SD, median, upper and lower quartiles, minimum and maximum for values and changes from Baseline. Categorical safety data will be analyzed using frequency tables and, if applicable, shift tables.

Vital signs will be listed by subject and summarized by visit.

Scores from the LTS will be listed by subject and summarized by visit.

10.4.3. Cardiodynamic Assessments

10.4.3.1. Baseline

Time-matched Baseline will be derived from measurements on Day -1 and the morning (pre-dose) of Day 1 for all ECG parameters.

10.4.3.2. By-Time Point Analysis

The QT/QTc analysis set will be used for the by-time point analysis of cardiodynamic ECG parameters. The analysis for QTcF will be based on a linear mixed-effects model with ΔQTcF as the dependent variable, time (i.e., time point: categorical), treatment (tapinarof), and time-by-treatment interaction as fixed effects, and Baseline QTcF as a covariate. An unstructured covariance matrix will be specified for the repeated measures at post-dose time points within subjects. If the model with an unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. From this analysis, the least squares (LS) mean and 2-sided 90% confidence interval (CI) will be calculated at each post-dose time point, separately.

For HR, PR, and QRS intervals, the analysis will be based on the ΔHR, ΔPR, and ΔQRS, respectively. The same (by-time point analysis) model will be used as described for QTcF. The

LS mean, standard error, and 2-sided 90% CI from the statistical modeling for change from Baseline values will be listed in the tables and graphically displayed.

10.4.3.3. Categorical Analysis

10.4.3.4. Concentration-QTc Analysis (Potential Exploratory Analysis)

The PK/QTc analysis set will be used in the potential exploratory concentration-QTc analysis. A potential exploratory concentration-QTc analysis will be performed if a sufficient number of PK samples are above lower limit of quantification to provide a PK profile in most subjects. In this analysis, the relationship between tapinarof plasma concentrations and ΔQTcF will be investigated using a linear mixed-effects modeling approach. The following 3 linear models will be considered:

- Model 1: a linear model with an intercept
- Model 2: a linear model with mean intercept fixed to 0 (with variability)
- Model 3: a linear model with no intercept

Time-matched tapinarof plasma concentration will be included in the model as a covariate, and subject as a random effect for both intercept and slope, when applicable. The model that fits the data best (i.e., has the smallest Akaike information criterion and the model-predicted CIs similar to the observed CIs) will be used for predicting population average ΔQTcF and its corresponding 2-sided 90% CI at the geometric mean peak tapinarof plasma concentration.

The plot of the observed median-quantile tapinarof plasma concentrations and associated mean ΔQTcF (90% CI), together with the mean (90%CI) predicted ΔQTcF (as described by Tornøe, 2011), will be used to evaluate the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration-QTc relationship. Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis) and the justification for the choice of pharmacodynamic model (linear versus nonlinear), as follows.

Investigation of Hysteresis

Hysteresis will be assessed by graphical methods based on the LS mean of ΔQTcF for each post-dose time point and the mean tapinarof plasma concentrations at the same time points. In addition, hysteresis plots will be given for mean ΔQTcF and the mean concentrations. If a QT effect (ΔQTcF) > 10 msec cannot be excluded in the by-time point analysis and if a delay between peak plasma levels and peak QT effect (ΔQTcF) in the plot (ΔQTcF versus tapinarof plasma concentration) of more than 1 hour is present, other concentration-QTc models such as a model with an effect compartment may be explored. With the provision stated above, hysteresis will be assumed if the curve of hysteresis plot shows a counterclockwise loop.

Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal Q-Q plots for the standardized residuals and the random effects, and plots of standardized residuals versus concentration and versus fitted values will be produced. The scatter plot of standardized residuals versus concentration by LOESS fitting (i.e., locally weighted scatter plot smoothing as described by [Cleveland, 1979]) will also be produced with an optimal smoothing parameter selected by the Akaike information criterion with a correction [Hurvich, 1998]. In addition, a model with the original term and a quadratic term in concentration will be fitted and the quadratic term will be tested on the 2 sided 5% level. If there is an indication that a linear model is inappropriate, additional models will be fitted, in particular an E_{max} model. The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

10.4.4. Pharmacokinetic Analysis

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 ($AUC_{0-\tau}$, C_{max}, t_{max}, and $t_{½}$) will be derived using non-compartmental methods based on the actual sampling times recorded in the study.

10.4.5. Efficacy Analyses

All efficacy analyses will be performed based on the safety analysis set.

PGA Assessments

The PGA will be summarized for the actual, change from Baseline, and percent change from Baseline. The mean and 95% CI for change and percentage change from Baseline will be presented along with p-values based on a one sample t-test.

%BSA Assessments

The %BSA will be summarized for the actual, change from Baseline, and percent change from Baseline. The mean and 95% CI for change and percentage change from Baseline will be presented along with p-values based on a one sample t-test.

PASI Assessments

The PASI will be summarized for the actual, change from Baseline, and percent change from Baseline. The mean and 95% CI for change and percentage change from Baseline will be presented along with p-values based on a one sample t-test.

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 (ICH) 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 US 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 US 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 of reportable interests during the study and for one 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 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's brochure, this protocol, eCRFs, 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 two categories: 1) Investigator's study file, and 2) subject clinical source documents.

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

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Participation in trial (including trial number);
- Trial discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol-specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end dates (including dose regimen) of study drug (preferably drug dispensing and return should be documented as well);

- Record of all AEs 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 motivated);
- 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., US, 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.

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period up to 10 years for purposes of this study.

11.1.6. Electronic Case Report Forms

For each subject enrolled, an eCRF must be completed and signed by the Investigator or sub-Investigator (as appropriate). 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 eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

11.1.7. Drug Accountability

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

At study initiation, the monitor will evaluate the site's procedure for study drug 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 study drug 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 study drug supplies.

All study 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 GmbH, 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 GmbH 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 GmbH 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 GmbH 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 before enrollment of subjects begins. 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 eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs 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 eCRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.3.2. Access to Information for Auditing or Inspections

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

Authorized representatives of Dermavant Sciences GmbH, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Dermavant Sciences GmbH 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 ICH, and any applicable regulatory requirements. The Investigator should contact Dermavant Sciences GmbH immediately if contacted by a regulatory agency about an inspection.

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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APPENDICES

APPENDIX 1. PHYSICIAN GLOBAL ASSESSMENT

Each assessment should be made as a visual 'average' of the severity of all treated areas at the time of the assessment.

Scoring should not be influenced by extent of plaques, participant symptoms, or impact on participant's quality of life.

Score/Grade		Description
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable erythema; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all plaques

Langley RGB, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat. 2015;26(1):23-31.

APPENDIX 2. CALCULATION OF PERCENT BODY SURFACE AREA AFFECTED AND PSORIASIS AREA AND SEVERITY INDEX

The %BSA affected and PASI will be calculated using the following regional body areas:

- Head and neck
- Trunk, includes internal axillae and groin
- Upper extremities, includes arms, external axillae, and hands
- Lower extremities, includes legs, buttocks, and feet

Note: At Screening, Baseline and for all efficacy assessments, plaques on scalp, palms, fingernails, toenails, and soles will not be included in the calculation of %BSA affected as these areas will not be included in the efficacy analyses.

Complete the %BSA assessment before the PASI.

Calculation of %BSA Affected:

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 plaques are "pushed together." Each region can have up to 100% involvement.

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

Estimates of the % involvement in each body region will be multiplied by the fraction of total body area to obtain the total %BSA involved by region and overall.

Body Region	% Involvement for Each Region (0-100%)	Multiplier	Regional %BSA Involvement
Head and neck		x 0.1	=
Arms / upper extremities		x 0.2	=
Trunk		x 0.3	=
Legs / lower extremities		x 0.4	=
TOTAL Involved %BSA – sum of the 4 regional values (0-100%)			=

Note: Shaded cells are either fixed values or will be calculated in the eCRF. Multiplier is a fixed number representing fraction of total body area.

Abbreviations: %BSA = percent body surface area.

Calculation of PASI:

After the %BSA involvement for each region is determined, convert each percentage to individual area scores (0 to 6; PASI Item 5) based on the following categories:

	Percentage of skin covered with psoriasis for <u>each of the 4</u> areas						
Affected	<1%	1 - < 10%	10 - < 30%	30 - < 50%	50 - < 70%	70 - < 90%	≥ 90%
Score	0	1	2	3	4	5	5

Using the table below, for Items 1, 2, and 3, generate an average score for erythema, thickness, and scale for each of the 4 body areas using the following 5-point scale:

0 = None; 1 = Slight; 2 = Mild; 3 = Moderate; 4 = Severe

			Body Area			
Item	**Assessment**		**Head/Neck**	**Upper extremities (arms)**	**Trunk (to groin)**	**Lower extremities (leg to top of buttocks)**
1	Erythema (redness)	(0-4)				
2	Induration (thickness)	(0-4)				
3	Scale (desquamation)	(0-4)				
4	**Sum of Items 1, 2, and 3**	**(0-12)**				
5	Area Score	(0-6)				
	Area Multiplier		0.1	0.2	0.3	0.4
6	Score of (Item 4) x (Item 5) x (Area Multiplier)		Item 4x Item 5x 0.1	Item 4x Item 5x 0.2	Item 4x Item 5x 0.3	Item 4x Item 5x 0.4
7	Sum of Item 6 for each column is the total **PASI** score	(0-72)				

Note: Items in shaded rows will be calculated in the eCRF.

Abbreviations: eCRF = electronic case report form; PASI = Psoriasis Area and Severity Index