CLINICAL STUDY PROTOCOL

Title	A Phase 3 Efficacy and Safety Study of Tapinarof for the Treatment of Plaque Psoriasis in Adults	
Sponsor	Dermavant Sciences GmbH Viaduktstrasse 8 4051 Basel, Switzerland	
Compound Name	Tapinarof (DMVT-505)	
Protocol Number	DMVT-505-3001	
Indication	Plaque Psoriasis	
Development Phase	3	
IND #	104601	
Version/ Effective Date:	Original Protocol Amendment 1 (Version 1.1) Amendment 2 (Version 2.0)	25-JANUARY-2019 08-MAY-2019 08-AUGUST-2019

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SPONSOR SIGNATURE PAGE

Study Title: A Phase 3 Efficacy and Safety Study of Tapinarof for the Treatment of Plaque Psoriasis in Adults

Protocol Number: DMVT-505-3001

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

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/Serious Adverse Event (SAE) Contact Information

Study Sponsor

This study is sponsored by Dermavant Sciences GmbH.

Dermavant Sciences GmbH Registered Address

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USA

INVESTIGATOR STATEMENT

Study Title: A Phase 3 Efficacy and Safety Study of Tapinarof for the Treatment of Plaque Psoriasis in Adults

- 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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Description
AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
AhR	aryl hydrocarbon receptor
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Anti-HBc	anti-hepatitis B core antigen
AST	aspartate aminotransferase
BLQ	below the limit of quantification
BMI	body mass index
BSA	body surface area
%BSA	percent of total body surface area
BUN	blood urea nitrogen
BWTP	Beijing Wenfeng Tianji Pharmaceuticals
CBP	child-bearing potential
CFR	Code of Federal Regulations
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
D/d	day(s)
Dermavant	Dermavant Sciences GmbH
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FCS	Fully Conditional Specification
F-U	follow-up
GSK	GlaxoSmithKline
HADS	Hospital Anxiety and Depression Scale
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation

Term	Description
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent-to-Treat
LTS	Local Tolerability Scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputations
MSDS	Material Safety Data Sheet
NA	not applicable
Nrf2	nuclear factor erythroid 2-related factor 2
NRS	Numeric Rating Scale
PASI	Psoriasis Area Severity Index
PC	phone contact
PK	Pharmacokinetic(s)
PND	postnatal day
RBC	red blood cell(s)
PP	Per-Protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SF-36	Short Form-36
TAMA	therapeutic AhR-modulating agent
TF	Treatment Failure
ULN	upper limit of normal
US; USA	United States (of America)
UV	ultraviolet
V	visit
WBC	white blood cell(s)
WOCBP	women of child-bearing potential
WHO-DDE	World Health Organization Drug Dictionary Enhanced

SYNOPSIS

Name of Sponsor/Company:

Dermavant Sciences GmbH

Name of Investigational Product:

DMVT-505 (tapinarof cream, 1%)

Name of Active Ingredient:

Tapinarof

Protocol Number: DMVT-505-3001	**Phase**: 3	**Country:** United States (US) and Canada

Title of Study:

A Phase 3 Efficacy and Safety Study of Tapinarof for the Treatment of Plaque Psoriasis in Adults

Study Center(s):

Approximately 50 to 60 sites in the United States (US) and Canada

Objectives:

Primary:

- To evaluate the efficacy of tapinarof cream, 1% compared with vehicle control in adults with plaque psoriasis

Secondary:

- To further characterize the efficacy of tapinarof cream, 1% compared with vehicle control over time
- To describe the effect of tapinarof cream, 1% on psoriasis symptom severity and the associated impact on daily activities and attitudes in adults with plaque psoriasis
- To evaluate the safety and tolerability of tapinarof cream, 1% in adults with plaque psoriasis
- To characterize the pharmacokinetics (PK) of tapinarof in adults with plaque psoriasis

Methodology:

This is a double-blind, randomized, vehicle-controlled, Phase 3, multicenter study to evaluate the efficacy and safety of topical tapinarof cream, 1% compared with vehicle-control cream in adults with plaque psoriasis.

Following a 34-day screening period, eligible subjects will be randomized at a 2:1 ratio to receive once daily treatment with tapinarof cream, 1% or vehicle cream. Subjects will return to the clinic at Weeks 2, 4, 8, and 12 for efficacy and safety assessments. Additionally, subjects will be contacted by phone at Weeks 6 and 10 to assess adverse events (AEs) and concomitant medications, to review study drug administration instructions, and to confirm subject's continued participation in this study.

Study drug will be dispensed 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 lesions and lesions/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 fingernails, toenails, palms, soles, and scalp lesions with study drug; however, efficacy analyses will not include assessment of improvement of psoriasis in these areas.) Subjects will be instructed to maintain the approximate dosing time chosen at the beginning of the study for their full study participation. At the phone contacts at Weeks 6, and 10, subjects should be reminded to complete their daily diary and bring it with them to the next clinic visit.

Study drug application instructions will be reviewed at all post-randomization clinic visits and during any planned study phone calls. On clinic visit days, subjects will be instructed/reminded 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 efficacy and safety assessments have been completed. The time of the dose application and assessments will depend on the time of the clinic visit. Therefore, the timing of the clinic visit may lead to a change in the subject's chosen dosing time,

At the end of the 12 weeks of treatment in this study, subjects will have the option to enroll in a separate open-label long-term safety and efficacy study for an additional 40 weeks of treatment. Subjects who choose not to participate in the open-label long-term study, who fail to qualify for participation in the open-label long-term study, or who qualify to participate in the open-label long-term study but ultimately elect not to enroll in that study, will complete a Follow-up Visit approximately 4 weeks (Week 16 visit) after the end of treatment in this study. Subjects who withdraw from the study before Week 12 will complete an Early Termination Visit.

Number of Subjects:

Approximately 500 subjects ages 18 to 75 years will be enrolled in the study as follows:

- Approximately 500 subjects will be randomized at a 2:1 ratio to receive tapinarof cream, 1% (approximately 333 subjects) or vehicle cream (approximately 167 subjects)

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 clinical diagnosis of chronic plaque psoriasis and stable disease for at least 6 months prior to the study.
2. Body surface area (BSA) involvement ≥ 3% and ≤ 20% (the subject's scalp, palms, fingernails, toenails, and soles should be excluded from the percent of total BSA (%BSA) calculations).
3. A Physician's Global Assessment (PGA) score of 2 (mild), 3 (moderate) or 4 (severe) at screening and baseline (pre-randomization). Subjects with mild and severe psoriasis will be limited to approximately 10% each of the total randomized population; the majority of the enrolled subjects (approximately 80%) will have a PGA of 3, signifying moderate disease.
4. Females of child-bearing potential 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 partner with vasectomy, OR
   - Male condom AND partner use of 1 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-child-bearing 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 IU/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. Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Day 1).

5. 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 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 lesions.
3. Concurrent conditions or history of other diseases:
   a. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome) or medical history of positive human immunodeficiency virus (HIV) antibody at Screening.
   b. Chronic or acute systemic 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, 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) ≥ 1.5x the upper limit of normal (ULN).
5. Screening total bilirubin > 1.5 x ULN; total bilirubin > ULN and ≤ 1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%.
6. Corrected QT (QTcF) interval > 475 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. Subjects with a history of HCV infection who were medically cured and have an undetectable viral load are eligible to enroll. Subjects with a history of stable non-alcoholic fatty liver disease without evidence of active inflammation (elevated ALT/AST ≥ 1.5x ULN) or cirrhosis are eligible to enroll.
8. Ultraviolet (UV) light therapy or prolonged exposure to natural or artificial sources of UV radiation (eg, 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 (double-blind and open-label phases) 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.

   - Minimum of 5 half-lives for biologic agents: eg, 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 D3 and analogs (> 5000 IU/day), retinoids (eg, acitretin, isotretinoin), psolarens, corticosteroids, or adrenocorticotropic hormone analogs
   - 2 weeks for immunizations with a live viral component; drugs known to possibly worsen psoriasis, such as beta-blockers (eg, propranolol), lithium, iodides, angiotensin-converting enzyme inhibitors, and indomethacin, unless on a stable dose for > 12 weeks

- With the exception of non-medicated emollients, 2 weeks for topical treatments including corticosteroids, antihistamines, immunomodulators, anthralin (dithranol), Vitamin D derivatives (eg, calcipotriene, calcipotriol), retinoids (Note: 4 weeks for 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 drugs, 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 product 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 study drug (whichever is longer).
15. Current or a history of cancer within 5 years except for aqequately treated skin basal cell carcinoma, squamous cell carcinoma or carcinoma in situ of the cervix (surgical excision or electrodessication and curettage).
16. Subjects with active systemic infection that required oral, intramuscular, or intravenous administration of antibiotics, antifungal or antiviral agents within 4 weeks of Baseline/Day 1.
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 cardiovascular (CV) system abnormalities or laboratory abnormality that will affect the health of the subject or interfere with interpretation of the results.

Investigational Product, Dosage and Mode of Administration:

Tapinarof cream, 1% is a white to off-white cream containing 1% (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.

Reference Therapy, Dosage and Mode of Administration:

Vehicle cream is a white to off-white cream, 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 3 study and who fail to qualify for participation in the open-label long-term study, or who qualify to participate in the open-label long-term study but ultimately elect not to enroll in that study is approximately 20 weeks in total (including approximately 34 days screening, 12 weeks of treatment, and a 4-week follow-up period).

- Subjects randomized to tapinarof cream, 1% will receive tapinarof for 12 weeks.
- Subjects randomized to vehicle cream will receive treatment with vehicle cream for 12 weeks.

Criteria for Evaluation:

Efficacy Assessments: Investigator assessment of PGA, %BSA affected, and Psoriasis Area Severity Index (PASI).

Functional Outcomes and Quality of Life Assessments: Dermatology Life Quality Index (DLQI), Psoriasis Symptom Diary (PSD), Short Form-36 (SF-36), and Peak Pruritus-Numeric Rating Scale (NRS).

Safety Assessments: AEs, vital signs, physical examinations, clinical laboratory tests, and Local Tolerability Scale (LTS).

Pharmacokinetic Assessments: Plasma concentration of tapinarof.

Study Endpoints:

Primary:

- Proportion of subjects who achieve a PGA score of clear (0) or almost clear (1) with a minimum 2-grade improvement from Baseline at Week 12

Secondary:

- Proportion of subjects with ≥ 75% improvement in PASI from Baseline at Week 12
- Proportion of subjects with a PGA score of 0 or 1 at Week 12
- Mean change in percent of total body surface area (%BSA) affected from Baseline to Week 12
- Proportion of subjects with ≥ 90% improvement in PASI score from Baseline to Week 12

Exploratory Endpoints

- Time to achieve a PGA score of 0 or 1 with a minimum 2 grade improvement from Baseline
- Change in Peak Pruritus-Numeric Rating Scale (Peak Pruritus-NRS) from Baseline at Weeks 2, 4, 8, and 12
- Proportion of subjects with a PGA score of 0 or 1 at Weeks 2, 4, 8, and 12
- Proportion of subjects who achieve a PGA score of 0 or 1 with a minimum 2-grade improvement from Baseline at Weeks 2, 4, and 8
- Mean absolute and percent change in PASI score from Baseline to Weeks 2, 4, 8, and 12
- Proportion of subjects with ≥ 50% improvement in PASI score from Baseline to Weeks 2, 4, 8, and 12
- Proportion of subjects with ≥ 75% improvement in PASI score from Baseline to weeks 2, 4, and 8
- Proportion of subjects with ≥ 90% improvement in PASI score from Baseline to weeks 2, 4, and 8
- Mean change in %BSA affected from Baseline to Weeks 2, 4, and 8
- Change over time in psoriasis impact on daily activities, as measured by the DLQI total and individual dimension scores
- Change over time in psoriasis symptoms, as measured by the PSD
- Change over time in physical component score and mental component score, as measured by the SF-36 questionnaire

Safety:

- Incidence, frequency, and duration of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Clinically significant change from Baseline in laboratory values
- Clinically significant change from Baseline in vital signs
- Mean LTS scores by visit

Pharmacokinetic:

- Plasma concentration of tapinarof at Weeks 4 and 12

Statistical Methods:

Determination of Sample Size: It is assumed that the proportion of subjects who achieve PGA score of clear (0) or almost clear (1) with a minimum 2-grade improvement from Baseline at Week 12 will be 40% for subjects receiving tapinarof cream, 1% compared with 15% for subjects receiving vehicle control cream. With 500 subjects randomized in a 2:1 ratio (approximately 333 subjects receiving tapinarof cream, 1% and approximately 167 subjects receiving vehicle cream), there will be > 99% power for a statistical significance (2-sided $p < 0.05$). If the tapinarof response rate is 35%, and the vehicle response rate is 20%, the power will be > 94%. The power is calculated from a Fisher Exact sample size calculation which is conservative. It is assumed that up to 25% of the subjects will be lost to follow-up by 12 weeks. These subjects will be included in the primary analysis using the multiple imputation method.

Efficacy Analyses: All efficacy analyses will be based on the Intent-to-Treat (ITT) population and will be repeated for the Per Protocol (PP) population only for the primary and secondary efficacy endpoints as supportive analysis. The primary efficacy endpoint will be analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by PGA score at Baseline (PGA scores of 2, 3, or 4). The same method used for the primary analyses will be used to analyze all dichotomized secondary endpoints. The secondary endpoints will be tested sequentially in order, and testing will stop if non-significance (2-sided $p \geq 0.05$) is observed. Other efficacy endpoints will be analyzed

using CMH test for proportions, and analysis of covariance (ANCOVA) model for continuous variables. CMH tests will be stratified by baseline PGA score, and ANCOVA models will include PGA score as a covariate. Open-label data will be summarized using summary statistics without testing.

Safety Analyses: The Safety Population will be used in the analysis of safety data. Data will be listed by subject and treatment and summarized by treatment. No formal statistical comparisons will be made for safety data. The number and proportion of subjects with TEAEs will be summarized by treatment, system organ class, and preferred term for all TEAEs, all TEAEs considered by the Investigator to be related to study drug, all SAEs, and all TEAEs leading to study drug discontinuation. All TEAE summaries will include information for AEs that occurred after administration of the first dose of study drug until completion of the final study visit. Data listings will be provided for subjects who discontinued the study due to an AE and for subjects with an SAE. Selected laboratory data will be analyzed using descriptive summary statistics and will be presented by study visit and treatment group, including the number of non-missing observations, mean and standard deviation, 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.

Functional Outcomes and Quality of Life Analysis: Change from Baseline in the subject reported DLQI, PSD, SF-36, and Peak Pruritus-NRS scores will be analyzed using an ANCOVA model with treatment as a main effect, and baseline as a covariate.

Pharmacokinetic Analyses: Plasma concentration data will be listed and summarized by study visit.

SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

Procedures and Assessment	Screening	Baseline	Double-Blind Vehicle-Controlled Treatment Phase						FU[a]	ET[b]
	V 1	V 2	V 3	V 4	P/C[c]	V 5	P/C[c]	V 6	V 7	NA
	Day -34 to Day -1	Day 1	Week 2 D 15 (±2 d)	Week 4 D 29 (±2 d)	Week 6 D 43 (±2 d)	Week 8 D 57 (±2 d)	Week 10 D 71 (±2 d)	Week 12 D 85 (±2 d)	Week 16 D 113 (±4 d)	NA
Informed consent	X									
Demographics	X									
Medical history[d]	X	X[e]								
Assess/confirm eligibility	X	X								
Serum/urine pregnancy test (WOCBP)[f]	X	X[g]		X		X		X	X	X
Brief physical examination	X[h]	X		X		X		X	X	X
Vital signs[i]	X	X	X	X		X		X	X	X
ECG	X									
Blood sample for clinical laboratory tests[j]	X			X				X	X	X
Urinalysis	X								X	X
HADS	X									
Subject randomization		X								
Photograph representative area of disease area[k]		X		X		X		X		
PK blood sample collection[l]				X				X		
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Investigator Assessed:										
PGA score[m]	X	X	X	X		X		X	X	X
%BSA affected[n]	X	X[o]	X	X		X		X	X	X
PASI		X	X	X		X		X	X	X
LTS[p]			X	X		X		X	X	X

Procedures and Assessment	Screening	Baseline	Double-Blind Vehicle-Controlled Treatment Phase						FU[a]	ET[b]
	V 1	V 2	V 3	V 4	P/C[c]	V 5	P/C[c]	V 6	V 7	NA
	Day -34 to Day -1	Day 1	Week 2 D 15 (±2 d)	Week 4 D 29 (±2 d)	Week 6 D 43 (±2 d)	Week 8 D 57 (±2 d)	Week 10 D 71 (±2 d)	Week 12 D 85 (±2 d)	Week 16 D 113 (±4 d)	NA
Completed by Subject:										
DLQI		X		X				X	X	X
SF-36		X		X				X	X	X
PSD		X	X	X		X		X	X	X
LTS			X	X		X		X	X	X
Peak Pruritus NRS[q]		X	X	X	X	X	X	X	X	X
Dispense/collect diary[r]		D	C/D	C/D		C/D		C		C
Review subject diaries for treatment compliance			X	X		X		X		X
Dispense (D)/Collect (C) study drug		D	C/D	C/D		C/D		C		C
Review instructions for study drug application[s]		X	X	X	X	X	X			
Study drug application under supervision[t]		X	X	X		X				
Enrollment (optional) in long-term study								X		

AE = adverse event (s); BMI = body mass index; BSA = body surface area; %BSA = percent of total BSA; D/d = day(s); DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; eCRF = electronic Case Report Form; ET = early termination; FU = follow-up; HADS = Hospital Anxiety and Depression Scale; LTS = Local Tolerability Scale; NA = not applicable; NRS = Numeric Rating Scale; PASI = Psoriasis Area and Severity Index; P/C = phone contact; PGA = Physician Global Assessment; PK = Pharrmacokinetics; PSD = Psoriasis Symptom Diary; SF-36 = 36−Item Short Form Survey; V = Visit; WOCBP = women of child-bearing potential.

[a] The Follow-Up Visit will be performed for any subject who: (a) prematurely withdraws from the study, (b) fails to qualify for participation in the open-label long-term study, or (c) qualifies to participate in the open-label long-term study but elects not to enroll in that study.

[b] Subjects who withdraw from the study before 12 weeks (Visit 6) will complete an Early Termination Visit.

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

[d] Medical history will include year of plaque psoriasis diagnosis, CV medical history and risk factors (including height, weight, smoking history, medical conditions, and family history of premature CV disease) and family history of liver disease.

[e] Record any changes to medical history.

[f] Serum pregnancy test to be performed at the Screening visit only and urine pregnancy test to be performed at subsequent clinic visits.

[g] Urine pregnancy test to be performed before randomization.

[h] Physical examination will include height, weight, and BMI at the Screening visit; a brief physical examination will be performed at other visits (Section 6.3.2).

[i] Vital signs will include blood pressure, pulse, and body temperature.

[j] Including serum chemistry and liver chemistry tests, and hematology.

[k] Photography will be performed in a subgroup of subjects at selected (8 to 10) study centers; this is not required of subjects for participation in the study. Informed consent/assent and photographic release will be required.

[l] Blood sample collection for PK will be performed at a subset of sites in a subset of subjects. Sample to be collected prior to study drug application in clinic.

[m] The PGA assessment should be performed before the %BSA and PASI assessments.

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

[o] %BSA affected calculation should be completed before the PASI assessment. Note that lesions on scalp, palms, fingernails, toenails, and soles will not be included in the calculation of %BSA affected as these areas will be excluded from the efficacy analyses.

[p] The LTS assessment also consists of a subject-assessed component (Section 6.3.5).

[q] Subjects should perform the Peak Pruritus NRS assessment daily (Section 6.2.2.4) and record the results in their diary. On study visit days, subjects will not complete the diary at home; application time and NRS will be recorded in the clinic.

[r] Subjects will be instructed on when and how to complete diaries.

[s] Subjects will be instructed to apply study drug once daily at the approximate same time each day, based on subject preference (Section 5.1.5).

[t] At clinic visits, study drug will be applied after safety and efficacy assessments have been conducted (see Section 5.1.5 for additional details on timing of application of study drug during clinic visits).

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 and/or school 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 cardiovascular (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 GSK2894512, 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 atopic dermatitis (AD) and plaque psoriasis. The compound (number WBI 1001) was initially developed by Welichem Biotech Inc. (Welichem; Burnaby, British Columbia, Canada) and then was acquired by GlaxoSmithKline (GSK) on 31 July 2012 for further development in the rest of the world except China. Beijing Wenfeng Tianji Pharmaceuticals (BWTP) is developing a compound in China identified as Benvitimod (active ingredient corresponds to tapinarof) with a unique topical formulation. Dermavant acquired the drug from GSK on 20 August 2018 for continued development.

Tapinarof cream, 1% is a white to off-white, oil-in-water emulsion intended for topical application to AD and psoriatic skin lesions, which has a novel mechanism of action. 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 AD and psoriasis. Rather, the profile of biological responses elicited by tapinarof most closely matches that of the dual activation properties of coal tar, a common nonprescription treatment for psoriasis. Together, existing data identify tapinarof as a non-steroid, therapeutic AhR-modulating agent (TAMA), 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 7 Phase 1/2 studies in subjects with AD and psoriasis 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 with vehicle, in both psoriasis and AD.

Four randomized, double-blind, vehicle-controlled, clinical studies to evaluate the safety and efficacy of topically applied tapinarof cream in subjects with AD or psoriasis were conducted by Welichem; one 28-day and one 12-week study was 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% (Formulation C) 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 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, dermatitis contact, 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 AD and psoriasis, with a favorable safety profile.

The first clinical study with Formulation F (Study 201851) 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 AD; 5 subjects were treated with the 2% dose and 6 subjects were treated with the 1% dose. Headache was the most frequently reported (100% and 60% of subjects at the 1% and 2% doses, respectively) nondermatological AE.

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

1.1.2. Study Rationale

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

1.2. Rationale for Study Design, Dose, and Control Groups

This study is a 12 week double-blind, vehicle-controlled treatment study in which subjects will be randomized to receive tapinarof cream, 1% or vehicle cream once daily for 12 weeks. The study will be conducted at multiple study centers in more than 1 country to enhance the possibility of inclusion of a wider range of population groups and to increase generalizability of the results.

The randomized, double-blind, vehicle-controlled study design will minimize the potential for subjective bias related to possible identification of which subjects are receiving active treatment and will minimize selection and allocation bias by balancing potential prognostic factors. The 12-week treatment endpoint is expected to be an adequate duration to measure full response to treatment. Clinical studies in skin conditions have historically shown a notable vehicle (as well as placebo) response rate, which could be attributable to the effects of skin moisturization or to the increased emphasis on proper skin care while participating in a clinical study. A vehicle control group is included to provide a control for comparison and to ensure study sensitivity for characterization of the safety and efficacy profile of tapinarof cream, 1%.

Subjects who complete this Phase 3 study will have the option to enroll in a separate open-label long-term safety and efficacy study for an additional 40 weeks of treatment. Subjects who do not enroll in the open-label long-term study will complete a follow-up visit approximately 4 weeks after end of treatment in this study (at Week 16).

Tapinarof cream has been investigated in prior studies at concentrations from 0.5% to 8.0% and at once daily 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 GSK Phase 2b clinical 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 faster onset of action was observed with 1% dosing groups compared with the 0.5% dosing groups in both studies; fast onset of action is an important consideration for topical medications. 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. In addition, once daily application may improve treatment adherence compared with more frequent dosing administrations. Based on the efficacy and safety data from Study 203120, 1% once daily was chosen as the tapinarof concentration and dosing frequency to be investigated in this study and intended for registration.

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 203120 in psoriasis, the most frequently reported dermatologic AEs were folliculitis and contact dermatitis. In the dose-ranging study 203121 in AD, the most frequently reported dermatologic AEs were folliculitis and AD. 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 (Formulation C), AEs of skin hyperpigmentation, application site dermatitis, papular rash, pruritus, contact dermatitis, folliculitis, erythema, and skin burning sensation were reported.

To mitigate these potential risks, subjects with a known or suspected intolerance to tapinarof or its excipients will be excluded from enrollment. Subjects' skin will be evaluated routinely for signs of irritation or allergic reaction, and if needed, study treatment may be interrupted and an appropriate treatment provided.

1.3.1.2. Systemic Adverse Events

Nasopharyngitis and headache were the most frequently-reported nondermatological AEs in dose-ranging Study 203120 in psoriasis. In dose-ranging Study 203121 in AD, the most frequently reported nondermatological AEs were nasopharyngitis, upper respiratory tract infection, and headache. In the initial clinical studies (in AD and psoriasis) using a different tapinarof formulation (Formulation C), nasopharyngitis, and headache were the most frequently reported nondermatological AEs. In the open-label PK Study 201851 with BID dosing of Formulation F of tapinarof cream (n=11), 1% and 2%, headache was the 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 intravenous (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 heart rate. 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 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). Monthly pregnancy testing will be conducted. 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 study treatment. 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 (eg, 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 • To evaluate the efficacy of tapinarof cream, 1% compared with vehicle control in adults with plaque psoriasis	• Proportion of subjects who achieve a Physician Global Assessment (PGA) score of clear (0) or almost clear (1) with a minimum 2-grade improvement from Baseline at Week 12
Secondary • To further characterize the efficacy of tapinarof cream, 1% compared with vehicle control over time	**Secondary:** • Proportion of subjects with ≥ 75% improvement in Psoriasis Area and Severity Index (PASI) from Baseline at Week 12 • Proportion of subjects with a PGA score of 0 or 1 at Week 12 • Mean change in percent of total body surface area (%BSA) affected from Baseline to Week 12 • Proportion of subjects with ≥90% improvement in PASI score from Baseline to Week 12 **Exploratory Endpoints:** • Time to achieve a PGA score of 0 or 1 with a minimum 2-grade improvement from Baseline • Proportion of subjects with a PGA score of 0 or 1 at Weeks 2, 4, 8, and 12 • Proportion of subjects who achieve a PGA score of 0 or 1 with a minimum 2-grade improvement from Baseline at Weeks 2, 4, and 8 • Mean absolute and percent change in PASI score from Baseline to Weeks 2, 4, 8, and 12 • Proportion of subjects with ≥ 50% improvement in PASI score from Baseline to Weeks 2, 4, 8, and 12 • Proportion of subjects with ≥ 75% improvement in PASI score from Baseline to weeks 2, 4, and 8 • Proportion of subjects with ≥ 90% improvement in PASI score from Baseline to weeks 2, 4, and 8 • Mean change in %BSA affected from Baseline to Weeks 2, 4, and 8
• To describe the effect of tapinarof cream, 1% on psoriasis symptom severity and the associated impact on daily activities and attitudes in adults with plaque psoriasis	• Change in Peak Pruritus-Numeric Rating Scale (Peak Pruritus-NRS) from Baseline at Weeks 2, 4, 8, and 12 • Change over time in psoriasis impact on daily activities, as measured by the Dermatology Life Quality Index (DLQI) total and individual dimension scores • Change over time in psoriasis symptoms, as measured by the Psoriasis Symptom Diary (PSD) • Change over time in physical component score and mental component score, as measured by the Short Form-36 (SF-36) questionnaire
• To evaluate the safety and tolerability of tapinarof cream, 1%	**Safety:** • Incidence, frequency, and duration of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)

Objectives	Associated Endpoint
in adults with plaque psoriasis	• Clinically significant change from Baseline in laboratory values • Clinically significant change from Baseline in vital signs • Mean Local Tolerability Scale (LTS) scores by visit
• To characterize the PK of tapinarof in adults with plaque psoriasis	**Pharmacokinetic:** • Plasma concentration of tapinarof at Weeks 4 and 12

3. STUDY DESIGN

3.1. Overall Design

This is a double-blind, randomized, vehicle-controlled, Phase 3, multicenter study to evaluate the efficacy and safety of topical tapinarof cream, 1% compared with vehicle-control cream in adults with plaque psoriasis.

Following a 34-day screening period, eligible subjects will be randomized at a 2:1 ratio to receive once daily treatment with tapinarof cream, 1% or vehicle cream for 12 weeks. Subjects will return to the clinic at Weeks 2, 4, 8, and 12 for efficacy and safety assessments. Additionally, subjects will be contacted by phone at Weeks 6 and 10 to assess AEs and concomitant medications, to review study drug administration instructions, and to confirm subject's continued participation in this study.

Study drug will be dispensed 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 lesions and lesions/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 fingernails, toenails, palms, soles, and scalp lesions with study drug; however, efficacy analyses will not include assessment of improvement of psoriasis in these areas.) Subjects will be instructed to maintain the approximate dosing time chosen at the beginning of the study for their full study participation. At the phone contacts at Weeks 6, and 10, subjects should be reminded to complete their daily diary and bring it with them to the next clinic visit.

Study drug application instructions will be reviewed at all post-randomization clinic visits and during any planned study phone calls. On clinic visit days, subjects will be instructed/reminded 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 at the clinic under the supervision of site personnel, after efficacy and safety assessments have been completed. The time of the dose application and assessments will depend on the time of the clinic visit. Therefore, the timing of the clinic visit may lead to a change in the subject's chosen dosing time.

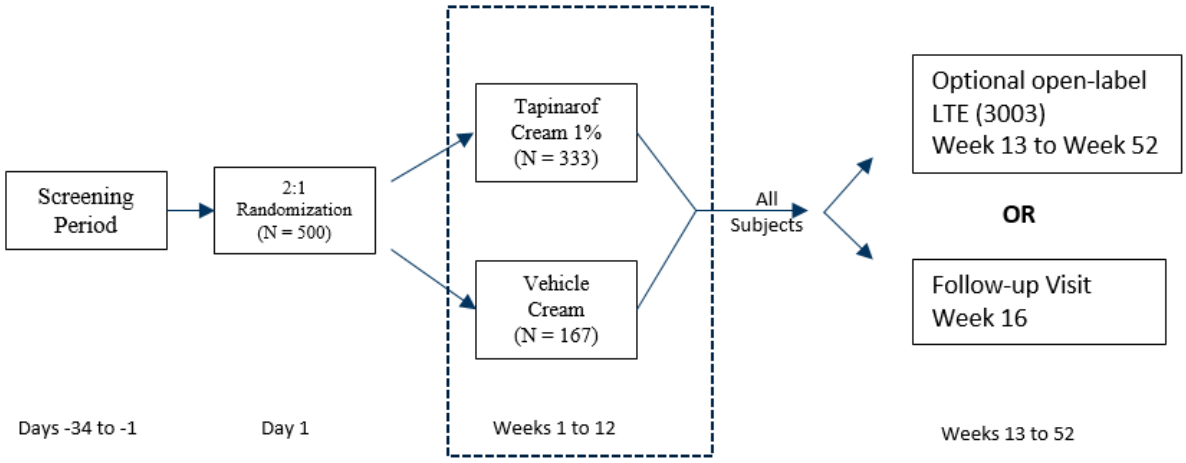
At the end of the 12 weeks of treatment in this study, subjects will have the option to enroll in a separate open-label long-term safety and efficacy study for an additional 40 weeks. Subjects who choose not to participate in the open-label long-term study, who fail to qualify for participation in the open-label long-term study, or who qualify to participate in the open-label long-term study but ultimately elect not to enroll in that study, will complete a Follow-up Visit approximately 4 weeks (Week 16 visit) after the end of treatment in this study. Subjects who withdraw from the study before Week 12 will complete an Early Termination Visit. Study duration for subjects who complete this Phase 3 study and who fail to qualify for participation in the open-label long-term study, or who qualify to participate in the open-label long-term study but ultimately elect not to enroll in that study is approximately 20 weeks in total. Study duration for subjects who complete this Phase 3 study and are eligible and decide to participate in the open-label long-term study is approximately 16 weeks in total.

Efficacy assessments will include Investigator assessment of PGA score, %BSA affected, PASI, and subject-reported DLQI, SF-36, Peak Pruritus-NRS, and PSD. Safety assessments will

include AEs, clinical laboratory tests, physical examination, vital signs, and LTS. Pharmacokinetics will be assessed at a subset of sites in a subset of subjects at Week 4 and Week 12.

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. The study schema is presented in Figure 1.

Figure 1: Study Schema



3.2. Treatment Groups and Duration

This 12-week, Phase 3 study is a double-blind, vehicle-controlled treatment study in which subjects will be randomized in a 2:1 ratio to receive once daily treatment with either tapinarof cream, 1% or matching vehicle cream.

At the conclusion of the 12 weeks of treatment in this study, subjects will have the option to enroll in a separate Phase 3 open-label long-term safety and efficacy study of 40 weeks in duration. Details of that study are provided in a separate clinical trial protocol.

A subject will be considered to have completed this study when he/she completes all required procedures/visits for the 12-week double-blind treatment phase.

The end of study is defined as when the last active subject has completed the Week 16 Follow-up Visit 4 weeks after the end of treatment (if subject does not enroll in the separate long-term study) OR the last active subject has completed the 12 weeks of treatment in this study (if subject enrolls in the separate long-term study).

4. STUDY POPULATION

4.1. Type and Number of Subjects

Approximately 500 adult subjects with plaque psoriasis will be enrolled in the study at approximately 50 to 60 study sites in the US and Canada.

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 clinical diagnosis of chronic plaque psoriasis and stable disease for at least 6 months prior to the study
2. Body surface area involvement ≥ 3% and ≤ 20% (the subject's scalp, palms, fingernails, toenails, and soles should be excluded from the %BSA calculations).
3. A PGA score of 2 (mild), 3 (moderate) or 4 (severe) at screening and baseline (pre-randomization). Subjects with mild and severe psoriasis will be limited to approximately 10% each of the total randomized population; the majority of the enrolled subjects (approximately 80%) will have a PGA of 3, signifying moderate disease.
4. Females of child-bearing potential 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 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-child-bearing 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 IU/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.

Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Day 1).

5. 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 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 lesions
3. Concurrent conditions or history of other diseases:

a. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome) or medical history of positive human immunodeficiency virus (HIV) antibody at Screening
b. Chronic or acute systemic 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, 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) ≥ 1.5x the upper limit of normal (ULN)
5. Screening total bilirubin > 1.5 x ULN; total bilirubin > ULN and ≤ 1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%.
6. Corrected QT (QTcF) interval > 475 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. Subjects with a history of HCV infection who were medically cured and have an undetectable viral load are eligible to enroll. Subjects with a history of stable non-alcoholic fatty liver disease without evidence of active inflammation (elevated ALT/AST ≥ 1.5x ULN) or cirrhosis are eligible to enroll.
8. Ultraviolet (UV) light therapy or prolonged exposure to natural or artificial sources of UV radiation (eg, 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.

   - Minimum of 5 half-lives for biologic agents: eg, 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 D3 and analogs (> 5000 IU / day), retinoids (eg, acitretin, isotretinoin), psolarens, corticosteroids, or adrenocorticotropic hormone analogs.
   - 2 weeks for immunizations with a live viral component; drugs known to possibly worsen psoriasis, such as beta-blockers (eg, propranolol), lithium, iodides, angiotensin-converting enzyme inhibitors, and indomethacin, unless on a stable dose for > 12 weeks.
   - With the exception of non-medicated emollients, 2 weeks for topical treatments including corticosteroids, antihistamines, immunomodulators, anthralin (dithranol), Vitamin D derivatives (eg, calcipotriene, calcipotriol), retinoids (Note: 4 weeks for 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 drugs, 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 product 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 study drug (whichever is longer).
15. Current or a history of cancer within 5 years except for adequately treated skin basal cell carcinoma, squamous cell carcinoma or carcinoma in situ of the cervix (surgical excision or electrodessication and curettage).
16. Subjects with active systemic infection that required oral, intramuscular, or intravenous administration of antibiotics, antifungal or antiviral agents within 4 weeks of Baseline/Day 1.
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; the Medical Monitor should be consulted if needed.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. 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 treatment at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. Subjects withdrawn from the study will not be replaced.

4.6.1. Reasons for Withdrawal from the Study

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

- Subject has an AE that is considered to be related to study drug or procedures AND is severe enough to warrant treatment discontinuation, as determined by the Investigator (Section 8.1).
- 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. If the subject is discontinued from study drug, they may remain in the study for safety assessments as needed, at the discretion of the Investigator and Medical Monitor.
- Pregnancy
- Any Grade 3 or 4 AE considered causally related to study drug (Section 8.2.2)

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 7.5).

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(s), the Investigator must make every effort to perform an Early Termination Visit (Section 7.5) 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 descriptions of the study drugs, tapinarof cream, 1% and the vehicle cream, are presented in Table 2.

Table 2: Tapinarof and Vehicle Cream

Study Drug	Tapinarof (DMVT-505)	Vehicle Cream
Physical description	White to off-white cream	White to off-white cream
Unit dose strength/how supplied	1% (10 mg/gram)/30-gram tube	NA/30-gram tube
Route of administration/duration	Topical/12 weeks	Topical/12 weeks
Dosing instructions	Once daily topical application of thin layer to affected areas (Section 5.1.5)	Once daily topical application of thin layer to affected areas (Section 5.1.5)
Manufacturer	GlaxoSmithKline	GlaxoSmithKline

NA = not applicable.

The excipients included in tapinarof cream and vehicle cream are propylene glycol, diethylene glycol monoethyl ether, polysorbate 80, medium chain triglycerides, emulsifying wax non-ionic, polyoxyl stearyl ether 2, polyoxyl stearyl ether 20, benzoic acid, butylated hydroxytoluene, purified water, sodium citrate, citric acid monohydrate, and edetate disodium.

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

5.1.2. Storage

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

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 (MSDS)/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; subjects are to choose the application time they prefer and to apply the study drug at that approximate time each day of study participation.
- If a subject misses a daily dose, it will be recorded as a protocol deviation. The subject should continue dosing the next day and should not apply more than once daily to make up for the missed dose on the previous day.
- If chosen application time is in the evening, the dose should be applied at least 30 minutes prior to bedtime.
- Study drug should be applied to dry, clean skin.
- Wash hands after application, unless treating lesions on the hands or fingernails.
- Study drug should be applied to all lesions, including newly appearing lesions and lesions that have improved during the study.
- Subjects are allowed, but not required, to treat fingernails, toenails, palms, soles, and scalp lesions with study drug; however, efficacy analyses will not include assessment of improvement of psoriasis in these areas. If using study drug on the scalp, no other treatment for scalp psoriasis is permitted during the study.
- If there is residual cream visible on the disease-affected lesional 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.
- Subjects 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 safety and efficacy 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. Therefore, the timing of the clinic visit may differ from the subject's chosen dosing time. The intention is to allow flexibility to accommodate subjects' schedules.

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

5.2. Randomization/Treatment Assignment

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

Randomization in Double-Blind, Vehicle-Controlled Phase	
Regimen	**Number of Subjects**
Tapinarof cream, 1% once daily for 12 weeks	Approximately 333 Subjects
Vehicle cream once daily for 12 weeks	Approximately 167 Subjects

Randomization will be stratified by baseline PGA score so that subjects with mild and severe psoriasis (PGA scores of 2 and 4, respectively) will be limited to approximately 10% each of the total randomized population, and the majority of the enrolled subjects (approximately 80%) will have a PGA score of 3, signifying moderate disease.

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

5.3. Blinding

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

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

- The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study drug is essential for the appropriate clinical management or welfare of the subject as judged by the Investigator.
- Investigators have direct access to the system for unblinding an individual study subject.
- The Investigator should make every effort to first contact the Medical Monitor or appropriate study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If the Sponsor personnel are not contacted before the unblinding, the Investigator must notify the Sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF.
- A subject will be withdrawn if the subject's treatment code is unblinded by the Investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the source documents and eCRF.
- The Sponsor or their designee may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one

or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to Investigators in accordance with local regulations.

5.4. Compliance with Study Drug Administration

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

5.5. Treatment after the End of the Study

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

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

5.6. Prior and Concomitant Therapy

Any medication (including over the counter or prescription medication, vitamins and/or herbal supplements) administered to the subject up to 34 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 is not planned to change from the Baseline visit to the completion of the treatment phase (Week 12) 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 (>5,000 IU/day), retinoids (eg, acitretin, isotretinoin), psoralens, corticosteroids, or adrenocorticotropic hormone analogs
- **Ultraviolet light**: therapy or prolonged exposure to natural or artificial sources of UV radiation (eg, 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, antihistamines, immunomodulators, anthralin (dithranol), Vitamin D derivatives (eg, calcipotriene, calcipotriol), retinoids (eg, tazarotene), or coal tar
- **Drugs known to possibly worsen psoriasis (unless on a stable dose for > 12 weeks)**: beta blockers (eg, propranolol), lithium, iodides, angiotensin-converting enzyme inhibitors, and indomethacin
- **Immunizations:** live, attenuated vaccines (inactivated or subunit vaccines are acceptable when required)
- **Other:** any investigational products or 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. Demography, Medical History, and Baseline Characteristics

6.1.1. Demographics

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

6.1.2. Medical History

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

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

6.1.3. Baseline Characteristics

Single 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Subjects should be in a supine or semi-supine position for at least 5 minutes before ECG is measured.

The Hospital Anxiety and Depression Scale (HADS) will be used to evaluate the subject for symptoms of depression and anxiety at Screening. An example of the HADS questionnaire is provided in Appendix 1.

6.2. Efficacy Assessments

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

6.2.1. Assessments Completed by Investigator

6.2.1.1. Physician Global Assessment

The PGA will be used to assess the primary endpoint in this study. The PGA is a clinical tool for assessing the current state/severity of a subject's psoriasis at a given timepoint. 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 6.2.1.1 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 2 for details). The PGA should be performed first, prior to %BSA and PASI assessments.

6.2.1.2. Body Surface Area Affected

The assessment of the %BSA affected is an estimate of the percentage of total involved skin with psoriasis. For the purpose of clinical estimation, the total palmar surface of the subject's palm and digits may be assumed to be approximately equivalent to 1% BSA. The %BSA affected by psoriasis will be evaluated (from 0% to 100%). Details on calculation of approximate %BSA involvement in each subject (total and individual are provided in Appendix 3). Percentage BSA is a static assessment made without reference to previous scores.

Note: at screening, baseline, and for all efficacy assessments, lesions on the subject's scalp, palms, fingernails, toenails, and soles will not be included in the calculation of %BSA affected as these areas will be excluded from the efficacy analyses.

6.2.1.3. 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 3.

6.2.2. Assessments Completed by Subject

6.2.2.1. Dermatology Life Quality Index

Subjects will complete the DLQI questionnaire. The DLQI is simple dermatology-specific 10-question validated questionnaire to assess the impact of the disease on a subject's quality of life (Cardiff University, Department of Dermatology, Quality of Life Questionnaires). The DLQI has become an important outcome measure in dermatology clinical trials and is the most frequently used instrument in studies of randomized controlled trials in dermatology [Basra, 2015]. The DLQI can be analyzed as a total score (where a higher score indicates greater impairment in quality of life) and can also be scored for the following dimensions: Symptoms and Feelings (items 1 and 2), Daily Activities (items 3 and 4), Leisure (items 5 and 6), Work and School (item 7), Personal Relationships (items 8 and 9), and Treatment (item 10). An example of this assessment is provided in Appendix 4.

6.2.2.2. 36−Item Short Form Survey

The SF-36 is a self-administered questionnaire about physical functioning, bodily pain, role limitations due to physical health or personal or emotional problems, emotional well-being, social functioning, energy/fatigue, general health perceptions, and perceived change in health [Maruish, 2011]. Eight domain scores and 2 summary component (physical and mental) scores

can be calculated; higher scores represent better health status. This study will use the RAND SF-36 Version 1.0. An example of this assessment is provided in Appendix 5.

6.2.2.3. Psoriasis Symptom Diary

The Psoriasis Symptom Diary is a 16-item (24-hour recall) assessment that measures self-reports of psoriasis symptoms, and impact on functional health [Lebwohl 2014; Strober, 2013; Strober, 2016]. The participant will complete the diary at the study site at each in-office visit. The severity and bother of psoriasis- related itching, stinging, burning, pain, and scaling and impact items about the embarrassment, avoidance of activities with other people, and movement restrictions are assessed. Each item is rated on a 0 to 10 NRS, with unlabeled numbers in between the labeled anchors. Higher scores indicate more severe symptoms, bother, or impact. An example of this assessment is provided in Appendix 6.

6.2.2.4. Peak Pruritus-Numeric Rating Scale

The Peak Pruritus-NRS is used to quickly assess itch/pruritus severity over a 24-hour period. The subject will utilize the scale to assess peak pruritus once daily and record the results in their daily diaries. On clinic visit days, the Peak-Pruritis NRS will be assessed in the clinic and not recorded in the diary. An example of the Peak Pruritus-NRS is provided in Appendix 7.

6.2.3. Optional Clinical Photography

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

Photographs will be taken of a representative area of the subject's disease area at the time points specified in the Schedule of Assessments (Table 1; see also Section 7). Three photographs of the selected skin area will be taken in a standardized fashion (ie, same camera, angle, background, distance). Procedures for the clinical photography will be contained in the Study Reference Manual or Photography Manual.

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 Examination

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 measurements of systolic and diastolic blood pressure, pulse rate, and body temperature. Subjects should be in a seated position for at least 5 minutes before vital signs measurement.

6.3.4. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual or Laboratory Manual and the protocol Schedule of Assessments (Table 1). Laboratory requisition forms must be completed, and samples must be clearly labeled with the subject number, protocol number, site/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 • Hepatitis C antibody • Anti-HBc	• Pregnancy tests: (serum at Screening and urine at other visits; women of CBP only) • FSH (as needed in women of non-CBP only) • At the Investigator's discretion, subjects may be screened for alcohol and illicit drug use.	
Serum Chemistry		
• BUN • Creatinine • Glucose (fasting not required) • Sodium • Potassium • Chloride	• Total carbon dioxide • Calcium • AST • ALT • Alkaline phosphatase	• Uric acid • Total bilirubin (+fractionated if required) • Total protein • Albumin
Hematology		
• Platelet count • RBC count • WBC count (absolute) • Reticulocyte count • Hemoglobin • Hematocrit	• RBC Indices: • MCV • MCH • MCHC • Reticulocyte percentage	• WBC Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils
Urinalysis		
• Specific gravity • Microscopic examination (if blood or protein is abnormal		• Dipstick: pH, Glucose, Protein, Blood Ketones

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

6.3.5. 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 Appendix 8). The score will ideally represent an "average" across all application sites. To the fullest extent possible, the same Investigator (or designated evaluator) will perform all tolerability assessments for an individual subject throughout the study. If the subject is applying study treatment to "sensitive areas" (eg, genitals, face, neck, and skin folds), then the degree of irritation for these areas should also be assessed by the investigator.

Additionally, at each specified study visit, the participant will use a 5-point LTS to assess the presence and degree of burning/stinging and itching at the treatment areas. The score will ideally represent an "average" across all application sites.

6.4. Treatment of Study Drug Overdose

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

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

- Contact Medical Monitor to discuss the event
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities
- Provide general symptomatic treatment as necessary
- Document the quantity of the excess dose as well as the duration of the overdosing 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

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

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

7. TIMING OF PROCEDURES AND ASSESSMENTS

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

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

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

7.1. Visit 1; Screening Period (Day -34 to Day -1)

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

- Demography recording
- Serum pregnancy test (females of child-bearing potential)
- Medical history recording
- ECG recording
- Brief physical examination (including weight, height, and body masss index [BMI])
- Vital signs measurements
- HADS assessment
- PGA score
- %BSA affected calculation; subject's scalp, palms, and soles should be excluded from the %BSA calculations used to determine patient's eligibility
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- AE recording (from the time the ICF is signed)
- Concomitant medication recording (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. The Medical Monitor should be consulted if needed.

7.2. Visit 2; Baseline (Day 1)

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

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

- Urine pregnancy test (females of child-bearing potential)
- Changes to medical history will be recorded
- Brief physical examination
- Vital signs measurement
- Photography of a representative area of the subject's disease area (optional; at a subsection of study sites)
- PGA score
- %BSA affected calculation (performed before PASI); subject's scalp, palms, and soles should be excluded from the %BSA calculations used to confirm patient's eligibility
- PASI
- DLQI
- SF-36
- PSD
- Peak Pruritus-NRS
- AE recording
- Concomitant medication recording (from the time ICF is signed)
- Diary dispensed (subjects will be instructed in how and when to complete diary)
- Subject randomized to study treatment and registered in IVRS
- Study drug dispensed
- Instruction on how to apply study drug
- Study drug application under supervision

7.3. Double-Blind, Vehicle-Controlled Phase

Subjects will return to the study site at Weeks 2, 4, 8, and 12 and will be contacted by phone at Weeks 6 and 10 of the double-blind phase of the study.

7.3.1. Visit 3; Week 2 (Day 15 ±2 Days)

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

- Vital signs
- PGA score
- %BSA affected calculation (performed before PASI)
- PASI
- LTS
- PSD

- Peak Pruritus-NRS
- AE recording
- Concomitant medication recording
- Collect and dispense subject diaries
- Review subject diaries for treatment compliance
- Collect and dispense study drug
- Review instructions on how to apply study drug
- Study drug application under supervision

7.3.2. Visit 4; Week 4 (Day 29 ±2 Days)

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

- Urine pregnancy test (females of child-bearing potential)
- Brief physical examination
- Vital signs measurement
- Photography of a representative area of the subject's disease area (optional; at a subset of study sites)
- Blood sample collection for PK analysis (subset of sites and subjects)
- Blood sample collection for clinical laboratory tests
- PGA score
- %BSA affected calculation (performed before PASI)
- PASI
- LTS
- DLQI
- SF-36
- PSD
- Peak Pruritus-NRS
- AE recording
- Concomitant medication recording
- Collect and dispense subject diaries
- Review subject diaries for treatment compliance
- Collect and dispense study drug
- Review instructions on how to apply study drug
- Study drug application under supervision

7.3.3. Visit 5; Week 8 (Day 57 ±2 Days)

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

- Urine pregnancy test (females of child-bearing potential)
- Brief physical examination

- Vital signs measurement
- Photography of a representative area of the subject's disease area (optional; at a subset of study sites only)
- PGA score
- %BSA affected calculation (performed before PASI)
- PASI
- LTS
- PSD
- Peak Pruritus-NRS
- AE recording
- Concomitant medication recording
- Collect and dispense subject diaries
- Review subject diaries for treatment compliance
- Collect and dispense study drug
- Review instructions on how to apply study drug
- Study drug application under supervision

7.3.4. Visit 6; Week 12 (Day 85 ±2 Days)

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

- Urine pregnancy test (females of child-bearing potential)
- Brief physical examination
- Vital signs measurement
- Photography of a representative area of the subject's disease area (optional, at a subsection of study sites)
- Blood sample collection for PK analysis (subset of sites and subjects)
- Blood sample collection for clinical laboratory tests
- PGA score
- %BSA affected calculation (performed before PASI)
- PASI
- LTS
- DLQI
- SF-36
- PSD
- Peak Pruritus-NRS
- AE recording
- Concomitant medication recording
- Collect subject diaries
- Review subject diaries for treatment compliance

- Collect study drug

7.3.5. Phone Contact at Weeks 6 (Day 43 ±2 Days) and 10 (Day 71 ±2 Days)

Subjects will be contacted by phone at Weeks 6 and 10 to review study drug application instructions and to record AEs and concomitant medication use. Subjects should be reminded to complete their daily diary and bring it with them to the next clinic visit.

7.4. Follow-Up Visit 7; Week 16 (Day 113 ±4 Days)

Subjects who do not enroll in the open-label long-term study will return to the study site at Week 16 to complete follow-up assessments as follows:

- Urine pregnancy test (females of child-bearing potential)
- Brief physical examination
- Vital signs measurement
- Blood sample collection for clinical laboratory tests
- Urinalysis
- PGA score
- %BSA affected calculation (performed before PASI)
- PASI
- LTS
- DLQI
- SF-36
- PSD
- Peak Pruritus-NRS
- AE recording
- Concomitant medication recording

7.5. Early Termination Visit

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

- Urine pregnancy test (females of child-bearing potential)
- Brief physical examination
- Vital signs measurement
- Blood sample collection for clinical laboratory tests
- Urinalysis
- PGA score
- %BSA affected calculation (performed before PASI)
- PASI
- LTS
- DLQI

- SF-36
- PSD
- Peak Pruritus-NRS
- AE recording
- Concomitant medication recording
- Collect subject diaries
- Review subject diaries for treatment compliance
- Collect study drug

7.6. End of Study

The end of study is defined as when the last active subject has completed the Week 16 Follow-up Visit 4 weeks after the end of treatment (if subject does not enroll in the separate long-term study) OR the last active subject has completed the 12 weeks of treatment in this study (if subject is eligible and enrolls in the separate long-term study).

8. SAFETY MONITORING AND REPORTING

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

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

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

8.1.1. Definition of Adverse Events

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

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

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

- Any abnormal laboratory test results (hematology, clinical chemistry) or other safety assessments (eg, 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 (eg, 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- Symptomatic complaints at the site of local application (eg, 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 (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

8.1.2. Definition of Serious Adverse Event

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

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

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

the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.1.3. Adverse Events of Special Interest

In prior clinical studies, 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 on Investigator judgment, and may be restarted when the event resolves:

- Contact dermatitis: the study site should collect location, duration, size, associated symptoms (itching, burning, pain), severity (mild, moderate, severe), and photograph the affected site (if possible). If the subject contacts the study site to report significant skin irritation at or near the site of study drug application between study visits, the subject should be brought in for an unscheduled visit, if possible.
- Folliculitis: the study site should collect the location, duration, size, associated symptoms (itching, burning, pain), severity (mild, moderate, severe), indicate whether pustular, and photograph the affected site (if possible).
- Headache: the study site should collect duration, severity (mild, moderate, severe), onset, and location (e.g., frontal, temporal, occipital, diffuse).

Additional AESIs may be identified by the Drug Safety Physician and if applicable by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. 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 Averse 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 4 should be used to determine the grade severity.

Table 4: Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

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

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.

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the subject's source documents.

8.2.1.2. Toxicity Management Criteria

8.2.1.2.1. Grade 1 or Grade 2 Adverse Event

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

8.2.1.2.2. Grade 3 Adverse Event

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

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

8.2.1.2.3. Grade 4 Adverse Event

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

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

8.2.1.2.4. 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 (eg, laboratory tests or vital signs, etc.) as judged by the Investigator.

8.2.2. Assigning Causal Relationship to Study Drug

The Principal 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 adverse event to study drug is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The following definitions are to be used for the relationship of the adverse event to study drug:

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

Any AEs /SAEs assessed as related to study participation (eg, 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 (ie, 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 Reporting

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

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

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

8.3.2. Follow-Up of Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and nonserious AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or 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; source documentation should not be sent with the SAE Report Form unless requested.

Follow-up information received on SAEs should be faxed to the Sponsor within 1 business day of receipt (refer to Medical Monitor/Sponsor Information page for contact information). This information should be included on a follow-up SAE form and 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 a SAE(s) or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.5. Pregnancy Management and Reporting

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

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

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

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

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, eg, errors will be corrected, and inconsistencies queried in the data.

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

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

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

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

10.1. General Considerations

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

10.2. Determination of Sample Size

It is assumed that the proportion of subjects who achieve PGA score of clear (0) or almost clear (1) with a minimum 2-grade improvement from Baseline at Week 12 will be 40% for subjects receiving tapinarof compared with 15% for subjects receiving vehicle control. With 500 subjects randomized in a 2:1 ratio (approximately 333 subjects receiving tapinarof cream, 1% and approximately 167 subjects receiving vehicle cream) there will be > 99% power for a statistical significance (2-sided $p< 0.05$). If tapinarof response rate is 35%, and vehicle response rate is 20%, the power will be > 94%. The power is calculated from a Fisher Exact sample size calculation which is conservative. It is assumed that up to 25% of the subjects will be lost to follow-up by 12 weeks. These subjects will be included in the primary analysis using the multiple imputation method.

10.3. Analysis Populations

10.3.1. Safety

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

10.3.2. Intent-To-Treat

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

10.3.3. Per-Protocol

All subjects in the ITT population who did not have any major protocol deviations will be included in the Per Protocol (PP) population. Subjects will be analyzed as treated.

10.3.4. Pharmacokinetic

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

10.4. Planned Analyses

All efficacy and safety measures over the course of the study will be presented. Details of planned analyses 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 ITT population, including frequency and percentages for categorical variables and mean, standard deviation, median, minimum, and maximum for continuous variables.

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

10.4.2. Efficacy Analyses

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

10.4.2.1. Primary Endpoint Analyses

The primary efficacy endpoint is proportion of subjects who achieve PGA score of clear (0) or almost clear (1) with a minimum 2-grade improvement from Baseline at Week 12. The primary efficacy endpoint will be analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by PGA score at Baseline (PGA scores of 2, 3 or 4).

10.4.2.2. Secondary and Exploratory Efficacy Endpoint Analyses

The secondary efficacy endpoints are as follows:

- Proportion of subjects with ≥ 75% improvement in PASI from Baseline at Week 12
- Mean change in %BSA affected from Baseline to Week 12
- Proportion of subjects with a PGA score of 0 or 1 at Week 12
- Proportion of subjects with ≥90% improvement in PASI score from Baseline to Week 12

Exploratory efficacy endpoints are as follows:

- Time to achieve a PGA score of 0 or 1 with a minimum 2-grade improvement from Baseline
- Proportion of subjects with a PGA score of 0 or 1 at Weeks 2, 4, and 8
- Proportion of subjects who achieve a PGA score of 0 or 1 with a minimum 2-grade improvement from Baseline at Weeks 2, 4, and 8
- Mean absolute and percent change in PASI score from Baseline to Weeks 2, 4, 8, and 12
- Proportion of subjects with ≥ 50% improvement in PASI score from Baseline to Weeks 2, 4, 8, and 12
- Proportion of subjects with ≥ 75% improvement in PASI score from Baseline to Weeks 2, 4, and 8

- Proportion of subjects with ≥ 90% improvement in PASI score from Baseline to Weeks 2, 4, and 8
- Mean change in %BSA affected from Baseline to Weeks 2, 4, and 8

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

Other efficacy endpoints will be analyzed using CMH test for proportions, and analysis of covariance (ANCOVA) model for continuous variables. CMH tests will be stratified by baseline PGA score, and ANCOVA models will include PGA score as a covariate.

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

10.4.3. Safety Analyses

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

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

Selected laboratory data will be analyzed using descriptive summary statistics and will be presented by study visit and treatment group, 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.

Mean scores from the LTS will be summarized by visit.

10.4.4. Analysis of Functional Outcomes and Quality of Life Endpoints

The subject-reported endpoints to examine the effect of study drug on psoriasis symptom severity and the associated impact on daily activities and attitudes are as follows:

- Change in Peak Pruritus-NRS from Baseline at Weeks 2, 4, 8, and 12
- Change over time in psoriasis impact on daily activities, as measured by the DLQI total and individual dimension scores
- Change over time in psoriasis symptoms, as measured by the PSD
- Change over time in physical component score and mental component score, as measured by the SF-36 questionnaire

Change from baseline in DLQI , PSD, SF-36, and Peak Pruritus-NRS scores will be analyzed using an ANCOVA model with treatment as a main effect, and baseline as a covariate.

10.4.5. Pharmacokinetic Analyses

Data will be listed and summarized. Listings will be sorted by subject, day, and time; summaries will be presented by study visit and time from last dose.

Unless stated otherwise, descriptive summaries for continuous variables will include n, mean, SD, median, minimum, and maximum. If data permit, time to steady state will be assessed using the sampled trough values. Exploratory analyses may include relationships of plasma concentrations with patient demographics or AEs.

10.5. Interim Analyses

No interim analyses will be performed from a statistical standpoint.

10.6. Handling of Missing Data

Every effort will be made to collect complete data at all visits.

The primary method of handling of missing data will utilize Multiple Imputations (MI). For sensitivity analysis, Treatment Failure (TF) will be imputed for missing data.

For the MI model, 100 imputations will be generated using PROC MI of SAS. Fully Conditional Specification (FCS) model using the regression method will be used with the response (eg, PGA score) at prior post-baseline visits, baseline strata, and treatment group as covariates, The ROUND and MINIMUM options will be utilized to ensure imputed values are non-negative integers. The seed to be used is 20180330. The results of the 100 analyses will be transformed into a normal statistic and combined into a single analysis using PROC MIANALYZE.

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 United States Investigational New Drug Application (IND), the Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

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

11.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator 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 (ie, not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The Investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The Investigator agrees that all information received from the Sponsor, including but not limited to the Investigator Brochure, this protocol, 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 2 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, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Participation in trial (including trial number)
- Trial discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end dates (including dose regimen) of trial medication (preferably drug dispensing and return should be documented as well)
- Record of all adverse events and other safety parameters (start and end date, and preferably including causality and intensity)
- Concomitant medication (including start and end dates, dose if relevant; dose changes should be 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 (ie, United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The Investigator must notify the Sponsor before destroying any clinical study records.

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

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

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 electronic case report form (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 adverse event, thorough efforts should be made to clearly document the outcome.

11.1.7. Drug Accountability

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

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

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

11.1.8. Inspections

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

11.1.9. Protocol Compliance

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

11.2. Sponsor Responsibilities

11.2.1. Protocol Modifications

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

11.2.2. Study Report and Publications

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

After conclusion of the study and without prior written approval from Dermavant Sciences 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 Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Dermavant Sciences 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 International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Dermavant Sciences GmbH immediately if contacted by a regulatory agency about an inspection.

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

11.3.3. Study Discontinuation

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

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13. APPENDICES

APPENDIX 1. HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Hospital Anxiety and Depression Scale (HADS)

GL Assessment

Name:_____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D		A	D
		I feel tense or "wound up"		
3		Most of the time		
2		A lot of the time		
1		From time to time, occasionally		
0		Never		
		I enjoy the things I used to enjoy		
	0	Definitely		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and fairly badly		
2		Yes, but not too badly		
1		Sometimes, but it doesn't worry me		
0		Never		
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Never		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Almost never		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Always		
1		Usually		
2		Not often		
3		Never		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Never		0
		I get a sort of anxious feeling like "butterflies" in the stomach		
		Never	0	
		Occasionally	1	
		Often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		Often I don't take as much care as I should		2
		Sometimes I don't take as much care as I should		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Definitely	3	
		Quite a lot	2	
		Not very much	1	
		Never	0	
		I look forward with enjoyment to things		
		As much as I ever have		0
		Somewhat less than I used to		1
		Much less than I used to		2
		Rarely		3
		I get sudden feelings of panic		
		Very often	3	
		Often	2	
		Not very often	1	
		Never	0	
		I can enjoy a good book, radio or television program		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Please make sure you have answered all the questions.

	A	D
TOTAL		

APPENDIX 2. PHYSICIAN GLOBAL ASSESSMENT (PGA)

Each assessment should be made as a visual "average" of the severity of all treated areas at the time of the assessment. Following the Baseline visit, assessments will be made without reference to Baseline state or any other previous scores.

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

Score/Grade		Description
0	Clear	No signs of psoriasis; postinflammatory 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 lesions

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APPENDIX 3. CALCULATION OF PERCENT BODY SURFACE AREA (%BSA) AFFECTED AND PSORIASIS AREA SEVERITY INDEX (PASI)

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, lesions 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 approximately1% of their total BSA.

Estimate the involved regional area by determining the number of "full" handprints plus the number of handprints covered if several smaller lesions are "pushed together." 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 and/or the IVRS/IWRS. Multiplier is a fixed number representing fraction of total body area.

Calculation of PASI:

Use the % Involvement for Each Region (0-100%) from the table above to 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 each of the 4 areas						
Affected	0%	< 10%	10 - < 30%	30 - < 50%	50 - < 70%	70 - < 90%	≥ 90%
Score	0	1	2	3	4	5	6

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.

Item	Assessment		Body Area			
			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 4 x Item 5 x 0.1	Item 4 x Item 5 x 0.2	Item 4 x Item 5 x 0.3	Item 4 x Item 5 x 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.

APPENDIX 4. DERMATOLOGY LIFE QUALITY INDEX (DLQI) AGES 16 AND UP

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes	☐	
		No	☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot	☐	
		A little	☐	
		Not at all	☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much	☐	
		A lot	☐	
		A little	☐	
		Not at all	☐	Not relevant ☐

APPENDIX 5. 36−ITEM SHORT FORM SURVEY; VERSION 1.0 (SF-36)

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:
   - 1 – Excellent
   - 2 – Very good
   - 3 – Good
   - 4 – Fair
   - 5 – Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?
   - 1 – Much better now than one year ago
   - 2 – Somewhat better now than one year ago
   - 3 – About the same
   - 4 – Somewhat worse now than one year ago
   - 5 – Much worse now than one year ago

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	o 1	o 2	o 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	o 1	o 2	o 3
5. Lifting or carrying groceries	o 1	o 2	o 3
6. Climbing **several** flights of stairs	o 1	o 2	o 3
7. Climbing **one** flight of stairs	o 1	o 2	o 3
8. Bending, kneeling, or stooping	o 1	o 2	o 3
9. Walking **more than a mile**	o 1	o 2	o 3
10. Walking **several blocks**	o 1	o 2	o 3
11. Walking **one block**	o 1	o 2	o 3
12. Bathing or dressing yourself	o 1	o 2	o 3

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	o 1	o 2
14. **Accomplished less** than you would like	o 1	o 2
15. Were limited in the **kind** of work or other activities	o 1	o 2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	o 1	o 2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	o 1	o 2
18. **Accomplished less** than you would like	o 1	o 2
19. Didn't do work or other activities as **carefully** as usual	o 1	o 2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

    - o 1 – Not at all
    - o 2 – Slightly
    - o 3 – Moderately
    - o 4 – Quite a bit
    - o 5 - Extremely

21. How much **bodily** pain have you had during the **past 4 weeks**?

    - o 1 – None
    - o 2 – Very mild
    - o 3 – Mild
    - o 4 – Moderate
    - o 5 – Severe
    - o 6 – Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

    - o 1 – Not at all
    - o 2 – A little bit
    - o 3 – Moderately
    - o 4 – Quite a bit
    - o 5 - Extremely

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks…**

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	o 1	o 2	o 3	o 4	o 5	o 6
24. Have you been a very nervous person?	o 1	o 2	o 3	o 4	o 5	o 6
25. Have you felt so down in the dumps that nothing could cheer you up?	o 1	o 2	o 3	o 4	o 5	o 6
26. Have you felt calm and peaceful?	o 1	o 2	o 3	o 4	o 5	o 6
27. Did you have a lot of energy?	o 1	o 2	o 3	o 4	o 5	o 6
28. Have you felt downhearted and blue?	o 1	o 2	o 3	o 4	o 5	o 6
29. Did you feel worn out?	o 1	o 2	o 3	o 4	o 5	o 6
30. Have you been a happy person?	o 1	o 2	o 3	o 4	o 5	o 6
31. Did you feel tired?	o 1	o 2	o 3	o 4	o 5	o 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

    - o 1 – All of the time
    - o 2 – Most of the time
    - o 3 – Some of the time
    - o 4 – A little of the time
    - o 5 – None of the time

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	o 1	o 2	o 3	o 4	o 5
34. I am as healthy as anybody I know	o 1	o 2	o 3	o 4	o 5
35. I expect my health to get worse	o 1	o 2	o 3	o 4	o 5
36. My health is excellent	o 1	o 2	o 3	o 4	o 5

APPENDIX 6. PSORIASIS SYMPTOM DIARY (PSD)

1. Overall, how **severe** was your psoriasis-related itching over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No itching										Itching as bad as you can imagine

2. Overall, how **bothered** were you by your psoriasis-related itching over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not bothered at all										Bothered as bad as you can imagine

3. Overall, how **severe** was your psoriasis-related stinging over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No stinging										Stinging as bad as you can imagine

4. Overall, how **bothered** were you by your psoriasis-related stinging over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not bothered at all										Bothered as bad as you can imagine

5. Overall, how **severe** was your psoriasis-related burning over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No burning										Burning as bad as you can imagine

6. Overall, how **bothered** were you by your psoriasis-related burning over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not bothered at all										Bothered as bad as you can imagine

7. Overall, how **severe** was the pain from your psoriasis-affected skin cracking over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

8. Overall, how **bothered** were you by the pain from your psoriasis-affected skin cracking over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not bothered at all										Bothered as bad as you can imagine

9. Overall, how **severe** was your psoriasis-related pain over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

10. Overall, how **bothered** were you by your psoriasis-related pain over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not bothered at all										Bothered as bad as you can imagine

11. Overall, how **severe** was your psoriasis scaling over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No scaling										Scaling as bad as you can imagine

12. Overall, how **bothered** were you by your psoriasis scaling over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Not bothered at all										Bothered as bad as you can imagine

13. Overall, how noticeable did you think the color of your psoriasis-affected skin was over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No at all noticeable										Noticeable as bad as you can imagine

14. Overall, how much did you try to hide your psoriasis-affected skin over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
Did not try to hide at all										Totally avoided being seen by others

15. Overall, how much did your psoriasis cause you to avoid activities with other people over the past 24 hours?

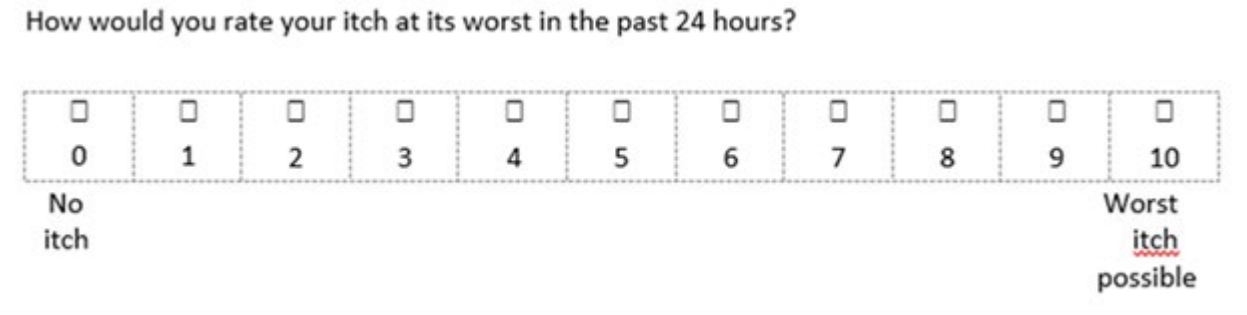
0	1	2	3	4	5	6	7	8	9	10
You did not avoid other people										Avoided other people as much as you ever have

16. Overall, how embarrassed were you because of your psoriasis over the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No embarrassment										Embarrassment as bad as you can imagine

APPENDIX 7. PEAK PRURITUS-NUMERIC RATING SCALE (PRURITUS-NRS)

Peak Pruritus-NRS is a scale used to quickly assess itch/pruritus severity over a 24-hour period. The subject will utilize the scale shown daily to assess peak pruritus.



APPENDIX 8. LOCAL TOLERABILITY SCALE ASSESSMENT

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

If the participant is applying study treatment to "sensitive areas" (eg, genitals, face, neck, and skin folds), then also assess the degree of irritation for these areas.

Local Tolerability – Dryness, Erythema, and Peeling

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

At each specified study visit, the participant will use 5-point tolerability scale presented in the table below to assess the presence and degree of burning/stinging and itching at the treatment areas. The score will ideally represent an "average" across all application sites.

Local Tolerability – Burning/Stinging and Itching

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

APPENDIX 9: PROTOCOL AMENDMENT SUMMARY OF CHANGES

The protocol has been updated with the following changes. Edits to the protocol are shown in **bold**.

Table 1. Schedule of Assessment

Urinalysis and clinical laboratory tests added to the Early Termination visit.

Section 1.1, page 23. Background Information

Correction made to reflect language in study report; "contact dermatitis" changed to "dermatitis contact."

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 **contact**, folliculitis, erythema, and skin burning sensation.

Section 1.3.1.2. Clarification on study design added;

In **the open-label PK** Study 201851 **with BID dosing** of Formulation F of tapinarof cream **(n=11)**, 1% and 2%, headache was the most frequently reported during the study (reported for 100% and 60% of subjects at the 1% and 2% doses, respectively).

Section 3.1 Overall Design

Clarified wording around time of dosing each day and protocol violations which is further addressed in Section 5.1.5 (Administration of Study Drug)

Section 4.3. Exclusion criteria #3b and #16

Corrected inconsistencies between 2 criteria in systemic infections requiring treatment prior to enrollment as **4 weeks** before the baseline visit.

Section 4.3. Exclusion criterion #7

Clarified that a subject with previous HCV infection who had been treated and who has an undetectable viral load is eligible to enroll. Clarified that a subject with stable non-alcoholic fatty liver disease without evidence of active inflammation or cirrhosis is eligible to enroll.

Section 4.3. Exclusion criterion #9 and Section 5.6.2 Prohibited Medications and Nondrug Therapies

Added a daily dose for the oral Vitamin D3 and analogs exclusion and added topical antihistamines as prohibited medications

Section 4.3. Exclusion criterion #15

Clarified exemptions for current or history of cancer to "**adequately treated** skin basal cell carcinoma, squamous cell carcinoma or carcinoma in situ of the cervix **(surgical excision or electrodessication and curettage)."**

Section 4.5 Screening / Baseline Failures and Section 7.1. Visit 1; Screening Period

Revised wording regarding repeat lab and procedures based on the Investigator's discretion with consultation of the Medical Monitor on an "as needed" basis.

Section 5.1.5. Administration of Study Drug

Added clarification wording around missed doses and protocol deviations: "**If a subject misses a daily dose, it will be recorded as a protocol deviation. The subject should continue dosing the next day and should not apply more than once daily to make up for the missed dose on the previous day.**"

Section 6.2.2.4. Peak Pruritus-Numeric rating Scale

Added clarification wording: "**On clinic visit days, the Peak-Pruritis NRS will be assessed in the clinic and not recorded in the diary**."

Section 7.2, page 48. 7.2. Visit 2; Baseline (Day 1)

Removed the collection of a PK sample to be consistent with Table 1, Schedule of Assessments

Section 7.5 Assessments

Addition of additional safety assessments. Urinalysis and clinical laboratory tests added at Early Termination visit.

Section 8.1.1. Definition of Adverse Events

To avoid confusion, the wording that defines local adverse events has been edited since "evaluation of local tolerability" is being assessed with a specific scale (Appendix 8).

Appendix 1. HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Revised HADS example added.

Appendix 3, page 75. CALCULATION of BSA and PASI

Clarification of body surface area calculation and correction in table for calculation of PASI; score of 0 changed from 1% to 0% skin covered with psoriasis and score of 1 changed from 1 - <10% to <10% consistent with published paper (Feldman Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis.2005;64 (suppl II):ii65-ii68.)

	Percentage of skin covered with psoriasis for each of the 4 areas						
Affected	**0%**	< 10%	10 - < 30%	30 - < 50%	50 - < 70%	70 - < 90%	≥ 90%
Score	0	1	2	3	4	5	6

Appendix 8, page 85. LOCAL TOLERABILITY SCALE ASSESSMENT

Removed unnecessary footnote under the Local Tolerability – Dryness, Erythema, and Peeling table.