CLINICAL STUDY PROTOCOL

Title	A Long-Term, Open-Label, Extension Study to Evaluate the Safety and Efficacy of Tapinarof Cream, 1% for the Treatment of Plaque Psoriasis in Adults
Sponsor	Dermavant Sciences GmbH Viaduktstrasse 8 4051 Basel, Switzerland
Compound Name	DMVT-505 (tapinarof)
Protocol Number	DMVT-505-3003
Indication	Plaque Psoriasis
Development Phase	3
IND Number	104601
Version/ Effective Date:	Original Protocol 30-JANUARY-2019 Amendment 1 (Version 1.0) 16-DEC-2019

SPONSOR SIGNATURE PAGE

Study Title: A Long-Term, Open-Label, Extension Study to Evaluate the Safety and Efficacy of Tapinarof Cream, 1% for the Treatment of Plaque Psoriasis in Adults

Protocol Number: DMVT-505-3003

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

[redacted]

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 Long-Term, Open-Label, Extension Study to Evaluate the Safety and Efficacy of Tapinarof Cream, 1% 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

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ABBREVIATIONS

Term	Description
AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
AhR	aryl hydrocarbon receptor
ALT	alanine aminotransferase
Anti-HBc	anti-hepatitis B core antigen
AST	aspartate aminotransferase
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
BWTP	Beijing Wenfeng Tianji Pharmaceuticals
C	collect
CBP	childbearing potential
CFR	Code of Federal Regulations
CTCAE	Common Terminology Criteria for Adverse Events
D	dispense
DLQI	Dermatology Life Quality Index
eCRF	electronic case report form
ET	early termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
F-U	follow-up
GSK	GlaxoSmithKline
HBsAg	hepatitis B surface antigen
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intention to Treat
IV	intravenous
LOCF	Last Observation Carried Forward

Term	Description
LTS	Local Tolerability Scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
MCV	mean corpuscular volume
MSDS	Material Safety Data Sheet
Nrf2	nuclear factor-erythroid 2-related factor-2
OC	Observed Cases
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PK	pharmacokinetic
PND	postnatal day
RBC	red blood cells
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
TAMA	therapeutic AhR-modulating agent
TEAE	treatment-emergent adverse event
UNSCH	unscheduled
US; USA	United States (of America)
UV	ultraviolet
WBC	white blood cells
WHO	World Health Organization

SYNOPSIS

Name of Sponsor/Company: Dermavant Sciences GmbH		
Name of Investigational Product: DMVT-505 (tapinarof cream, 1%)		
Name of Active Ingredient: Tapinarof		
Protocol Number: DVT-505-3003	**Phase:** 3	**Country:** US and Canada
Title of Study: A Long-Term, Open-Label, Extension Study to Evaluate the Safety and Efficacy of Tapinarof Cream, 1% for the Treatment of Plaque Psoriasis in Adults		
Study Centers: Approximately 100 to 120 sites in the United States (US) and Canada		
Objectives: • To evaluate the safety and tolerability of tapinarof cream, 1% in adults with plaque psoriasis • To describe the efficacy of tapinarof cream, 1% over an extended period of time in adults with plaque psoriasis • 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		
Methodology: This is a long-term, open-label, multicenter, study to evaluate the safety and efficacy of topical tapinarof cream, 1% in adults with plaque psoriasis. Subjects in this study completed treatment with tapinarof in 1 of 2 Phase 3 pivotal efficacy and safety studies (Study DMVT-505-3001 or Study DMVT-505-3002). This study will consist of up to 40 weeks of treatment and a 4-week safety follow-up period. At the completion of the Week-12 visit of the pivotal study (Baseline [Day 1] in this study), all eligible subjects will be offered enrollment in the long-term extension study. Study visits during the treatment period for all subjects will occur every 4 weeks (± 3 days). Unscheduled visits may occur, as needed. Subjects who withdraw from the study before Week 40 will return to the study center for an Early Termination visit. The total duration of study participation will be approximately 44 weeks. Subjects in the study will be treated based on their PGA score from the Week 12 visit in the pivotal study. Subjects entering with a PGA $\geq$ 1 will receive treatment with tapinarof cream, 1% until they achieve a PGA score of 0, at which time treatment will be discontinued and subjects monitored for durability of response. If disease worsening occurs, as evidenced by a PGA $\geq$ 2, treatment will then be re-initiated and continued until a PGA of 0 is observed. Subjects entering with a PGA of 0 will have treatment discontinued and be monitored for durability of response. If disease worsening occurs, as evidenced by a PGA $\geq$ 2, then treatment will be re-initiated and continued until a PGA of 0 is observed. This treatment and re-treatment pattern of use will be continued until the end of the study (i.e., subjects may receive study treatment up until the Week 40 visit). Study drug will be dispensed to subjects during the study visits and will be administered at home between study 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 or affected 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. Study drug application instructions will be reviewed at subsequent study visits. During subsequent study visits, subjects will		

apply the daily dose of study drug while at the site, under the supervision of site personnel, after efficacy and safety assessments have been completed, if applicable. The time of the study drug application and assessments will depend on the time of the study visit (either morning or afternoon visit). Therefore, the timing of the study visit may lead to a change from the subject's chosen dosing time; if this occurs, it will NOT be considered a protocol deviation; the subject should resume their chosen dosing time the day following any such study visit study drug application. This should only occur for subjects receiving study treatment.

Rescue medications may be initiated with consultation of the medical monitor.

Sample Size Justification:

The sample size of this study is based on the International Conference on Harmonisation (ICH) E1 guideline on extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions. An estimated 850 subjects who complete Study DMVT-505-3001 or Study DMVT-505-3002 will be enrolled in this study across all regions. A high discontinuation rate is anticipated in this long-term extension study. Approximately 300 subjects are expected to complete the study (up to 40 weeks of treatment).

Number of Subjects (planned):

Approximately 850 subjects ages 18 to 75 years of age

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

1. Completed the 12-week treatment period in 1 of the 2 pivotal studies (Study DMVT-505-3001 or Study DMVT-505-3002);
2. Male or female;
3. Female subjects of childbearing potential and male subjects who are engaging in sexual activity that could lead to pregnancy should use one of the following acceptable birth control methods while on study and for 4 weeks after the last exposure to study drug. Acceptable contraception methods are:
    - Female subject or male subject's female partner is surgically sterile (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) for a minimum of 3 months prior to the first dose of study drug
    - Female subject or male subject's female partner has had an intrauterine device in place for at least 3 months prior to the first dose of study drug
    - Double barrier methods (e.g., condom plus diaphragm, condom or diaphragm plus spermicide) starting at least 14 days prior to the first dose of study drug
    - Subjects who claim abstinence as their method of contraception are allowed provided they agree to use a double barrier method (e.g., condom plus diaphragm, condom or diaphragm plus spermicide) should they become sexually active from Screening to 1 month after the last dose of study drug
    - Surgical sterilization of male subject or female subject's male partner (vasectomy) a minimum of 3 months prior to first dose of study drug
    - Female subject or male subject's female partner is taking hormonal contraceptives starting at least 3 months prior to the first dose of study drug. If hormonal contraceptives were started less than 3 months prior to the first dose of study drug, subjects must agree to use a double barrier method (e.g., condom plus diaphragm, condom or diaphragm plus spermicide) from Screening through 3 months after the initiation of hormonal contraceptives.

    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-CBP is defined as premenarchal or premenopausal 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 ml/U is confirmatory. Documented verbal history from the subject is acceptable.

Female subjects of CBP must have a negative urine pregnancy test at Baseline (Day 1).

4. Capable of giving signed 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:

1. Used a prohibited concomitant product or procedure to treat psoriasis during pivotal study
2. Had a serious adverse event (SAE) that was potentially related to treatment or experienced an adverse event (AE) that led to permanent discontinuation of treatment in the pivotal study
3. 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 completion of the study
4. Known hypersensitivity to tapinarof or excipients

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.

Duration of treatment:

Subjects enrolling in this study may receive treatment for up to 40 weeks. The duration of treatment is based on PGA score and disease worsening.

Reference Therapy, Dosage and Mode of Administration:

Not applicable

Criteria for Evaluation:

Efficacy:

5-point static PGA (0 to 4 scale), percent of total body surface area (%BSA) affected, and the Psoriasis Area and Severity Index (PASI)

Functional Outcomes and Quality of Life:

Dermatology Quality of Life Index (DLQI)

Safety:

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

Study Endpoints:

Safety:

- Incidence, frequency, and nature of AEs and SAEs
- Change over time in clinical laboratory tests and frequency of clinically significant abnormal test results
- Change over time in vital signs and frequency of clinically significant abnormal results
- [redacted]

Efficacy:

- Proportion of subjects who experience a PGA ≥ 2 at least one time in the study and the median time from baseline to first worsening (PGA ≥ 2) for subjects entering the study with a PGA score of clear (0)
- Proportion of subjects who achieve a PGA score of 0 at least one time in the study [redacted]
- Duration of each treatment episode, defined as time from each treatment initiation/re-initiation to each subsequent treatment success (PGA score of 0).
- [redacted]
- Proportion of subjects who never achieve a PGA ≥ 2 throughout the study
- Proportion of subjects who never achieve a PGA score of 0 or 1 throughout the study
- [redacted]

- Change and percent change from baseline in %BSA affected by visit (OC and LOCF)
- Change and percent change in PASI score by visit (OC and LOCF)
- Change in disease impact on daily activities, as measured by the DLQI total and individual dimension scores

Statistical Methods:

All study data will be summarized overall and by treatment group in the pivotal studies using descriptive statistics using the intent-to-treat (ITT) analysis set of subjects. Categorical variables will be reported using frequency and percentage (e.g., sex, race). Continuous variables will be reported using number of subjects, mean, standard deviation (SD), median, minimum, and maximum. All safety and efficacy data will be listed by subject.

Demographics, baseline characteristics, and all safety assessments (including LTS assessments), will be analyzed using descriptive statistics. The Kaplan-Meier product limit method will be used to estimate the median time (if estimable) from baseline to first disease worsening and first treatment success. If the median is not estimable (e.g., < 50% of subjects worsen), other methods for estimating the median and/or other percentiles of worsening will be applied. All other efficacy assessments will be analyzed using descriptive statistics.

SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

		Long-term Extension Period													
	Visit 1	Phone Call	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Other Visits	
Procedures and Assessment	Base-line[a] Day 1	Week 2 Day 15 ±3 Days	Week 4 Day 29 ±3 Days	Week 8 Day 57 ±3 Days	Week 12 Day 85 ±3 Days	Week 16 Day 113 ±3 Days	Week 20 Day 141 ±3 Days	Week 24 Day 169 ±3 Days	Week 28 Day 197 ±3 Days	Week 32 Day 225 ±3 Days	Week 36 Day 253 ±3 Days	Week 40 Day 281 ±3 Days	Week 44 (F-U) Day 309 ±3 Days	UNSCH[b]	ET[c]
Informed consent	X														
Confirm eligibility	X														
Demographics/ Medical History	X[d]														
Brief physical examination	[X]		X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (pulse, BP, temperature)[e]	[X]		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (all females of CBP)	[X]		X	X	X	X	X	X	X	X	X	X	X	As needed	X
Clinical laboratory tests[f]	[X]		X		X							X	X	As needed	X
Urinalysis	X											X	X	As needed	X
Photography, if applicable[g]	[X]		X	X	X	X	X	X	X	X	X	X	X	X	X
Investigator assessed:[e]															
PGA	[X]		X	X	X	X	X	X	X	X	X	X	X	X	X
BSA affected[h]	[X]		X	X	X	X	X	X	X	X	X	X	X	X	X
PASI	[X]		X	X	X	X	X	X	X	X	X	X	X	X	X
LTS[i]			X	X	X	X	X	X	X	X	X	X		X	X

		Long-term Extension Period													
	Visit 1	Phone Call	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Other Visits	
Procedures and Assessment	Base-line[a] Day 1	Week 2 Day 15 ±3 Days	Week 4 Day 29 ±3 Days	Week 8 Day 57 ±3 Days	Week 12 Day 85 ±3 Days	Week 16 Day 113 ±3 Days	Week 20 Day 141 ±3 Days	Week 24 Day 169 ±3 Days	Week 28 Day 197 ±3 Days	Week 32 Day 225 ±3 Days	Week 36 Day 253 ±3 Days	Week 40 Day 281 ±3 Days	Week 44 (F-U) Day 309 ±3 Days	UNSCH[b]	ET[c]
Completed by subject:[e]															
DLQI	[X]		X	X	X	X	X	X	X	X	X	X	X		X
LTS[i]			X	X	X	X	X	X	X	X	X	X		X	X
Patient Satisfaction Questionnaire												X			X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense/collect diary[j]	X		X	X	X	X	X	X	X	X	X	X		X	X
Review diaries for treatment compliance			X	X	X	X	X	X	X	X	X	X		X	X
Dispense/collect study drug[k]	D		C/D	C/D	C/D	C/D	C/D	C/D	C/D	C/D	C/D	C		As needed	C
Review instructions for study drug application[l]	X	X	X	X	X	X	X	X	X	X	X			As needed	
Study drug application under supervision[m]	X		X	X	X	X	X	X	X	X	X			X	

BP = blood pressure; BSA = body surface area; C = collect; CBP = child-bearing potential; D = dispense; DLQI = Dermatology Life Quality Index; ET = early termination; F-U = follow-up; LTS = Local Tolerability Scale; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; UNSCH = unscheduled.

[a] Visit to occur at the time of completion of Visit 6 (Week 12) in pivotal study. The last assessment completed as part of the pivotal study will be used as the baseline value for assessments with a bracketed "X."

[b] Subjects who experience disease worsening (PGA ≥2) between scheduled study visits may contact the study site to arrange an unscheduled visit (see Section 5.1.5.1). If disease worsening is confirmed, a new treatment course will be initiated.

[c] Subjects who withdraw from the study before Week 40 will complete an ET visit.

[d] As collected at Screening/Baseline in pivotal study.

[e] Performed prior to study drug application on study visit days.

[f] Serum chemistry (including liver chemistry tests) and hematology.

[g] Photography will be performed in a subgroup of subjects at selected (approximately 20) study centers; this is not required of subjects for participation in the study. Informed consent and photographic release will be required.

[h] %BSA affected must be performed before PASI. (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

[i] The LTS assessment is only required to be completed if the subject was applying study drug for the period before the current visit.

[j] Study diary should only be dispensed if study product is dispensed.

[k] Subjects will be monitored for disease worsening (PGA ≥2), and study drug administration may be started at any time during the observation period (see Section 5.1.5.1)

[l] Subjects will be instructed to apply study drug once daily at the approximate same time each day, based on subject preference. This should only occur for subjects receiving study treatment.

[m] Study drug will be applied after safety assessments have been conducted, . Subjects will be instructed and reminded on how to apply study drug at each visit, except during the final treatment visit (see Section 5.1.5.3 for additional details on timing of study drug application during study visits). This should only occur for subjects receiving study treatment.

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 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 topically applied corticosteroids and Vitamin D analogs, alone or in combination. Vitamin D analogs are moderately efficacious as monotherapy, while 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 that permits application to a large body surface area (BSA) without restrictions on duration of treatment.

DMVT-505 (tapinarof), 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 I clinical pharmacology studies in healthy volunteers and 7 Phase I/II 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 to 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 adverse event.

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 40-week, Phase 3, open-label extension study is being conducted as part of a clinical development program to evaluate the long-term safety and continued efficacy of tapinarof cream, 1% for the topical treatment of plaque psoriasis in adults with psoriasis. Subjects in this study will be selected from those subjects who complete 1 of 2 Phase 3 pivotal efficacy and safety studies (pivotal Study DMVT-505-3001 or pivotal Study DMVT-505-3002) and meet the predefined criteria to enroll into this study.

1.2. Rationale for Study Design and Dose

As in the pivotal studies, this Phase 3 study continued to 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 subsequently increase generalizability of the results. Tapinarof cream is intended for long-term, intermittent use in non-life-threatening inflammatory dermatologic conditions. Therefore, the 40-week duration of long-term, intermittent use of tapinarof in this study, in addition to the treatment received in the pivotal study, is expected to be an adequate duration to assess safety and efficacy of repeated treatment courses of tapinarof as recommended in the International Conference on Harmonisation E1 (ICH E1) guideline on the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions [ICH, 1994], which recommends a minimum of 100 subjects be treated with the intended clinical dose and to be followed for AEs over at least 1 year.

The once daily topical application of tapinarof cream, 1% concentration administered in the pivotal studies will be continued in this open-label extension study.

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 will be interrupted and an appropriate treatment provided. Note that after cessation of exposure, dermatological reactions generally subside spontaneously or with topical treatments.

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 AE 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/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 (CBP)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 (e.g., physical examination, laboratory tests). Subjects in the study will also contribute to the process of developing a novel anti-inflammatory agent for the topical treatment of psoriasis.

1.3.3. Overall Benefit/Risk

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

2. OBJECTIVES AND ENDPOINTS

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

Objectives	Associated Endpoints
• To evaluate the safety and tolerability of tapinarof cream, 1% in adults with plaque psoriasis	• Incidence, frequency, and nature of AEs and SAEs • Change over time in clinical laboratory tests and frequency of clinically significant abnormal test results • Change over time in vital signs and frequency of clinically significant abnormal results • [redacted]
• To describe the efficacy of tapinarof cream, 1% over an extended period of time in adults with plaque psoriasis	• Proportion of subjects who experience a PGA ≥ 2 at least 1 time in the study and the median time from baseline to first worsening (PGA ≥ 2) for subjects entering the study with a PGA score of clear (0) • Proportion of subjects who achieve a PGA score of 0 at least 1 time in the study [redacted] • Duration of each treatment episode, defined as time from each treatment initiation/re-initiation to each subsequent treatment success (PGA score of 0). • [redacted] • Proportion of subjects who never achieve a PGA ≥ 2 throughout the study • Proportion of subjects who never achieve a PGA score of 0 or 1 throughout the study • [redacted] [redacted] • Change and percent change from baseline in %BSA affected by visit (OC and LOCF) • Change and percent change in PASI score by visit (OC and LOCF) •
• 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 disease impact on daily activities, as measured by the Dermatology Life Quality Index (DLQI) total and individual dimension scores

3. STUDY DESIGN

3.1. Overall Design

This is a long-term, open-label, multicenter, study to evaluate the safety and efficacy of topical tapinarof cream, 1% in adults with plaque psoriasis. Subjects in this study completed treatment with tapinarof or vehicle in 1 of 2 pivotal Phase 3 pivotal efficacy and safety studies (Study DMVT-505-3001 or Study DMVT-505-3002). The study will consist of up to 40 weeks of treatment and a 4-week safety follow-up period.

At the completion of the Week-12 Visit of the pivotal study (Baseline [Day 1] in this study), eligibility of the subjects opting to enroll in this extension study will be confirmed. Study visits during the treatment period for all subjects will occur every 4 weeks (±3 days). A Phone Call will be performed at Week 2 (Day 15). Unscheduled visits may occur, as needed. Subjects who withdraw from the study before Week 40 will return to the study center for an Early Termination Visit. The total duration of study participation will be approximately 44 weeks.

Subjects in the study will be treated as follows based on their PGA score from the Week 12 visit in the pivotal study (DMVT-505-3001 or DMVT-505-3002).

- Subjects entering with a PGA ≥ 1 will receive treatment with tapinarof cream, 1% until they achieve a PGA score of 0, at which time treatment will be discontinued and subjects monitored for durability of response. If/when disease worsening occurs, as evidenced by a PGA ≥ 2, treatment will then be re-initiated and continued until a PGA of 0 is observed.
- Subjects entering with a PGA of 0 will have treatment discontinued and be monitored for durability of response. If/when disease worsening occurs, as evidenced by a PGA ≥ 2, treatment will then be re-initiated and continued until a PGA of 0 is observed.
- This treatment and re-treatment pattern of use will be continued until the end of the study (ie, subjects may receive study treatment up until the Week 40 visit) (see Section 5.1.5.2).

Study drug will be dispensed, and subjects will be instructed on how to apply study drug. Subjects will apply the daily dose of study drug while at the site, under the supervision of site personnel, after efficacy and safety assessments have been completed.

Study drug will be dispensed to subjects during the study visits and will be administered at home between study 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 or affected 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. Study drug application instructions will be reviewed at subsequent study visits. During subsequent study visits, subjects will apply the daily dose of study drug while at the study 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 study visit (either morning or afternoon visit). Therefore, the timing of the study visit may lead to a change in the subject's chosen dosing time; if this occurs, it will NOT be considered a protocol deviation; the subject should resume their chosen dosing time the day following any such clinic visit application.

Rescue medications may be initiated with consultation of the medical monitor.

Safety assessments will include AEs, local (application site) tolerability, clinical laboratory tests, vital signs, physical examinations, and investigator-assessed LTS. Efficacy assessments will include a 5-point static PGA (0-4 scale), %BSA affected, the PASI, and subject-reported DLQI.

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

Table 1) for timing of procedures and assessments.

3.2. Treatment Groups and Duration

Subjects entering with a PGA ≥ 1 will receive treatment with tapinarof cream, 1% until they achieve a PGA score of 0, at which time treatment will be discontinued and subjects monitored for durability of response. If or when disease worsening occurs, as evidenced by a PGA ≥ 2, treatment will then be re-initiated and continued until a PGA of 0 is observed. Subjects entering with a PGA of 0 will have treatment discontinued and be monitored for durability of response. If/when disease worsening occurs, as evidenced by a PGA ≥ 2, treatment will then be re-initiated and continued until a PGA of 0 is observed. (Section 5.1.5.2).

A subject will be considered to have completed the study when he/she completes all required procedures/visits for the 40-week (Visit 11) treatment period. The end of the study is defined as when the last active subject has completed the Follow-up Visit.

4. STUDY POPULATION

4.1. Type and Number of Subjects

Approximately 850 subjects who completed pivotal Study DMVT-505-3001 or pivotal Study DMVT-505-3002 will be enrolled in this study at approximately 100 to 120 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 be enrolled in this study:

1. Completed the 12-week treatment period in 1 of the 2 pivotal studies (Study DMVT-505-3001 or Study DMVT-505-3002)
2. Male or female
3. Female subjects of child-bearing potential and male subjects who are engaging in sexual activity that could lead to pregnancy should use one of the following acceptable birth control methods while on study and for 4 weeks after the last exposure to study drug. Acceptable contraception methods are:
    - Female subject or male subject's female partner is surgically sterile (bilateral tubal ligation, hysterectomy, bilateral oophorectomy) for a minimum of 3 months prior to the first dose of study drug
    - Female subject or male subject's female partner has had an intrauterine device in place for at least 3 months prior to the first dose of study drug
    - Double barrier methods (e.g., condom plus diaphragm, condom or diaphragm plus spermicide) starting at least 14 days prior to the first dose of study drug
    - Subjects who claim abstinence as their method of contraception are allowed provided they agree to use a double barrier method (e.g., condom plus diaphragm, condom or diaphragm plus spermicide) should they become sexually active from Screening to 1 month after the last dose of study drug
    - Surgical sterilization of male subject or female subject's partner (vasectomy) a minimum of 3 months prior to first dose of study drug
    - Female subject or male subject's female partner is taking hormonal contraceptives starting at least 3 months prior to the first dose of study drug. If hormonal contraceptives were started less than 3 months prior to the first dose of study drug, subjects must agree to use a double barrier method (e.g., condom plus diaphragm, condom or diaphragm plus spermicide) from Screening through 3 months after the initiation of hormonal contraceptives

    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-CBP is defined as premenarchal or premenopausal 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 ml/U is confirmatory. Documented verbal history from the subject is acceptable.

Female subjects of CBP must have a negative urine pregnancy test at Baseline (Day 1), as collected from Week 12 of 1 of the 2 pivotal studies (Study DMVT-505-3001 or Study DMVT-505-3002).

4. Capable of giving signed 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

Any subject who meets any of the following criteria will be ineligible to be enrolled in this study:

1. Used a prohibited concomitant product or procedure to treat psoriasis during pivotal study
2. Had an SAE that was potentially related to treatment or experienced an AE that led to permanent discontinuation of treatment in the pivotal study
3. 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 completion of the study
4. Known hypersensitivity to tapinarof or excipients

4.4. Lifestyle Restrictions

Subjects should avoid prolonged exposure to natural or artificial sources of ultraviolet (UV) radiation (e.g., sunlight or tanning booth) and UV light therapy during this study, because UV light may affect the subject's psoriasis. The use of sunscreen on nonlesional areas is allowed.

4.5. Screening Failure

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transpivotal 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. These data will also be linked to subject data from the initial study.

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 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 concomitant 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 7.7).

4.6.2. Temporary Discontinuation

A subject will discontinue study drug when the Investigator determines a PGA of 0 has been achieved as described in Section 5.1.5.1. While actively treating an episode of disease worsening or during the treatment course for a PGA ≥ 2, there are no specific provisions for temporary discontinuation of treatment during this study, with the exception of the interruption of study treatment for skin irritation (see Section 1.3). If study treatment is interrupted due to a safety issue, the Medical Monitor will be contacted and the event documented in the electronic case report form (eCRF).

4.6.3. 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 eCRF. If a subject is prematurely discontinued from study drug(s), the Investigator must make every effort to perform an Early Termination Visit (Section 7.7) 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 re-schedule 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 non-compliance. 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 will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

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

5. STUDY TREATMENT

5.1. Study Drug

5.1.1. Description, Packaging, and Labeling

The description of the study drug is presented in Table 2.

Table 2 Tapinarof Cream

Drug name:	DMVT-505 (tapinarof)
Physical description	White to off-white cream
Unit dose strength/how supplied	1% (10 mg/g)/30 gram, tube
Route of administration/duration	Topical/up to 40 weeks
Dosing instructions:	Once daily topical application of thin layer to all affected areas (see Section 5.1.5)
Manufacturer	GlaxoSmithKline

Study drug will be dispensed to subjects at the clinical site in appropriately labeled tubes. All labels for tapinarof cream, 1% to be distributed in the participating countries will meet all applicable requirements of those countries.

5.1.2. Storage

All study drug must be stored in a secure environmentally-controlled and monitored (manual or automated) area in accordance with the labelled 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

5.1.5.1. Treatment by Physician Global Assessment Score

Subjects entering with a PGA ≥ 1 will receive treatment with tapinarof cream, 1% until they achieve a PGA score of 0. If/when disease worsening occurs, as evidenced by a PGA ≥ 2, treatment will then be re-initiated and continued until a PGA of 0 is observed. Subjects entering with a PGA of 0 will have treatment discontinued and be monitored for durability of response. If/when disease worsening occurs, as evidenced by a PGA ≥ 2, treatment will then be re-initiated and continued until a PGA of 0 is observed. This treatment and re-treatment pattern of use will be continued until the end of the study (i.e., subjects may receive study treatment up until the Week 40 visit).

Subjects who experience suspected disease worsening between scheduled study visits may contact the study site to arrange an unscheduled visit (Section 7.5). **See Disease Worsening (PGA≥2) During the Study** (Section 5.1.5.2) for further instructions. Upon confirmation of disease worsening, subjects will restart treatment with study drug.

5.1.5.2. Disease Worsening (Physician Global Assessment Score ≥ 2) During the Study

If disease worsening is suspected between scheduled study visits, an unscheduled visit may be performed.

- If disease worsening (ie, PGA ≥ 2) is not confirmed, the subject will continue to be assessed at routine, scheduled visits (see Table 1).
- For each confirmed episode of disease worsening (ie, PGA ≥ 2) during the study (at either a scheduled or unscheduled visit), a treatment course of tapinarof cream (once daily) will be initiated and will continue until the subject achieves a PGA 0, as assessed at scheduled visits, approximately every 4 weeks (see Table 1).
- Subjects subsequently achieving a PGA of 0 will stop study drug and will then be assessed at routine, scheduled visits (see
- Table 1). Subjects who then experience suspected disease worsening between scheduled study visits may contact the study site to arrange an unscheduled visit (see
- Table 1).
  - If disease worsening is not confirmed, the subject will continue to be assessed at routine, scheduled visits.
  - If disease worsening is confirmed (ie, PGA ≥ 2) at either an unscheduled or a scheduled visit, subjects will initiate another treatment course of tapinarof cream (once daily) until a PGA 0 is achieved as described above.
- This treatment and re-treatment pattern of use will be continued until the end of the study (ie, subjects may receive study treatment up until the Week 40 visit).

5.1.5.3. Application of Study Drug

Study drug will be dispensed to subjects requiring treatment at the study visits specified in the Schedule of Assessments (

Table 1).

Subjects will take the tubes home and self-administer (or have a caregiver apply if necessary), except on study 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:

- For subjects with a PGA > 0, once daily application to affected areas including those areas treated in the pivotal study; subjects are to choose the application time they prefer and to apply the study drug at that time each day of study participation.
- Subjects with a PGA of 0 will not receive treatment but if they worsen and experience a PGA of ≥ 2, apply once daily to newly affected areas only.
- 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 study visit days, study drug should be applied in the clinic under the supervision of site personnel and after safety assessments have been completed
  NOTE: The time of the dose and assessments on study visit days will depend on the time of the study visit (either morning or afternoon visit). Therefore, the timing of the study visit may differ from the subject's chosen dosing time (morning or evening); if

this occurs, it should not be recorded as a protocol deviation and the subject should resume their chosen dosing time following any such study visit. The intention is to allow flexibility to accommodate subjects' schedules.

5.2. Randomization/Treatment Assignment

All subjects will receive treatment with tapinarof cream, 1% as needed per protocol.

5.3. Blinding

This study is an open-label study; blinding is not applicable.

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 in this extension study. Additionally, subjects will be asked to complete a daily diary with the time of each application of study drug. At each postbaseline 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.

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, 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 study 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 redispensed to study subjects at the current visit. Unopened tubes may only be dispensed one time. Opened, partially used tubes, or tubes with foil overlay removed are not to be redispensed to study subjects. If there is any question as to redispensation, 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. 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

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 study or discontinuation, and that the medication is not a prohibited medication as described in Section 5.6.2. 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 active treatment courses and should not be applied on the morning of study 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 (>5000 IU / day), retinoids (e.g., acitretin, isotretinoin), psoralens, corticosteroids, or adrenocorticotropic hormone analogs
- **Ultraviolet light:** therapy or prolonged exposure to natural or artificial sources of UV radiation (e.g., phototherapy, tanning beds/booths, or therapeutic sunbathing)
- **Topical treatments:** corticosteroids, antihistamines, immunomodulators, anthralin (dithranol), Vitamin D derivatives (e.g., calcipotriene, calcipotriol), retinoids (e.g., tazarotene), or coal tar
- **Drugs known to possibly worsen psoriasis (unless on a stable dose for >12 weeks):** beta blockers (e.g., propranolol), lithium, iodides, angiotensin-converting enzyme inhibitors, and indomethacin
- **Immunizations:** live, attenuated vaccines (inactivated or subunit vaccines are acceptable when required)
- **Other:** any Investigational products or procedures

6. STUDY ASSESSMENTS AND PROCEDURES

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

6.1. Medical History and Demography

6.1.1. Medical History

Medical, medication, and family history collected during the pivotal study will be used for this study.

6.1.2. Demographics

The demographic information collected during the pivotal study will be used for this study, including: age, sex, race, and ethnicity.

6.2. Efficacy Assessments

To minimize interobserver 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 by Investigator

6.2.1.1. Physician Global Assessment

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 6.2.1.2). Variations of the PGA are frequently used in clinical studies because it is a simple assessment that is more similar to the assessments actually used in clinical practice (see Appendix 1 for details). The PGA should be performed first, prior to %BSA, PASI, and LTS assessments.

6.2.1.2. Body Surface Area

The assessment of the %BSA 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 2). Percentage BSA is a static assessment made without reference to previous scores.

Note: 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 not be included in 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. See Appendix 2.

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 Appendix 3. For additional information, refer to the Study Reference Manual.

6.2.2.2. Patient Satisfaction Questionnaire

Subjects will complete the Patient Satisfaction Questionnaire. The Patient Satisfaction Questionnaire is provided in Appendix 5.

6.2.3. Optional Clinical Photography

Clinical photography may be performed in a subgroup of subjects at selected study centers that participated in photography in the pivotal study. This is not required of subjects for participation

in the study. Informed consent 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 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. Adverse events that began during the pivotal study and were ongoing at the end of that study will be reported as ongoing AEs. Additional safety information, including the definition of an AE and the methods for recording, evaluating, and assessing causality of AEs and the procedures for completing and transmitting SAE reports are provided in Section 8.

6.3.2. Brief Physical Examination

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). 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 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.

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 Protocol Schedule of Assessments. 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 virus • Anti-HBc	• Pregnancy tests: (urine; 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	• <u>RBC Indices</u>: MCV MCH MCHC Reticulocyte percentage	• <u>WBC Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Urinalysis		
• Specific gravity • Microscopic examination (if blood or protein is abnormal	• <u>Dipstick:</u> 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; GGT = gamma-glutamyltransferase; 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 and if the subject is receiving study drug, 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 4). The score will ideally represent an 'average' across all application sites. To the fullest extent possible, the same Investigator (or designated evaluator) will perform all tolerability assessments for an individual subject throughout the study. If the subject is applying study treatment to "sensitive areas" (e.g., 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 if receiving study drug, the subject 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 ingestion of the study drug is considered an overdose. Ingestion of a 30-gram tube of 1% cream would result in an oral dose of 300 mg.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator (or treating physician) should:

- Contact Medical Monitor to discuss the event
- In the event of excessive topical application, instruct the subject to wash study drug off of the skin and monitor for application-site AEs.
- Monitor subject for systemic AEs/SAEs and clinically significant laboratory abnormalities.
- Obtain blood sample within 2 days from the date of last application of study drug or date of ingestion to determine possible systemic exposure to study drug (if requested by the Medical Monitor; determined on a case-by-case basis)
- Provide general symptomatic treatment as necessary
- Document quantity of excess dose (e.g., by weighing the tube of cream) and duration of exposure, in the eCRF.

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

6.5. Pharmacokinetics/Pharmacodynamics

Pharmacokinetics/pharmacodynamics will not be performed in this study.

7. TIMING OF PROCEDURES AND ASSESSMENTS

This section lists the procedures and assessment to be performed at scheduled timepoints during the study as outlined in the Schedule of Assessments (

Table 1). Information on study procedures and assessments is provided in Section 6.

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

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

7.1. Visit 1; Baseline

On Day 1, subjects from the pivotal studies who were considered eligible for this study will sign the ICF and be reassessed to confirm eligibility to participate in this study. All subjects who continue to meet study eligibility criteria will be enrolled. Subjects entering with a PGA ≥ 1 will receive treatment with tapinarof cream, 1% until they achieve a PGA score of 0, at which time treatment will be discontinued and subjects monitored for durability of response. If/when disease worsening occurs, as evidenced by a PGA ≥ 2, treatment will then be re-initiated and continued until a PGA of 0 is observed. Subjects entering with a PGA of 0 will have treatment discontinued and be monitored for durability of response

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

- Brief physical exam (last assessment from pivotal study)
- Vital signs measurements (last assessment from pivotal study)
- Urine pregnancy test (females of CBP; last assessment from pivotal study)
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests; last assessment from pivotal study)
- Urinalysis
- Photography of a representative area of the subject's disease area (optional for subjects; at a subset of study centers) (last assessment from pivotal study)
- PGA score (last assessment from pivotal study)
- BSA affected calculation (last assessment from pivotal study)
- PASI (last assessment from pivotal study)
- DLQI (last assessment from pivotal study)
- AE recording (Including any ongoing AEs from the pivotal study and from the time the ICF is signed)
- Concomitant medication recording (from the time ICF is signed)
- Diary dispensed (subjects will be instructed in how and when to complete diary), if applicable
- Dispense study drug, if applicable

- Instruction on how to apply study drug, if applicable
- Study drug application under supervision, if applicable

7.2. Visits 2 to 10; Treatment Period

Subjects entering with a PGA ≥ 1 will receive treatment with tapinarof cream, 1% until they achieve a PGA score of 0, at which time treatment will be discontinued and subjects monitored for durability of response. If/when disease worsening occurs, as evidenced by a PGA ≥ 2, treatment will then be re-initiated and continued until a PGA of 0 is observed. Subjects entering with a PGA of 0 will have treatment discontinued and be monitored for durability of response. If/when disease worsening occurs, as evidenced by a PGA ≥ 2, treatment will then be re-initiated and continued until a PGA of 0 is observed. Subjects will return to the study site at least every 4 weeks (±3 Days) during the 40-week monitoring period. The following assessments will be performed:

- Brief physical exam
- Vital signs measurements
- Urine pregnancy test (females of CBP)
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests); Weeks 4, 12 only
- Photography of a representative area of the subject's disease area (optional for subjects; at a subset of study centers)
- PGA score
- BSA affected calculation
- PASI
- LTS (if patient has been applying study drug for the treatment period prior to the scheduled visit)
- DLQI
- AE recording
- Concomitant medication recording
- Collect and dispense diary, if applicable (subjects will be instructed in how and when to complete diary)
- Review diary for treatment compliance, if applicable
- Dispense and collect study drug, if applicable
- Instruction on how to apply study drug, if applicable
- Study drug application under supervision, if applicable

7.3. Visit 11;

The following procedures and assessments will be performed at the Week 40 Visit:

- Brief physical exam
- Vital signs measurements

- Urine pregnancy test (females of CBP)
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- Photography of a representative area of the subject's disease area (optional for subjects; at a subset of study centers)
- PGA score
- BSA affected calculation
- PASI
- LTS (if patient has been applying study drug for the treatment period prior to the scheduled visit)
- DLQI
- Patient Satisfaction Questionnaire
- AE recording
- Concomitant medication recording
- Collect diary, if applicable
- Review diary for treatment compliance, if applicable
- Collect study drug, if applicable

7.4. Follow-up Visit

Subjects will return to the study site 4 weeks (±3 days) after last treatment to complete follow-up assessments as follows:

- Brief physical exam
- Vital signs measurements
- Urine pregnancy test (females of CBP)
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- Photography of a representative area of the subject's disease area (optional for subjects; at a subset of study centers)
- PGA score
- BSA affected calculation
- PASI
- DLQI
- AE recording
- Concomitant medication recording

7.5. Phone Contact at Week 2 (Day 15 ±3 Days)

Subjects will be contacted by Phone at Week 2 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 study visit.

7.6. Unscheduled Visits

Unscheduled visits may occur, as needed. For subjects who experience suspected disease worsening (PGA ≥ 2) between scheduled study visits may contact the study site to arrange an unscheduled visit (see Section 5.1.5.2). The following assessments will be performed:

- Brief physical exam
- Vital signs measurements
- Urine pregnancy test (females of CBP), as needed
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests), as needed
- Urinalysis, as needed
- Photography of a representative area of the subject's disease area (optional for subjects; at a subset of study centers)
- PGA score
- BSA affected calculation
- PASI
- LTS (if patient has been applying study drug for the treatment period prior to the scheduled visit)
- AE recording
- Concomitant medication recording
- Collect and dispense diary, if applicable (subjects will be instructed in how and when to complete diary)
- Review subject diaries for treatment compliance, if applicable
- Collect and dispense study drug (if applicable)
- Instruction on how to administer study drug (if applicable)
- Study drug administration under supervision (if applicable)

If disease worsening is confirmed, a new treatment course will be initiated.

7.7. Early Termination

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

- Brief physical exam
- Vital signs measurements
- Urine pregnancy test (females of CBP)

- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- Photography of a representative area of the subject's disease area area (optional for subjects; at a subset of study centers)
- PGA score
- BSA affected calculation
- PASI
- LTS (if patient has been applying study drug for the treatment period prior to the scheduled visit)
- DLQI
- Patient Satisfaction Questionnaire
- AE recording
- Concomitant medication recording
- Collect and review subject diaries for treatment compliance
- Collect study drug

7.8. End of Study

The end of the study is defined as when the last active subject has completed the Follow-up Visit (Week 44).

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 event of special interest (AESI). At each visit/contact, subjects should be questioned in a general way so as not to introduce bias in detecting AEs and/or SAE. 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 would 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 that meet the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry) or other safety assessments (e.g., vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the Investigator
- Exacerbation of a chronic or intermittent pre-existing condition (e.g., 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 medication, 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 (e.g., burning/stinging, pruritus, erythema)

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

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

8.1.2. Definition of Serious Adverse Event

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

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

- Results in death
- Is life-threatening
  - The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; 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, this 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 out-patient setting. Complications that occur during hospitalization are AEs.
    If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious
    Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in disability/incapacity: a substantial disruption of a person's ability to conduct normal life functions
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (e.g., sprained ankle), which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Results in a congenital anomaly/birth defect
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.1.3. Adverse Events of Special Interest

In prior clinical studies, 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, and study drug may be restarted when 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 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

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 Adverse Event Severity

The Investigator will make an assessment of the severity of each AE and SAE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), v. 5.0, 2017. For terms not specified with the CTCAE, the criteria in Table 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 study drug at the discretion of the Investigator. Subjects who choose to withdraw from study due to a Grade 1 or 2 AE should have 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 study drug, 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 study drug should have the study drug discontinued. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of study drug should be followed weekly until resolution or stability of the AE and encouraged to have withdrawal study evaluations completed.

8.2.1.2.3. Grade 4 Adverse Event

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

Subjects experiencing Grade 4 AEs requiring permanent discontinuation of study drug should be followed weekly until resolution or stability of the AE and encouraged to have 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 (e.g., laboratory tests or vital signs, etc.) as judged by the Investigator

8.2.2. Assigning Causal Relationship to Study Drug

An Investigator is to make the causality assessment. Causality assessment may only be delegated to a Principal Investigator or Sub-Investigator; however, if it is delegated to any other staff, 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 readministration (rechallenge) with or withdrawal (dechallenge) from study drug, although information on drug withdrawal may be lacking or unclear
- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation

Any AEs/SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to study drug will be collected from the time a subject consents 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 adverse event, the primary reason for withdrawal (e.g., due to an adverse event) 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 (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) will be collected from the time a subject consented to participate in the study up to and including any follow-up contact.

All SAEs will be recorded in the 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 all 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 noninterventional postmarketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

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

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

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

8.5. Pregnancy Management and Reporting

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

If a pregnancy is reported, then the Investigator should complete a Pregnancy Report Form and submit via email or fax to the Pregnancy Reporting Contact 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 Sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the Sponsor or designee.

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

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 (WHODrugGlobal).

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

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

This study is intended to show that tapinarof cream has a favorable safety and efficacy profile during repeated, intermittent treatment courses over an extended period of time.

10.1. General Considerations

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

10.2. Determination of Sample Size

The sample size of this study is based on the ICH E1 guideline on extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions. An estimated 850 subjects who complete Study DMVT-505-3001 or Study DMVT-505-3002 will be enrolled in this study across all regions. A high discontinuation rate is anticipated in this long-term extension study. Approximately 300 subjects are expected to complete the study (40 weeks of treatment).

10.3. Analysis Populations

All subjects enrolled into the study will be included in the intent-to-treat (ITT) analysis set.

10.4. Planned Analyses

All efficacy and safety measures over the course of the study will be presented. All analyses will be based on the ITT population. Details of planned analyses will be described in the Statistical Analysis Plan (SAP), which will be finalized prior to database lock.

10.4.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized and include frequency and percentages for categorical variables and mean, SD, median, minimum, and maximum for continuous variables.

10.4.2. Efficacy Analyses

All efficacy analyses will be performed based on the ITT analysis set as described above. Summaries will be presented by original treatment group assigned in the pivotal studies and overall. Summaries of efficacy endpoints by visit will be performed using observed cases (OC) and last observation carried forward (LOCF) methods.

Efficacy endpoints are as follows:

- Proportion of subjects who experience a PGA ≥ 2 at least 1 time in the study and the median time from baseline to first worsening (PGA ≥ 2) for subjects entering the study with a PGA score of clear (0)

- Proportion of subjects who achieve a PGA score of 0 at least 1 time in the study [redacted]
- Duration of each treatment episode, defined as time from each treatment initiation/re-initiation to each subsequent treatment success (PGA score of 0).
- [redacted]
- Proportion of subjects who never achieve a PGA ≥ 2 throughout the study
- Proportion of subjects who never achieve a PGA score of 0 or 1 throughout the study
- [redacted]
- Change and percent change from baseline in %BSA affected by visit (OC and LOCF)
- Change and percent change in PASI score by visit (OC and LOCF)

For analyses of time to event, such as the time to worsening (PGA ≥ 2) or the time to reaching a PGA score of 0, Kaplan-Meier product limit method will be used to estimate the median time (if estimable). If the median is not estimable (e.g., < 50% of subjects reach the event), other methods for estimating the median and/or other percentiles will be applied.

The remaining efficacy 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 number and percent of subjects with TEAEs will be summarized by system organ class and preferred term for all TEAEs, all TEAEs considered by the Investigator to be related to study drug, all SAEs, and all TEAEs leading to study drug discontinuation. All adverse event summaries will include information for adverse events 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 adverse event and for subjects with an SAE.

Selected clinical laboratory data will be analyzed using descriptive summary statistics, including the number of nonmissing 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

Descriptive statistics will be performed on the subject-reported endpoint to examine the effect of study drug on psoriasis symptom severity and the associated impact on daily activities and attitudes as follows:

Change in disease impact on daily activities, as measured by the subject-reported DLQI total and individual dimension scores

10.4.5. Analysis of Patient Satisfaction Questionnaire

Responses for each question of the Patient Satisfaction Questionnaire will be summarized by visit.

10.5. Interim Analyses

A data-cut will be made at the time of preparation of the marketing application to present interim results; the final analysis will be conducted after study completion (e.g., the last subject's last visit).

10.6. Handling of Missing Data

Summaries of efficacy endpoints by visit will be performed using observed cases (OC) and last observation carried forward (LOCF) methods.

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), 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 (US) 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 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 (e.g., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The Investigator must keep a screening log showing codes, names, and addresses for all Subjects screened and for all subjects enrolled in the trial.

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

11.1.5. Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 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 the following for each subject:

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, e.g., 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 date (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 date, 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 (e.g., US, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements (e.g., 25 years in Canada), 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 the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

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

11.1.6. Electronic Case Report Forms

For each Subject enrolled, an eCRF must be completed and signed by the Principal 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 (e.g., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational medicinal product, vehicles, and comparators. 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 CRFs for consistency.

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

11.3.2. Access to Information for Auditing or Inspections

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

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

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

11.3.3. Study Discontinuation

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

12. REFERENCES

Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY Dermatology. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data.2015;230(1):27-33.

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International Conference on Harmonisation, Guideline for the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions. 1994. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf.

Mason AR, Mason J, Cork M, Dooley G, Hancock H. Topical treatments for chronic plaque psoriasis. Cochrane Database of Systematic Reviews. 2013;(3):CD005028. doi: 10.1002/14651858.CD005028.pub3.

Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2012;133:377-385.

Zoetis T and Hurtt ME. Species comparison of anatomical and functional renal development. Birth Defects Research Part B. 2003;68:111-120.

13. APPENDICES

APPENDIX 1. PHYSICIAN GLOBAL ASSESSMENT

Each assessment should be made as a visual 'average' of the severity of all treated areas at the time of the assessment. 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, subject symptoms, or impact on subject'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

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

APPENDIX 2. CALCULATION OF PERCENT BODY SURFACE AREA (%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: 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 not be included in the efficacy analyses.

Complete the %BSA assessment before the PASI.

Calculation of %BSA Affected:

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

Estimate the involved regional area by determining the number of "full" handprints plus the number of handprints covered if several smaller 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%) column from 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 <u>each of the 4</u> 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

			Body Area			
Item	**Assessment**		**Head/Neck**	**Upper extremities (arms)**	**Trunk (to groin)**	**Lower extremities (leg to top of buttocks)**
1	Erythema (redness)	(0-4)				
2	Induration (thickness)	(0-4)				
3	Scale (desquamation)	(0-4)				
4	**Sum of Items 1, 2, and 3**	(0-12)				
5	Area Score	(0-6)				
	Area Multiplier		0.1	0.2	0.3	0.4
6	Score of (Item 4) x (Item 5) x (Area Multiplier)		Item 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 3. 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**? If "No", over the last week how much has your skin been a problem at **work** or **studying**?	Yes ☐ No ☐ A lot ☐ A little ☐ Not at all ☐	 Not relevant ☐
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 4. 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. The score will ideally represent an 'average' across all application sites. To the fullest extent possible, the same investigator (or designated evaluator) will perform all tolerability assessments for an individual subject throughout the study.

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

Local Tolerability – 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 subject will use a 5-point tolerability scale 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 5. PATIENT SATISFACTION QUESTIONNAIRE

You are being asked the below questions to better understand how you feel about the cream medication (study drug) you used to treat your psoriasis in this study and how it compares to other medications you have used to treat your psoriasis in the past. When answering each question, think about the cream medication (study drug) that you have been using as a patient in this study. Please circle the answer that most closely matches how you feel.

1. **I can easily manage my psoriasis with the study drug**
   Strongly Agree Agree Neutral Disagree Strongly Disagree

2. **The time spent applying the study drug every day was acceptable and did not affect my everyday life**
   Strongly Agree Agree Neutral Disagree Strongly Disagree

3. **I am satisfied with how well the study drug worked for my psoriasis**
   Strongly Agree Agree Neutral Disagree Strongly Disagree

4. **I have confidence in the study drug**
   Strongly Agree Agree Neutral Disagree Strongly Disagree

5. **The study drug cleared my skin and kept my psoriasis from coming back**
   Strongly Agree Agree Neutral Disagree Strongly Disagree

6. **If the study drug was available by prescription, I would recommend it to other patients with psoriasis**
   Strongly Agree Agree Neutral Disagree Strongly Disagree

7. **If the study drug was available by a prescription, I would use it again or continue on it**
   Strongly Agree Agree Neutral Disagree Strongly Disagree

8. **The study drug is easy to apply**
   Strongly Agree Agree Neutral Disagree Strongly Disagree

9. **The study drug is not greasy**
   Strongly Agree Agree Neutral Disagree Strongly Disagree

10. **The study drug quickly absorbs into my skin**
    Strongly Agree Agree Neutral Disagree Strongly Disagree

11. **The study drug feels good on my skin**
    Strongly Agree Agree Neutral Disagree Strongly Disagree

12. **I am satisfied with the look and feel of the study drug**
    Strongly Agree Agree Neutral Disagree Strongly Disagree

The below questions # 13-18 are comparing the study drug to other drugs you have used to treat your psoriasis in the past. When answering these questions, think about how this study drug compares to those other drugs you have used.

A topical drug is a drug that is applied to the skin like creams, ointments, lotions, gels, foams, sprays. A systemic drug is a drug that is taken by mouth like a capsule or tablet or injected through the skin with a needle like a shot or through a vein by a healthcare practitioner.

Have you used other topical drugs to treat your psoriasis in the past? Yes/no. If yes, please answer questions 13-15. If no, please go to question 16.

13. **The study drug is more effective than other topical drugs I have used to treat my psoriasis**
    Strongly Agree Agree Neutral Disagree Strongly Disagree

14. **The study drug is easier to use than other topical drugs I have used to treat my psoriasis**
    Strongly Agree Agree Neutral Disagree Strongly Disagree

15. **I prefer the study drug to other topical drugs I have used to treat my psoriasis**
    Strongly Agree Agree Neutral Disagree Strongly Disagree

Have you used systemic drugs to treat your psoriasis in the past? Yes/no. If yes, please answer the following questions. If no, that is the end of the questionnaire.

16. **The study drug is more effective than systemic drugs I have used to treat my psoriasis**
    Strongly Agree Agree Neutral Disagree Strongly Disagree

17. **The study drug is easier to use than systemic drugs I have used to treat my psoriasis**
    Strongly Agree Agree Neutral Disagree Strongly Disagree

18. **I prefer the study drug to systemic drugs I have used to treat my psoriasis**
    Strongly Agree Agree Neutral Disagree Strongly Disagree

Thank you very much for your participation in this clinical study and questionnaire.

APPENDIX 6. PROTOCOL AMENDMENT SUMMARY OF CHANGES

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

ABBREVIATIONS

Added LOCF (Last Observation Carried Forward). Added OC (Observed Cases); Updated WHODrugGlobal to WHO (World Health Organization)

SYNOPSIS

Added statement on use of rescue medication.

Inclusion criteria: revised contraception language for clarity.

The following efficacy study endpoints were **added**:

- Proportion of subjects who experience a PGA ≥ 2 at least 1 time in the study and the median time from baseline to first worsening (PGA ≥ 2) for subjects entering the study with a PGA score of clear (0)
- Proportion of subjects who achieve a PGA score of 0 at least 1 time in the study and the median time from baseline to first achieving a PGA score of 0 for subjects entering the study with a PGA score ≥ 1
- Duration of each treatment episode, defined as time from each treatment initiation/re-initiation to each subsequent treatment success (PGA score of 0).
- Duration of each treatment success (PGA score of 0) to each subsequent worsening (PGA ≥ 2)
- Proportion of subjects who never achieve a PGA ≥ 2 throughout the study
- Proportion of subjects who never achieve a PGA score of 0 or 1 throughout the study
- Proportion of subjects who never achieve a PGA score of 0 throughout the study
- PGA scores by visit (OC and LOCF)
- Change and percent change from baseline in %BSA affected by visit (OC and LOCF)
- Change and percent change in PASI score by visit (OC and LOCF)

The following study endpoints were **deleted**:

- Median time from each treatment success (PGA 0 or 1) to each subsequent worsening (PGA ≥ 2)
- Proportion of subjects who have a PGA score of clear (0) after treatment
- Proportion of subjects who have a PGA score of clear (0) or almost clear (1) after treatment
- Proportion of subjects who do not experience disease worsening (PGA ≥ 2)
- Change over time in percent of %BSA affected
- Mean duration of each treatment course
- Percent change over time in PASI score

The statistical method section was updated for clarification as follows:

All study data will be summarized **overall and** by treatment group **in the pivotal studies** using descriptive statistics using the intent-to-treat (ITT) analysis set of subjects.
The Kaplan-Meier product limit method will be used to estimate the median time (if estimable) from baseline to first disease worsening **and first disease success** ~~(PGA≥2)~~.

Duplicative section of Duration of Treatment was deleted

Table 1. Schedule of Assessment

Addition of clinical photography, as applicable at Visits 1-11. Removal of diary and study drug assessments for phone call check at Week 2. Removal of study drug application at the last visit (Week 40). Correction of footnote on disease worsening. LTS assessments completed by Investigator and Subject were removed for the Baseline Visit (Visit 1). Footnote i. was updated to include: This assessment is only required to be completed if the subject was applying study drug. Update to footnotes g-m to accommodate photography addition. Added Patient Satisfaction Questionnaire at Visit 11.

Section 1.1 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).

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

Section 2. Objectives and Endpoints

The following safety and tolerability endpoint was added to this section for consistency with other sections within this protocol: Mean scores by visit from LTS

The following efficacy endpoints were **added**:

- Proportion of subjects who experience a PGA ≥ 2 at least 1 time in the study and the median time from baseline to first worsening (PGA ≥ 2) for subjects entering the study with a PGA score of clear (0)
- Proportion of subjects who achieve a PGA score of 0 at least 1 time in the study and the median time from baseline to first achieving a PGA score of 0 for subjects entering the study with a PGA score ≥ 1
- Duration of each treatment episode, defined as time from each treatment initiation/re-initiation to each subsequent treatment success (PGA score of 0).

- Duration of each treatment success (PGA score of 0) to each subsequent worsening (PGA ≥ 2)
- Proportion of subjects who never achieve a PGA ≥ 2 throughout the study
- Proportion of subjects who never achieve a PGA score of 0 or 1 throughout the study
- Proportion of subjects who never achieve a PGA score of 0 throughout the study
- PGA scores by visit (OC and LOCF)
- Change and percent change from baseline in %BSA affected by visit (OC and LOCF)
- Change and percent change in PASI score by visit (OC and LOCF)
- Change in disease impact on daily activities, as measured by the DLQI total and individual dimension scores

The following study endpoints were **deleted**:

- Median time from each treatment success (PGA 0 or 1) to each subsequent worsening (PGA ≥ 2)
- Proportion of subjects who have a PGA score of clear (0) after treatment
- Proportion of subjects who have a PGA score of clear (0) or almost clear (1) after treatment
- Proportion of subjects who do not experience disease worsening (PGA ≥ 2)
- Change over time in percent of %BSA affected
- Mean duration of each treatment course
- Percent change over time in PASI score

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)

Added statement on use of rescue medication.

Section 4.2 Inclusion Criteria

Revised contraception language for clarity.

Section 5.1.5. Administration of Study Drug

Provided clarification on application to affected areas for those entering with a PGA score of 0 or > 0.

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 5.4

Clarified that unopened tubes may only be dispensed one time.

Section 5.6 Prior and Concomitant Therapy

Removed wording on collection of concomitant medication for 30 days prior to the baseline visit as these medications will already being collected as part of the prior pivotal study.

Section 6.2.1.1. Physician Global Assessment

Corrected typographical error: higher PGA scores represent more severe disease.

Section 6.2.2.2 patient Satisfaction Questionnaire

Added that subjects will complete the Patient Satisfaction Questionnaire and referenced Appendix 5.

Section 6.2.3. Optional Clinical Photography

Clinical photography may be performed in a subgroup of subjects at selected study centers that participated in photography in the pivotal study. This is not required of subjects for participation in the study. Informed consent 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 Photography Manual.

Section 6.3.5 Local Tolerability Scale

Clarified that the LTS will only be completed by those subjects who are receiving study drug.

Section 7.1 Visit 1; Baseline

Added photography of a representative area of the subject's disease area (optional; at a subsection of study centers) (last assessment from pivotal study)

Removed ~~LTS (last assessment from parent study)~~

Section 7.2 Visits 2 to 10~~1~~; Treatment Period

The title of the section was updated to accurately reflect the visits. Added Photography of a representative area of the subject's disease area (optional; at a subsection of study centers)

Section 7.3 Visit 11

This section was added, as the Patient Satisfaction Questionnaire is now included.

Section 7.4 Phone Contact at Week 2 (Day 15±3 Days)

The title of this section was renumbered to Section 7.5

Section 7.5 Unscheduled Visits

The title of this section was renumbered to Section 7.6. Added photography of a representative area of the subject's disease area (optional; at a subsection of study centers). Correction made to remove the requirement for a study visit. "If disease worsening is confirmed, a new treatment course will be initiated~~, and the subject will be scheduled to return to the study site after 2 weeks~~."

Section 7.6 Early Termination

The title of this section was renumbered to Section 7.7. Added the Patient Satisfaction Questionnaire.

Section 7.7 End of Study

The title of this section was renumbered to Section 7.8.

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).

Section 8.1.3. Adverse Events of Special Interest

Changed wording to state that "study drug ~~will~~ **may** be discontinued, and study drug may be restarted when event resolves", if a subject has an adverse event of special interest

Section 8.2.2 Assigning Causal Relationship to Study Drug

Updated to allow Principal Investigator to delegate causality assessment to sub-Investigators. Changed wording to state that "Causality assessment may only be delegated to a Principal Investigator or Sub-Investigator;"

Section 10.4.2. Efficacy Analyses

Updated with revised efficacy endpoints described in the synopsis and Section 2.

Section 10.4.5. Analysis of Patient Satisfaction Questionnaire

Statistical analysis of the Patient Satisfaction Questionnaire was added.

Section 10.6 Handling of Missing Data

Section updated as follows: ~~Missing data will not be imputed~~. **Summaries of efficacy endpoints by visit will be performed using observed cases (OC) and last observation carried forward (LOCF) methods**.

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

In addition, the Area Score has been shaded and will be auto-calculated in the eCRF.

Appendix 5. Patient Satisfaction Questionnaire

New appendix added with example questions.