Protocol Title:

A Phase 4, open-label study to investigate the efficacy and safety of VTAMA® (tapinarof) cream, 1% in the treatment of plaque psoriasis occurring in the head and neck region

Protocol Number: DMVT-505-4002

Product: VTAMA (tapinarof) cream, 1%

Brief Title:

A study to investigate efficacy and safety of VTAMA® (tapinarof) cream, 1% in plaque psoriasis in the head and neck region

Study Phase: 4

Sponsor Name: Dermavant Sciences, Inc.

Legal Registered Address: 3300 Paramount Parkway, Suite 150, Morrisville, NC, USA 27560

Regulatory Agency Identifier Number(s): IND 104601

Approval Date: 01 Nov 2022

eSignature Approval

[redacted] 01 Nov 2022

[redacted] Date Signed:

[redacted]

This protocol has been approved by a representative of Dermavant Sciences, Inc. This electronic signature is legally binding equivalent of traditional handwritten signatures and is captured in the audit trail of the document.

Medical Monitoring

Medical Monitor contact information can be found in the Study Reference Manual.

Serious Adverse Event (SAE)/Pregnancy should be reported to the North American Safety Mailbox:

[redacted]

Study Sponsor

This study is sponsored by Dermavant Sciences, Inc.

Sponsor Registered Address and Regulatory Contact

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

Table of Contents

[redacted]

List of Tables

List of Abbreviations

Term	Description
AE	adverse event
BSA	body surface area
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
[redacted]	[redacted]
eCRF	electronic case report form
CRF	case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HRT	hormonal replacement therapy
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IND	Investigational New Drug application
IRB	institutional review board
ITT	intent-to-treat
IU	international units
[redacted]	[redacted]
OC	observed case
[redacted]	[redacted]
PGA	Physician Global Assessment
[redacted]	[redacted]
PSO	psoriasis
QD	once daily
SAE	serious adverse event
SoA	schedule of activities
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
USA	United States of America
USPI	United States Prescribing Information
UV	ultraviolet
WOCBP	woman of childbearing potential
WONCBP	woman of nonchildbearing potential

1 Protocol Summary

1.1 Synopsis

Protocol Title: A Phase 4, open-label study to investigate the efficacy and safety of VTAMA® (tapinarof) cream, 1% in the treatment of plaque psoriasis occurring in the head and neck region

Brief Title: A study to investigate efficacy and safety of VTAMA® (tapinarof) cream, 1% in plaque psoriasis in the head and neck region

Regulatory Agency Identifier Number(s):

IND	104601

Rationale:

Plaque PSO in the head and neck region occurs commonly and is often underdiagnosed (Merola 2016). Scalp involvement occurs in 45% to 56% of individuals with PSO and facial PSO typically presents at a younger age and is estimated to affect nearly 50% of patients with PSO (Bagel 2018; Merola 2018). The majority of patients with facial PSO also have scalp involvement (Dopytalska 2018). Scalp PSO can cause patients to feel embarrassed and self-conscious. Facial PSO can be even more devastating because it cannot be hidden with clothing. Despite the small surface area affected, disease in this area can result in considerable psychosocial challenges that are not captured by traditional scoring systems.

Topical corticosteroids are often used to treat plaque PSO in the head and neck region; however, due to the safety profile their use is limited to only short-term therapy. Other topical therapies such as vitamin D analogs offer better safety profiles, but with moderate efficacy. The use of any topical treatment in this area presents challenges because application may be burdensome or cosmetically unacceptable (Mosca 2021). Because many commonly used topical agents are not embraced by patients for use in this area due to lack of tolerability and cosmetic acceptability, lack of adherence is an issue that compounds the lack of efficacy and poor safety profiles associated with these therapies. Systemic treatment, such as biologics and oral therapy, is reserved for the more severe and resistant cases due to the more severe adverse effects and cost associated with these agents (Beck 2018). Dermavant has developed an effective, steroid-free, locally acting, cosmetically elegant topical therapy that is safe and tolerable and offers patients the opportunity for a treatment-free remittive period. Application of the product to plaque PSO in the head and neck region was permitted in the Phase 3 registrational trials to assess tolerability, but efficacy was not specifically evaluated in this region.

VTAMA (tapinarof) cream, 1% was approved by the FDA in May 2022 for the treatment of plaque PSO in adults. Tolerability in sensitive areas was excellent in Phase 3 pivotal studies and the long-term extension study for a total duration of up to 52 weeks (Lebwohl 2021; data on file). This study will further assess efficacy and safety of VTAMA (tapinarof) cream, 1% when used to treat head and neck PSO.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of VTAMA (tapinarof) cream, 1% in adults with plaque PSO in the head and neck region	• Percentage of participants who achieve a PGA (target lesion) score of clear (0) or almost clear (1) with a ≥ 2-grade improvement from Baseline at Week 12
Secondary	
• To assess onset of effect of VTAMA (tapinarof) cream, 1% in adults with plaque PSO in the head and neck region	• Time to achieve a PGA (target lesion) score of 0 or 1 with a ≥ 2-grade improvement from Baseline
[redacted]	
• [redacted]	• [redacted]
[redacted]	
• [redacted]	• [redacted]

Overall Design Synopsis:

Brief Summary:

The purpose of this open-label study is to evaluate the efficacy and safety of tapinarof cream, 1% in adults with plaque PSO occurring in the head and neck region. A target plaque PSO lesion in the head and neck region will be identified at Baseline, and efficacy of tapinarof will be assessed with a PGA evaluation. [redacted] Safety and tolerability will be assessed by evaluation of AEs [redacted]

VTAMA will be dispensed and will be administered at home between clinic visits as instructed by site personnel. Application instructions will be reviewed at all clinic visits during the study, except during the final treatment/end-of-study visits. Participants will be instructed to apply cream QD to all affected areas on the head and neck, including the target lesion. Cream should be applied to newly appearing areas on the head and neck as well as areas in this region that improve or clear during the study. Participants may apply cream to any other lesions on the body although efficacy will only be assessed at the target lesion (PGA) [redacted]. Participants will apply sufficient cream to cover completely each lesion with a thin layer of medication and will record the time of application in a daily diary provided by the study site. Participants will be instructed to maintain the approximate dosing time chosen at the beginning of the study for their full study participation.

Number of Participants:

Approximately 30 participants will be enrolled.

Note: Enrolled means participants agreement to participate in a clinical study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening.

Study Arms and Duration:

VTAMA (tapinarof) cream, 1% is a white to off-white cream containing 1% weight/weight (10 mg/g) tapinarof, supplied in 60-gram tubes. VTAMA is to be administered by the participant QD via topical application of a thin layer to affected areas in accordance with instructions in the USPI.

Dosing may be interrupted if deemed necessary by the Investigator for management of AEs.

Study duration:

- The study duration will be up to 17 weeks.
- The treatment duration will be up to 12 weeks.
- The follow-up period will be up to 1 week.

Statistical Methods

Efficacy, safety, [redacted] will be summarized for the ITT population.

Every effort will be made to collect complete data at all visits. All efficacy data will be summarized based on OCs. The primary and exploratory efficacy endpoints will also be summarized utilizing the last observation

carried forward method to impute missing data [redacted]

Efficacy and Safety Analyses

Demographics and baseline characteristics, efficacy, and all safety assessments [redacted] will be summarized descriptively, no statistical comparisons will be performed. Continuous data will be summarized by number of participants, mean, SD, median, minimum, and maximum, and categorical data will be summarized by frequency counts and percentages. The 95% confidence intervals will be reported as appropriate. Median time to event analyses will use the Kaplan-Meier product limit method (if estimable).

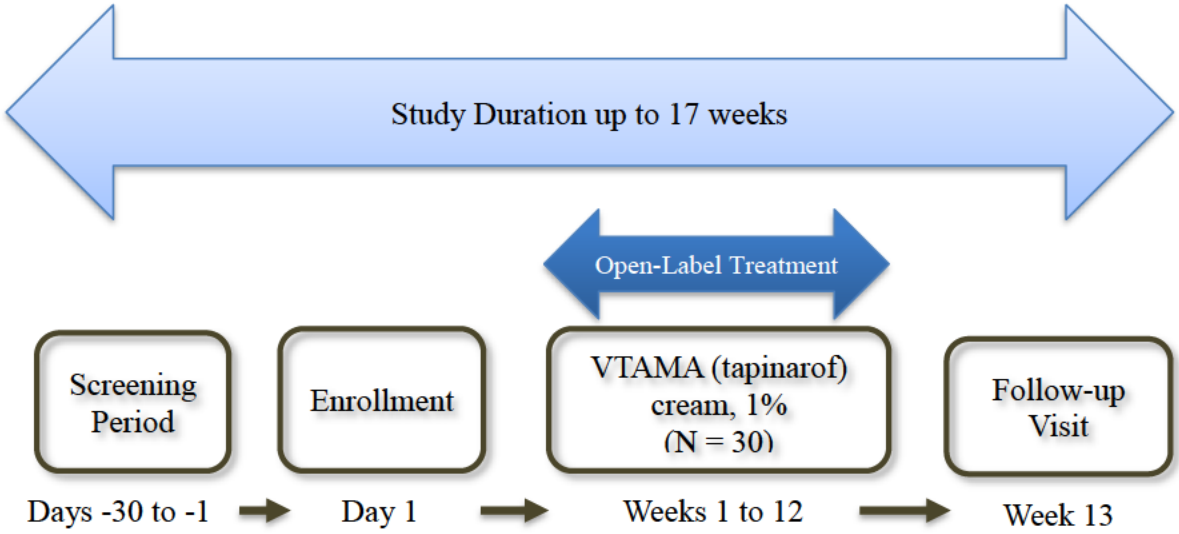
Determination of Sample Size

The sample size for this study is based on clinical considerations only. No formal sample size calculation will be performed. A total of 30 participants is planned for this study which is considered adequate to evaluate the efficacy and safety for the treatment of plaque PSO occurring in the head and neck region.

Data Monitoring/Other Committee:

No data monitoring committee has been appointed for this study.

1.2 Schema


Study Duration up to 17 weeks
Open-Label Treatment
Screening Period
Enrollment
VTAMA (tapinarof) cream, 1% (N = 30)
Follow-up Visit
Days -30 to -1
Day 1
Weeks 1 to 12
Week 13

1.3 Schedule of Activities

2 Introduction

VTAMA (tapinarof) cream, 1% was approved by the FDA in May 2022 for the treatment of plaque PSO in adults. Tolerability in sensitive areas, including the face, was excellent in Phase 3 pivotal studies and the long-term extension study for a total duration of up to 52 weeks (Lebwohl 2021; data on file).

2.1 Study Rationale

This study will further assess efficacy and safety of VTAMA (tapinarof) cream, 1% when used to treat PSO in the head and neck region.

2.2 Background

Occurrence in the head and neck region is common among patients with plaque PSO. Scalp involvement occurs in 45% to 56% of individuals with PSO, and facial PSO typically presents at a younger age and is estimated to affect nearly 50% of patients with PSO (Bagel 2018; Merola 2018). The majority of patients with facial PSO also have scalp involvement (Dopytalska 2018). Scalp PSO can cause patients to feel embarrassed and self-conscious. Facial PSO can be even more devastating because it cannot be hidden with clothing. Despite the small surface area affected, disease in this area can result in considerable psychosocial challenges that are not captured by traditional scoring systems.

Topical corticosteroids are often used to treat plaque PSO in the head and neck region; however, due to the safety profile, their use is limited to only short-term therapy. Other topical therapies such as vitamin D analogs offer better safety profiles but with moderate efficacy. The use of any topical treatment in this area presents challenges because application may be burdensome or cosmetically unacceptable (Mosca 2021). Because many commonly used topical agents are not embraced by patients for use in this area due to lack of tolerability and cosmetic acceptability, lack of adherence is an issue that compounds the lack of efficacy and poor safety profiles associated with these therapies. Systemic treatment, such as biologics and oral therapy, is reserved for the more severe and resistant cases due to the more severe adverse effects associated with systemic treatment (Beck 2018). There is a clear medical need for an effective, steroid-free, locally acting topical therapy that is safe and tolerable and offers patients the opportunity for a treatment-free remittive period given the challenges of treating this area.

VTAMA (tapinarof) cream, 1% is a novel, cosmetically elegant, steroid-free topical cream that has demonstrated clinically meaningful and highly statistically significant efficacy in the treatment of plaque PSO and, thus, has the potential to meet the need in patients with plaque PSO in the head and neck region.

Application of the product to plaque PSO in the head and neck region was permitted in the Phase 3 registrational trials to assess tolerability. In addition, efficacy assessments in registrational trials included evaluation of plaques located in the head and neck region as part of the overall response in treated areas. Although efficacy in the treatment of scalp PSO was not evaluated, the USPI does not restrict application of VTAMA to the scalp. A detailed description of the chemistry, pharmacology, efficacy, and safety of VTAMA (tapinarof) cream, 1% is provided in the IB.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of VTAMA (tapinarof) cream, 1% may be found in the IB.

2.3.1 Risk Assessment

No major safety concerns were identified during the development program; no deaths or SAEs were considered related to VTAMA (tapinarof) cream, 1%. Most AEs were mild localized skin reactions of a type commonly observed and managed by dermatologists. A low incidence of safety issues, serious or non-serious, were observed. The common AEs associated with the administration of VTAMA (tapinarof) cream, 1% in the clinical trials for plaque PSO were folliculitis, contact dermatitis, and headache. Folliculitis events were generally mild and well tolerated and did not worsen or progress over time with continued treatment. The vast majority of participants elected to continue with VTAMA (tapinarof) cream, 1%, suggesting the perceived benefit outweighs the burden of folliculitis. See Section 10.3.5 for further information on the management of follicular events. Observations suggest that the events of contact dermatitis experienced by participants with plaque PSO may not represent allergic contact dermatitis.

2.3.2 Benefit Assessment

VTAMA (tapinarof) cream is a novel, cosmetically elegant, steroid-free topical cream that has demonstrated clinically meaningful and highly statistically significant efficacy in the treatment of plaque PSO consistently across the clinical program. Benefits to participants include rapid improvement in signs and symptoms that persists with continued use, the ability to achieve complete disease clearance, and maintenance of disease control via a remittive effect after treatment discontinuation in a convenient once-daily topical therapy that can be administered for extended treatment durations with no limit to the size or location of the treatment area. The remittive effect off therapy observed for VTAMA (tapinarof) cream, 1% is a unique and differentiating attribute that, along with durability on therapy, provides patients with a new option for long-term disease management. These attributes are coupled with minimal systemic absorption and a favorable safety and tolerability profile.

2.3.3 Overall Benefit Risk Conclusion

Given the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with VTAMA (tapinarof) cream are justified by the anticipated benefits that may be afforded to participants with plaque PSO in the head and neck region. Please see USPI for the most up-to-date information.

3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of VTAMA (tapinarof) cream, 1% in adults with plaque PSO in the head and neck region	• Percentage of participants who achieve a PGA (target lesion) score of clear (0) or almost clear (1) with a ≥ 2-grade improvement from Baseline at Week 12
Secondary	
• To assess onset of effect of VTAMA (tapinarof) cream, 1% in adults with plaque PSO in the head and neck region	• Time to achieve a PGA (target lesion) score of 0 or 1 with a ≥ 2-grade improvement from Baseline
[redacted]	
• [redacted]	• [redacted]
[redacted]	
• [redacted]	• [redacted]

4 Study Design

4.1 Overall Design

This is a single-group, open-label, multicenter study to evaluate the safety and efficacy of VTAMA (tapinarof) cream, 1% in the treatment of plaque PSO in the head and neck region. Participants will treat plaque PSO in the head and neck region with VTAMA (tapinarof) cream, 1% QD for 12 weeks. Efficacy of the treatment of plaque PSO in the head and neck region will be assessed with a PGA evaluation of a target lesion selected as representative of the participant's disease in the head and neck region. [redacted] Participants will be allowed to treat plaque PSO in other body areas according to instructions provided in the USPI, but no assessments of efficacy will be performed outside of the head and neck region. Safety and tolerability will be assessed by evaluation of AEs [redacted]

Study duration:

- The study duration will be up to 17 weeks.
- The treatment duration will be up to 12 weeks.
- The follow-up period will be up to 1 week.

4.2 Scientific Rationale for Study Design

The safety and efficacy of VTAMA (tapinarof) cream, 1% in the treatment of plaque PSO were established in Phase 3 studies, which included the treatment of sensitive areas. This study is intended to broaden the understanding of the safety and efficacy of VTAMA (tapinarof) cream, 1% in the treatment of plaque PSO occurring in the head and neck region. Efficacy and tolerability in this area will also be assessed.

The PGA is a clinical tool for assessing the current state/severity of a participant's PSO at a given time point. It is a static 5-point morphological assessment of overall disease severity, as determined by the Investigator, using the clinical characteristics of erythema, scaling, and plaque thickness/elevation as guidelines; higher PGA scores represent more severe disease. Improvements in PGA generally correlate with improvements in quality of life. A target plaque PSO lesion in the head and neck region will be identified at Baseline and efficacy of tapinarof will be assessed with a PGA evaluation. The primary endpoint will assess the percentage of participants who achieve a PGA (target lesion) score of clear (0) or almost clear (1) with a ≥ 2-grade improvement from Baseline at Week 12. This type of endpoint is well established as a means of measuring the success of treatments in plaque PSO. The secondary endpoint will assess the time to achieve a PGA (target lesion) score of 0 or 1, as onset of action is incredibly important to patients in the clinic. [redacted]

4.3 Justification for Dose

The FDA-approved dosing regimen for VTAMA (tapinarof) cream, 1% for the treatment of plaque PSO is QD dosing and will be followed in this study. This regimen is based on the evaluation of various tapinarof regimens in participants with plaque PSO and atopic dermatitis and the success of this regimen in Phase 3 studies in participants with plaque PSO.

4.4 End-of-Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

5 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 years of age or older, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants with clinical diagnosis of plaque PSO, including lesion(s) in the head and neck region and stable disease in the head and neck region for at least 3 months prior to the study
3. Participant has a plaque PSO lesion in the head and neck region that is suitable for evaluation as the target lesion and has a PGA (target lesion) score of 2 (mild), 3 (moderate), or 4 (severe) at Screening and Baseline.

Sex and Contraceptive/Barrier Requirements

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

4. Female participants:

   A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

   - Is a WONCBP as defined in Appendix 4 Contraceptive and Barrier Guidance

     OR

   - Is a WOCBP and using an acceptable contraceptive method as described in Appendix 4 Contraceptive and Barrier Guidance during the treatment period, until after the last dose of study product. The Investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study product).
     - A WOCBP must have a negative urine pregnancy test before the first dose of study product, see Section 8.3.1 Pregnancy Testing.
     - The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol; written informed consent must be obtained prior to any study-related procedures.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Diagnosis of a type of psoriasis other than plaque PSO
2. Any sign of infection of any of the psoriatic lesions
3. Concurrent significant dermatologic or inflammatory condition other than plaque PSO that, in the Investigator's opinion, would make it difficult to interpret data or assessments during the study
4. A history of or ongoing serious illness or medical, physical, or psychiatric condition(s) that, in the Investigator's opinion, may interfere with participation in the study and ability to understand and give informed consent
5. History of sensitivity to the study product, or components thereof, or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates participation in the study

Prior/Concomitant Therapy

6. Previous OR current use of VTAMA
7. Use of any prohibited medication within the indicated period before the Baseline visit

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

   - Minimum of 5 half-lives for biologic agents: e.g., 12 months for rituximab; 8 months for ustekinumab; 5 months for secukinumab, risankizumab, or tildrakizumab; 12 weeks for golimumab or guselkumab; 10 weeks for ixekizumab or infliximab; 8 weeks for infliximab, adalimumab, alefacept, or brodalumab; and 4 weeks for etanercept
   - Four weeks for systemic treatments: deucravacitinib, 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), psolarens, corticosteroids, or adrenocorticotropic hormone analogs
   - Two weeks for immunizations with a live viral component; drugs known to possibly worsen PSO, such as beta-blockers (e.g., propranolol), lithium, iodides, angiotensin-converting enzyme inhibitors, and indomethacin, unless on a stable dose for > 12 weeks
   - One week for medicated shampoos containing corticosteroids, vitamin D analogs, salicylic acid, or coal tar and 2 weeks for topical minoxidil
   - With the exception of non-medicated emollients, 2 weeks for topical treatments including corticosteroids, roflumilast, antihistamines, immunomodulators, anthralin (dithranol), vitamin D derivatives (e.g., calcipotriene, calcipotriol), retinoids (Note: 4 weeks for tazarotene), or coal tar

     NOTE: If participants are on a stable regimen of non-medicated emollient(s), they may continue to use the same emollient(s) on nonlesional skin during the study.

Prior/Concurrent Clinical Study Experience

8. Current enrollment OR past participation in another investigational study in which tapinarof was administered
9. The participant has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives, or twice the duration of the biological effect of the study product (whichever is longer).

Other Exclusion Criteria

10. UV light therapy or prolonged exposure to natural or artificial sources of UV radiation (e.g., phototherapy, tanning beds/booths, or therapeutic sunbathing) within 4 weeks prior to the Baseline visit and/or plans to have such exposures during the study which could potentially impact the participant's PSO (as determined by the Investigator).

5.3 Lifestyle Considerations

Timing of Study Product Application

- Participants will be instructed to maintain the approximate dosing time chosen at the beginning of the study for their full study participation.
- Participants should avoid swimming, bathing, showering, or strenuous activities for at least 2 hours after application.
- If the participant elects to apply study product in the evening, the dose should be applied at least 30 minutes prior to bedtime.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time. Rescreened participants should be assigned a new participant number.

5.5 Criteria for Temporarily Delaying Enrollment

Not applicable

6 Study Intervention(s) and Concomitant Therapy

Study products are all prespecified, investigational and non-investigational medicinal products, medical devices, and other interventions (e.g., surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

Table 1: Study Intervention(s) Administered

Intervention Name	VTAMA (tapinarof) cream, 1%
Intervention Description	A thin layer of cream (tapinarof 1%) applied to lesions QD
Type	Drug
Dose Formulation	Cream
Unit Dose Strength(s)	Cream, 1%
Dosage Level(s)	Total dosage is dependent on BSA affected.
Route of Administration	Topical
Use	Experimental
IMP and NIMP/AxMP	IMP
Sourcing	Provided centrally by the Sponsor to study site for distribution
Packaging and Labeling	VTAMA (tapinarof) cream, 1% will be provided in 60-g commercial tubes and labeled to be distributed in the participating country and will meet all applicable requirements.
Current/ Former Names/Aliases	DMVT-505, formerly known as GSK2894512A, GSK2894512, STI-1001, WBI-1001, or JTE-061

AxMP = auxiliary medical product; BSA = body surface area; GSK = GlaxoSmithKline; IMP = investigational medicinal product; NIMP = non-investigational medical product; QD = once daily

Table 2: Study Arm(s)

Arm Title	**VTAMA (tapinarof) cream, 1%**
Arm Type	Experimental; open-label
Arm Description	Participants will apply sufficient study product to completely cover each lesion with a thin layer QD for 12 weeks. Participants will treat all lesions in the head and neck. Study product should be applied to newly appearing areas on the head and neck as well as areas in this region that improve or clear during the study. Participants may treat plaque PSO in other areas; however, improvement of PSO in these areas will not be included in any efficacy analyses. Participants will be instructed to maintain the same approximate dosing time chosen at the beginning of the study for their full study participation.

PSO = psoriasis; QD = once daily.

6.2 Preparation, Handling, Storage, and Accountability

1. The Investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study product received, and any discrepancies are reported and resolved before use of the study product.
2. Only participants enrolled in the study may receive study product, and only authorized site staff may supply study product.

3. All study product must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
4. The Investigator or authorized site staff is responsible for study product accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study products are provided in the Study Reference Manual.

6.3 Assignment to Study Intervention

Not applicable

6.4 Blinding

This is an open-label study.

6.5 Study Intervention Compliance

At Visit 2, study product will be dispensed, and participants will be instructed on how to apply cream and will apply the study product under supervision. During the study, participants will self-administer study product at home and will record the time of study product application in a daily diary provided by the study site. Participants will be instructed to maintain the same approximate dosing time chosen at the beginning of the study for their full study participation. Compliance with daily dosing will be assessed at each visit based on diary entries. Participants will be instructed to bring all used and unused tubes with them to each study visit. If a tube has been lost, discarded, or forgotten by the participant, then the site personnel will make a notation of this on the drug accountability logs. Forgotten tubes should be returned by the participant at the next study visit. Unopened tubes and opened, partially used tubes or tubes with foil overlay removed may only be re-dispensed once to study participants. A new tube may be dispensed if the current tube does not contain sufficient study product to last until the next visit. All tubes, including empty tubes, will be collected at Visit 7. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of study product dispensed to and administered by each participant must be maintained and reconciled with study product and compliance records. Intervention start and stop dates, including dates for temporary interruptions, will also be recorded.

6.6 Dose Modification

Dosing may be temporarily interrupted if deemed necessary by the Investigator for management of AEs.

6.7 Continued Access to Study Intervention after the End of the Study

VTAMA (tapinarof) cream, 1% is commercially available for the treatment of plaque PSO.

6.8 Treatment of Overdose

For this study, accidental or intentional oral ingestion of drug product will be considered an overdose. Ingestion of a 60-gram tube of VTAMA (tapinarof) cream, 1% would result in an oral dose of 600 mg of tapinarof.

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

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

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

6.9 Prior and Concomitant Therapy

Any medication or vaccine, including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements, as well as non-medicated emollients, that the participant is utilizing at the time of consent or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Concomitant medications for medical treatment of other conditions are allowed, under the condition that the dosage and administration of these treatments are not planned to change 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 5.2.

In the event of skin infection, topical antibacterial agents can be applied to the infected area; however, study product must not be applied to the area until the skin infection is healed.

Participants may use non-medicated shampoos (must not contain corticosteroids, vitamin D analogs, salicylic acid, or coal tar). If participants are on a stable regimen of non-medicated emollient(s), they may continue to use the same emollient(s) on nonlesional skin during the study. The same emollient should be used throughout participation in the study.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1.

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study product. If study product is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for safety. See the SoA for data to be collected at the time of discontinuation of study product and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary Interruption

Some dermatological reactions have been observed following treatment with VTAMA (tapinarof) cream, 1% (see Section 2.3.1). After cessation of exposure, dermatological reactions generally subside spontaneously or with topical treatments.

In this study, treatment of plaque PSO in the head and neck region with study product may be temporarily interrupted for dermatological reactions. If treatment is interrupted due to a safety issue, the Medical Monitor will be contacted, and the event documented in the eCRF.

See Section 10.3.5 for further information on the management of follicular events.

7.1.2 Rechallenge

If study product is temporarily interrupted due to dermatological reactions, treatment may be resumed at the Investigator's discretion when the reaction has subsided.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study product and the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3 Lost to Follow up

A participant will be considered lost to follow-up if the participant 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 participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution, and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.

8.1 Administrative and Baseline Procedures

8.1.1 Informed Consent

The Investigator is responsible for obtaining written informed consent 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 participant and the person obtaining consent.

8.1.2 Demographics

Demographic information collected will include age, sex, race, ethnicity, and Fitzpatrick skin type (Table 3).

Table 3: Fitzpatrick Skin Type Scale

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

8.1.3 Medical History

Medical history will be collected to ensure participants are eligible for participation in the study (per inclusion Section 5.1 and exclusion Section 5.2 criteria).

Data collected will include year of plaque PSO diagnosis, allergic conditions, and CV medical history and risk factors (medical conditions, and family history of premature CV disease).

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

8.1.4 Instructions for Dosing Regimen

Participants will self-administer study product at home, QD, and will record the time of application in a daily diary provided by the study site.

Application Instructions

Participants will be instructed to:

- Treat all lesions in the head and neck region, both newly appearing lesions and lesions that have improved or cleared during the study

  Note: Participants may treat plaque PSO in other areas according to instructions provided in the USPI. No other treatment for scalp PSO is permitted during the study.

- Apply cream to dry, clean skin in an amount sufficient to completely cover each lesion with a thin layer
- Continue to lightly rub any residual cream visible on the disease-affected skin until it is no longer visible
- Wash hands after application, unless treating lesions on the hands or fingernails

Timing of Application

Participants will be instructed to:

- Maintain the approximate time of day for dosing at home throughout their full study participation
- Record the time of application in the daily diary
- Apply cream at least 30 minutes prior to bedtime if their chosen application time is in the evening
- Avoid swimming, bathing, showering, or strenuous activities for at least 2 hours after application

Missed Doses

A missed daily dose will be recorded as a protocol deviation.

Participants will be instructed that if a dose is missed, they should continue dosing the next day and should not apply more than QD to make up for the missed dose on the previous day.

8.2 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA.

8.2.1 Efficacy Assessments Completed by Investigator

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

8.2.1.1 Physician Global Assessment of Target Lesion

The PGA is a clinical tool for assessing the current state/severity of a participant's PSO at a given time point. It is a static 5-point morphological assessment of overall disease severity, as determined by the Investigator, using the clinical characteristics of erythema, scaling, and plaque thickness/elevation as guidelines; higher PGA scores represent more severe disease (see Appendix 5).

In this study, the PGA should be used only to assess the target plaque PSO lesion in the head and neck region.

[redacted]

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Refer to the SoA for timing of periodic scheduled urine pregnancy tests.
- Additional urine or serum pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

[redacted]

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3.

The definitions of unsolicited and solicited AEs can be found in Appendix 3.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs that are serious, considered related to the study product or study procedures, or that caused the participant to discontinue the study product of study (see Section 7). This includes events reported by the participant.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

[redacted]

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the final visit at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded in the EDC and reported on the required form to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study product or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs (as defined in Appendix 3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study 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 study product under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review, acknowledge electronically, and retain a copy within the Study Reference Manual and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.4.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study product and until the last dose of study product.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of a male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study product by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study product or be withdrawn from the study.

8.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.10 Health Economics

Health economics parameters are not evaluated in this study.

9 Statistical Considerations

The statistical analysis plan will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section.

All study data will be summarized using descriptive statistics. Categorical endpoints will be summarized using frequency and percentage (e.g., gender, race). Continuous endpoints will be summarized using number of observations, mean, SD, median, minimum, and maximum. The 95% confidence intervals will also be reported as appropriate. All efficacy and safety data will be listed by participant.

9.1 Statistical Hypothesis

Not applicable. Demographic and baseline characteristics, efficacy, safety, [redacted] will be summarized descriptively. No inferential testing will be performed.

9.1.1 Multiplicity Adjustment

Not applicable

9.2 Analysis Sets

Efficacy, safety, [redacted] collected will be summarized for the ITT population.

Participant Analysis Set	Description
Intent-to-treat population (ITT)	All participants enrolled in the study.

9.3 Statistical Analyses

9.3.1 General Considerations

This study is intended to show that VTAMA (tapinarof) cream, 1% has a favorable safety and efficacy profile when applied to lesions in the head and neck region over a 12-week dosing period.

Objectives and endpoints are provided in Section 3.

Every effort will be made to collect complete data at all visits. All efficacy data will be summarized based on OCs. The primary and exploratory efficacy endpoints will also be summarized utilizing the last observation carried forward method to impute missing data [redacted]

9.3.2 Primary Endpoint Analysis

The primary efficacy endpoint will be summarized descriptively with frequency count, percentage, and 95% confidence interval.

9.3.3 Secondary Endpoint Analysis

The Kaplan-Meier product limit method will be used to estimate the median time to achieving a target lesion PGA score of 0 or 1 with a ≥ 2-grade improvement from Baseline (if estimable).

9.3.4 [redacted]

[redacted]

9.3.5 Safety Analyses

[redacted]

The number and percent of participants with TEAEs will be summarized by system organ class, and preferred term for all TEAEs; all TEAEs by system organ class, preferred term, and maximum CTCAE grade; all TEAEs considered by the Investigator to be related to study product; SAEs; TEAEs leading to study product discontinuation; and TEAEs leading to discontinuation from study.

9.4 Interim Analysis

Not applicable

9.5 Sample Size Determination

The sample size for this study is based on clinical considerations only. No formal sample size calculation will be performed. A total of 30 participants is planned for this study which is considered adequate to evaluate the efficacy and safety for the treatment of plaque PSO in the head and neck region.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation (if applicable per country- or region-specific regulations) except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators and Sub-investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

10.1.4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.5 Dissemination of Clinical Study Data

Anonymized Clinical Study Reports will be disclosed as required by regulatory authorities.

Study information and tabular study results will be posted on National Institutes of Health's website www.clinicaltrials.gov and other publicly accessible sites. Study results may be published in peer-reviewed publications or presented at scientific meetings.

Following an assessment of a rigorously defined research question from a third party, Dermavant may grant access to analyzable datasets from this study through a secure system.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF completion guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Reference Manual.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in source data acknowledgment.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site activated and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study product development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines

- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9 Publication Policy

- After conclusion of the study and without prior written approval from the Sponsor, Investigator(s) in this study may communicate, orally present, or publish in scientific journals or other scholarly media the study results only after the following conditions have been met:
  - The study results in their entirety have been publicly disclosed by or with the consent of the Sponsor, in an abstract, manuscript, or presentation; OR
  - The study has been completed at all study sites for at least 1 year.
- To allow the Sponsor to protect confidential and proprietary information and to provide comments, any proposed publication or presentation meeting the criteria set forth in the bullet point immediately above will be submitted to the Sponsor along with the respective scientific journal or presentation forum at least 30 days before submission of the proposed publication or presentation. Investigator(s) will comply with the Sponsor request to delete references to its confidential and/or proprietary information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days to allow the Sponsor or its affiliates obtain patent protection if deemed necessary.
- No such communication, presentation, or publication of the study results will include the Sponsor's confidential and/or proprietary information.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

No clinical laboratory tests will be performed in this study.

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study product, whether or not considered related to the study product.
- NOTE: 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 study product.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participant will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participant and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease, or more severe than expected for the participant's condition)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study product administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events not Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant'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 participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy): The condition that leads to the procedure is the AE.
- Situations in which 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

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term life threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission of any infectious agent via an authorized medicinal product

g. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant

or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by regulatory authorities. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to regulatory authorities.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- [redacted]

Assessment of Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study according to the National Cancer Institute 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

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
CTCAE = Common Terminology Criteria for Adverse Events.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study product and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study product administration, will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology, if applicable.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor or designee will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the

site can report this information on a paper SAE form (see next section) or to the Sponsor or designee by telephone.

- Contacts for SAE reporting can be found in Study Reference Manual.

SAE Reporting to Sponsor or Designee via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor or designee or the SAE coordinator.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the Study Reference Manual.

[redacted]

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study product, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following:
   a. Documented hysterectomy
   b. Documented bilateral salpingectomy
   c. Documented bilateral oophorectomy
   d. For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

2. Postmenopausal female

    a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

        i. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

        ii. Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)c
• Bilateral tubal occlusion
• Azoospermi[c] partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent Failure rate of < 1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Effective Methods[d] That Are Not Considered Highly Effective Failure rate of ≥ 1% per year when used consistently and correctly.
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c.) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. d) Considered effective, but not highly effective—failure rate of ≥ 1% per year. Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix 5: Physician Global Assessment of Target Lesion

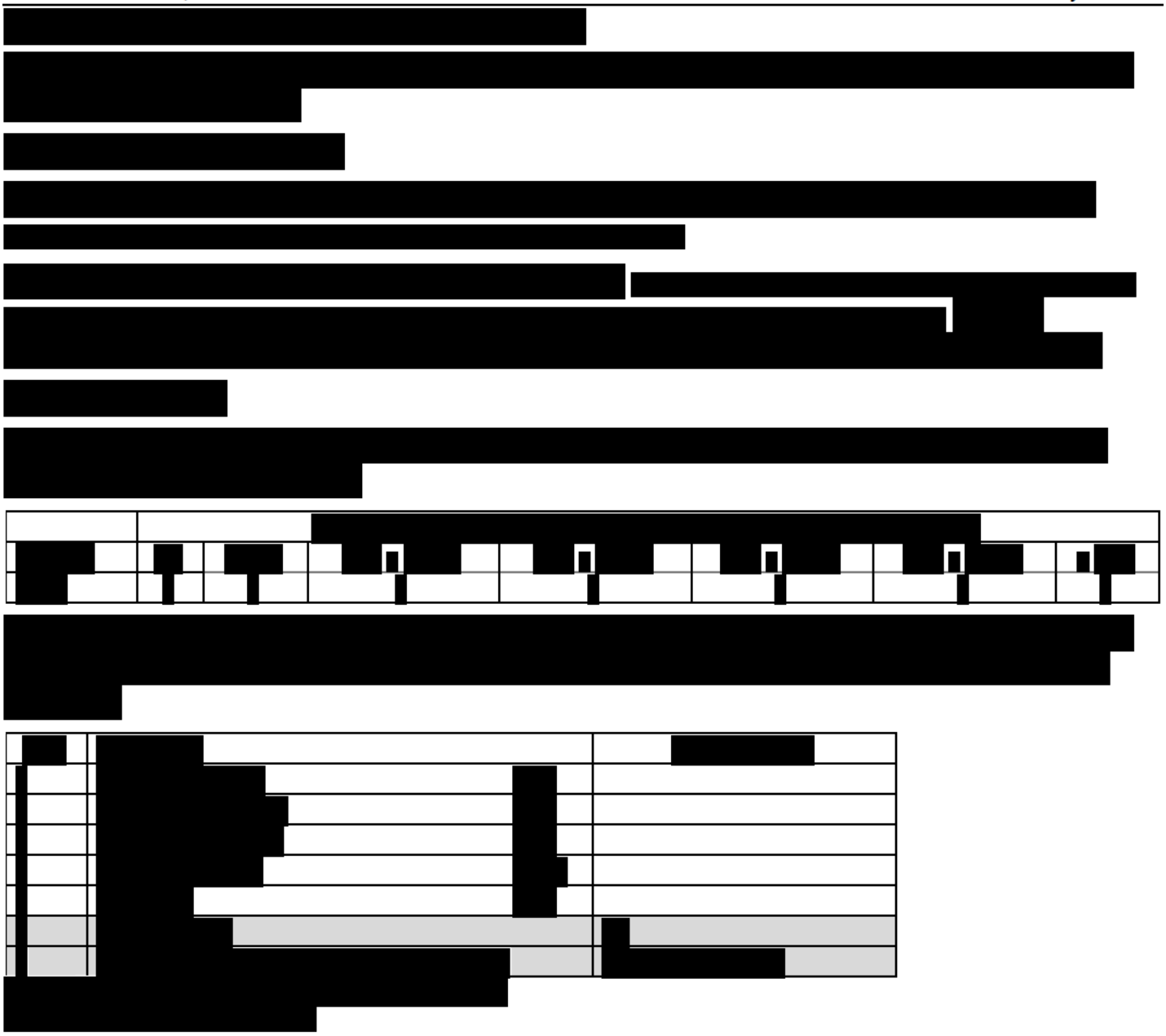
In this study, this PGA should be used only to assess the target plaque PSO lesion in the head and neck region.

Following the Baseline visit, assessments will be made without reference to Baseline state or any other previous scores.

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

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

Source: 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.



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11 References

Bagel J, Nelson E. An Open-label, Observational Study Evaluating Desoximetasone Topical Spray 0.25% in Patients with Scalp Psoriasis. J Clin Aesthet Dermatol. 2018;11(5):27-29.

[redacted]

Beck KM, Yang EJ, Sanchez IM, Liao W. Treatment of Genital Psoriasis: A Systematic Review. Dermatol Ther (Heidelb). 2018;8(4):509-525. doi:10.1007/s13555-018-0257-y.

Langley RG, 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. doi:10.3109/09546634.2013.865009.

Lebwohl MG, Stein Gold L, Strober B, Papp KA, Armstrong AW, Bagel J, Kircik L, Ehst B, Hong HC, Soung J, Fromowitz J, Guenthner S, Piscitelli SC, Rubenstein DS, Brown PM, Tallman AM, Bissonnette R. Phase 3 Trials of Tapinarof Cream for Plaque Psoriasis. N Engl J Med. 2021;385(24):2219-2229. doi:10.1056/NEJMoa2103629.

Merola JF, Li T, Li WQ, Cho E, Qureshi AA. Prevalence of psoriasis phenotypes among men and women in the USA. Clin Exp Dermatol. 2016;41(5):486-489. doi:10.1111/ced.12805

Merola JF, Qureshi A, Husni ME. Underdiagnosed and undertreated psoriasis: Nuances of treating psoriasis affecting the scalp, face, intertriginous areas, genitals, hands, feet, and nails. Dermatol Ther. 2018;31(3):e12589. doi:10.1111/dth.12589

Mosca M, Hong J, Hadeler E, Brownstone N, Bhutani T, Liao W. Scalp Psoriasis: A Literature Review of Effective Therapies and Updated Recommendations for Practical Management. Dermatol Ther (Heidelb). 2021;11(3):769-797. doi:10.1007/s13555-021-00521-z