[redacted]

dermavant

Statistical Analysis Plan

Study Title:	A Phase 4, open-label study to investigate the efficacy and safety of VTAMA® (tapinarof) cream, 1% in the treatment of plaque psoriasis in intertriginous areas
Study Number:	DMVT-505-4001
Product:	VTAMA (tapinarof) cream, 1%
Study Phase:	4
Sponsor Name:	Dermavant Sciences, Inc. 3300 Paramount Parkway, Suite 150 Morrisville, NC 27560
Prepared by:	[redacted]
SAP Version:	Version 1.0, 02JUN2023

SAP Signatures

I give my approval for the SAP, including the table, listing, and figure shells, dated 02JUN2023. The analysis methods and data presentations are acceptable.

Statistician (Author)

Name: [redacted] Title Senior Statistician

Signature: [redacted] Date: 02-Jun-2023 | 11:31 PDT

Statistician Reviewer (As applicable)

Name: [redacted] Title Statistician

Signature: [redacted] Date: 02-Jun-2023 | 11:34 PDT

Sponsor Approval

Name: [redacted] Title Director, Biostatistics

Signature: [redacted] Date: 02-Jun-2023 | 11:50 PDT

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VERSION HISTORY

SAP Version	Date	Change	Rationale
1.0	02JUN2023	Not applicable	Original version

LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical/Therapeutic/ Chemical
CCG	eCRF Completion Guidelines
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DMP	Data Management Plan
eCRF	electronic Case Report Form
ICH	International Council for Harmonisation
IND	Investigational New Drug application
iPGA	intertriginous Physician Global Assessment
ITT	Intent-To-Treat
LOCF	Last Observation Carried Forward
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
OC	Observed Cases
PGA	Physician Global Assessment
[redacted]	[redacted]
[redacted]	[redacted]
PSO	Plaque Psoriasis
PT	Preferred Term
QD	Once a Day
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedures
[redacted]	[redacted]
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
USA	United States of America
USPI	United States Prescribing Information
VTAMA	tapinarof
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) for the final analysis is based on the most recent approved clinical study protocol (Version 1.0 dated on 14 October 2022), electronic case report form (eCRF) (Version 1.1 dated on 09 February 2023), eCRF completion guidelines (CCG, Version 2.0 dated on 10 March 2023), and Data Management Plan (DMP, Version 1.0 dated on 02 November 2022).

This SAP (Methods) documents the planned statistical analyses and data presentations for the final analysis of study DMVT-505-4001. This SAP will be finalized and approved prior to the database lock. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of VTAMA (tapinarof) cream, 1% in adults with intertriginous PSO.

2.2. Secondary Objectives

The secondary objective of the study is to assess onset of effect of VTAMA (tapinarof) cream, 1% in adults with intertriginous PSO.

[redacted]

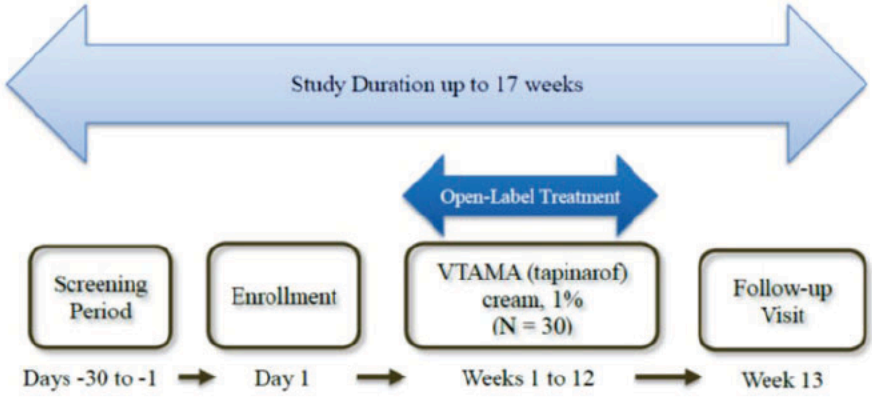
2.4. Safety Objectives

The safety objective of the study is to evaluate the safety and tolerability of VTAMA (tapinarof) cream, 1% in adults with plaque PSO in intertriginous areas.

3. STUDY DESIGN

3.1. 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 intertriginous areas. Participants will treat plaque PSO in intertriginous areas with VTAMA (tapinarof) cream, 1% QD for 12 weeks. Efficacy of the treatment of plaque PSO in intertriginous areas will be assessed with a PGA evaluation only of intertriginous areas (iPGA). [redacted] Participants will be allowed to treat plaque PSO in other body areas according to instructions provided in USPI, but no assessments of efficacy will be performed outside of intertriginous [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.

3.2. Study Assessments

Please refer to protocol Section 8 for descriptions of study procedures and assessments and protocol section 1.3 for timing of procedures and assessments (Schedule of Activities).

3.3. Assignment to Study Intervention

All subjects will be assigned to the study intervention of VTAMA (tapinarof) cream, 1% in the treatment of plaque PSO in intertriginous areas.

3.4. Blinding

This is an open-label study.

4. SAMPLE SIZE DETERMINATION

The sample size for this study is based on clinical considerations only. No formal sample size calculation will be performed. This study will enroll approximately 30 participants which is considered adequate to evaluate the efficacy and safety for the treatment of plaque PSO in the intertriginous areas.

5. STATISTICAL CONSIDERATIONS

5.1. General Considerations

[redacted] will perform the statistical analysis of the data. SAS version 9.4 or higher will be used to generate all statistical outputs (tables, listings, figures [TLFs], and datasets). The International Council for Harmonisation (ICH) numbering convention will be used for all TLFs. Continuous endpoints will be summarized by presenting the number of observations, means, standard deviations, medians, minimums, and maximums. The 95% confidence intervals will be reported as appropriate.

Time to event analyses will use the Kaplan-Meier product limit method (if estimable) based on observed cases.

Categorical endpoints will be summarized by presenting counts and percentages of subjects in corresponding categories. All possible categories as defined in the case report form (CRF) will be populated, even if they have zero counts. With the exception of ethnicity and race in the demographic table, percentages for missing values are omitted and do not account for the percent calculation of other categories. In certain tables (e.g., TEAEs), the total number of subjects is used as denominator. Footnotes will specify the percent basis in those cases.

Individual subject data obtained from the eCRFs and any derived data will be presented by subject in data listings.

5.2. Analysis Populations

The intent-to-treat (ITT) population will include all participants enrolled in the study.

5.3. Analysis Windowing

Study days are measured from date of first dose of study medication. Study days corresponding to measurements are calculated as:

- Assessment date – date of first dose + 1 if assessment date is on or after the date of first exposure of treatment.
- Assessment date – date of first dose if assessment date is before the date of first exposure of treatment.

All efficacy and safety endpoints will be analyzed according to the nominal visits (i.e. actual visit) except for assessments collected on early termination and unscheduled visits. Early termination and unscheduled visits will be re-numbered to an analysis visit based on their windowed visits defined by actual study day. If more than one visit occurs within a single visit window, then the analysis will take the one closest to the target day. If the 2 visits are equidistant from the target day, the visit with later date and time will be used.

The following analysis visit windows will apply to early termination and unscheduled visits:

Analysis Visit	Target Day	Analysis Visit Window
Baseline (1)	1	1
Week 1	8	Post first dose to Day 12
Week 2	15	Day 13 – Day 22
Week 4	29	Day 23 – Day 36
Week 6	43	Day 37 – Day 50
Week 8	57	Day 51 – Day 71
Week 12	85	Day 72 – Maximum (last day of treatment + 3 days, Day 87)
Week 13	92	> Maximum (last day of treatment + 3 days , Day 87)

5.4. Statistical Hypotheses

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

5.5. Multiplicity Adjustment

Not applicable

5.6. Missing Data

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

[redacted]

All efficacy data will be summarized based on observed cases (OC).

Imputation of Missing Efficacy Data

In addition to the efficacy analysis based on OC, the primary and exploratory efficacy endpoints will also be summarized utilizing the last observation carried forward (LOCF) method to impute missing data [redacted] Baseline will not be used when applying LOCF and LOCF will be implemented through Week 12 (i.e., Week 13 not included in LOCF). LOCF summaries will be considered supportive.

5.7. Interim Analysis

Not applicable

6. STUDY POPULATION

6.1. Subject Disposition

Subject disposition information will be summarized and will include number of subjects screened, number of subjects included in the ITT population, the number of subjects completing the treatment phase of the study, the number of subjects completing the study through follow-up and primary reason for discontinuation.

6.2. Protocol Deviations

Protocol deviations will be summarized by deviation category (major, minor). Additionally, protocol deviations will be presented in a data listing.

6.3. Eligibility

Participants not fulfilling the eligibility criteria will be presented in a data listing.

6.4. Demographic and Baseline Characteristics

Demographic variables include age, sex, ethnicity, race, and Fitzpatrick skin type. Age will be reported on the CRF and will be based on age at time of signing informed consent.

Baseline characteristics include intertriginous Physician Global Assessment (iPGA), [redacted]

Unless otherwise noted, baseline is defined as the last non-missing value recorded before the first dose of study drug. Unscheduled visits will be used in the determination of baseline values, when applicable.

6.5. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 26.0). The summary will show the system organ class (SOC) and preferred terms (PT) ordered alphabetically by SOC and descending PT frequency. The corresponding data listing by participant will be ordered by start date, end date, then alphabetically by preferred term.

Psoriasis history in the intertriginous areas will be summarized by duration of disease (<5 years, 5-10 years, >10 years) and by intertriginous areas affected.

6.6. Prior and Concomitant Therapy

Prior and concomitant medication verbatim terms will be mapped to Anatomical/Therapeutic/ Chemical (ATC) class and preferred names using the WHODrug global dictionary (Version B3 01MAR2023).

Prior (within the 30 days before screening, and with stop dates prior to first dose of study drug) and concomitant (ongoing or with stop dates on or after first dose of study drug) medications will be listed by subject. If the medication is ongoing or the stop year is missing, the medication will be considered as received for the entire duration of the study.

To distinguish prior vs concomitant medications, the following rules for stop dates will apply:

- If only year was recorded, and it is before Baseline, it is a prior medication; if year is same or after Baseline, it is assumed to be a concomitant medication.
- If day is missing, but month and year are before Baseline, it is a prior medication; if month and year are the same as Baseline, it is assumed to be a concomitant medication; if month and year are after Baseline, it is a concomitant medication.
- If start date is after Baseline, it is a concomitant medication regardless.

Prior and concomitant medications will be summarized separately by WHO ATC 2 and preferred name. Subjects may have more than 1 medication per ATC 2 and preferred name. At each level of subject summarization, a subject is counted once if he/she reported 1 or more medications at that level. Frequencies and percentages of prior and concomitant medications will be ordered alphabetically by ATC class and descending preferred name. The corresponding data listing by participant will be ordered by start date of administration, end date of administration, then alphabetically by preferred name.

7. EFFICACY ANALYSES

All efficacy analyses will be performed based in the ITT population.

7.1. Efficacy Endpoints

The primary efficacy endpoint is the percentage of participants who achieve an iPGA score of clear (0) or almost clear (1) with a ≥ 2-grade improvement from Baseline at Week 12.

The secondary efficacy endpoint is the time to achieve an iPGA score of clear (0) or almost clear (1) with a ≥ 2-grade improvement.

[redacted]

7.2. Efficacy Analyses

Categorical endpoints will be summarized by presenting counts and percentages of subjects in corresponding categories. Percentages for missing values are omitted and do not account for the percent calculation of other categories. 95% confidence intervals will be presented.

Continuous endpoints will be summarized by presenting the number of observations, means, standard deviations, medians, minimums, maximums, and 95% confidence intervals.

[redacted]

The Kaplan-Meier product limit method will be used to estimate the median time to achieving an iPGA score of 0 or 1 with a ≥ 2-grade improvement from Baseline, [redacted]

Categorical endpoints include:

- Percentage of participants who achieve an iPGA score of clear (0) or almost clear (1) with a ≥ 2-grade improvement from Baseline
- [redacted]

7.3. [redacted]

[redacted]

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

[redacted]

8. SAFETY ASSESSMENTS

8.1. Extent of Exposure

The following exposure and compliance parameters will be summarized descriptively by treatment:

- Total number of days exposed, defined as date of last dose of study drug - date of first dose of study drug + 1.
- Number of doses administered, calculated from the in-clinic dose at Baseline and the subject dose diary. If a subject is exposed to study drug for more than 1 day, and returns no diary records, then the total number of doses is regarded to be missing. Otherwise, for any day for which there is no diary record, it is assumed that no study drug was administered at home.
- Percent compliance will be calculated as the (Number of Doses Administered) / (Number of Days Exposed) * 100. Number of missed doses will be based on data from the summary of missed doses form.
- Subject compliance, defined as ≥80% compliance while enrolled in the study. If the percentage of study medication compliance cannot be computed, the subject is assumed to be less than 80% compliant.

A subject will be compliant with the dosing regimen if they applied ≥80% of the expected doses. Expected number of doses is based on length of time enrolled in the treatment-phase of the study.

8.2. Adverse Events

All AE summaries will be restricted to TEAEs, which are defined as those AEs that occurred after dosing and those pre-existing AEs (prior to first application of study treatment) that worsened during the study. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as TEAE. Verbatim terms in the eCRFs will be mapped to SOCs and PTs using MedDRA (Version 26.0).

Imputation of start and end dates of AEs

To calculate duration of AEs, the following rules will be used where applicable to impute partial or completely missing start dates or end dates:

- If only the day is missing for a start date, the 1st of the month will be imputed. If the new estimated date falls before the date of first dose, while the known month and year match the month and year of the first dose, the date of first dose will be used as the new estimated date. The AE will be considered as a treatment-emergent AE (TEAE).
- If only the day is missing for an end date, the last day of the month will be imputed. If the new estimated date falls after the date of last study visit, the date of last study visit will be used as the new estimated date. Last study visit is defined as the Week 13 visit.

- If both the day and the month are missing for a start date or end date, no imputation will be used, and the duration will not be calculated. However, if the year of start is the same or greater than the year of the first dose date, the AE will be considered as a TEAE.
- If the start date or end date is completely missing, duration will not be calculated. However, an event with completely missing start date will be considered as a TEAE.

Imputation of missing relationship and/or missing severity

If relationship to treatment is missing, the event will be conservatively treated as related to study drug.

If severity is missing and the AE is reported as serious and fatal, severity will be imputed as CTCAE=5. If severity is missing and the AE is reported as serious and not fatal, severity will be imputed as CTCAE=4. If severity is missing and the AE is not reported as serious, severity will be imputed as CTCAE=3.

All AEs will be listed by subject, detailing the verbatim term given by the investigator, the SOC, PT, onset date and time, end date and time, duration (days), common terminology criteria for adverse events (CTCAE) grade, outcome, relationship to study drug, action taken with study drug, other action taken to treat the event, seriousness, and criteria for seriousness. Serious AEs (SAEs), TEAEs related to study drug, TEAEs leading to study drug discontinuation, and TEAEs leading to study discontinuation will also be listed separately.

All AE will be summarized using frequency counts and percentages:

- Any TEAEs
- Related TEAEs
- TEAEs leading to study treatment discontinuation
- TEAEs leading to discontinuation from study
- Any Serious TEAE (non-Fatal)
- Any Serious TEAE (All)
- Death
- Treatment-related Serious TEAE
- Serious TEAE leading to study treatment discontinuation
- Serious TEAE leading to discontinuation from study

TEAEs will be ordered alphabetically by MedDRA SOC and by descending PT frequency. At each level of summarization, a subject will be counted once if he/she reported one or more events. The severity of TEAEs and relationship to study drug will be summarized in a similar manner. For summaries of relationship to study drug, a subject will be classified according related or not related. For summaries of TEAE CTCAE grade, a subject will be classified according to the worst grade.

8.3. [redacted]

[redacted]

9. REPORTING CONVENTIONS

Means and medians will be presented to 1 more decimal place than the raw data. Standard deviations will be presented to 2 more decimal places than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data. Percentiles (eg, 25%, median, 75%) will be presented to 1 decimal place more than the raw/derived data.

10. QUALITY ASSURANCE OF STATISTICAL PROGRAMMING

[redacted] Standard Operating Procedures (SOPs) governing the statistical analysis and programming will be followed.

11. MODIFICATIONS

11.1. Modifications to Protocol-Specified Analyses

Week 13 will be included in the summaries of iPGA, [redacted].

[redacted]

12. REFERENCES

1. [redacted]