Statistical Analysis Plan

Dermavant Sciences, Inc.

DMVT-505-3101

A Phase 3 Efficacy and Safety Study of Tapinarof for the Treatment of Moderate to Severe Atopic Dermatitis in Children and Adults

Protocol Version/Date: 4.0 09AUG2022

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1.0	10AUG2022
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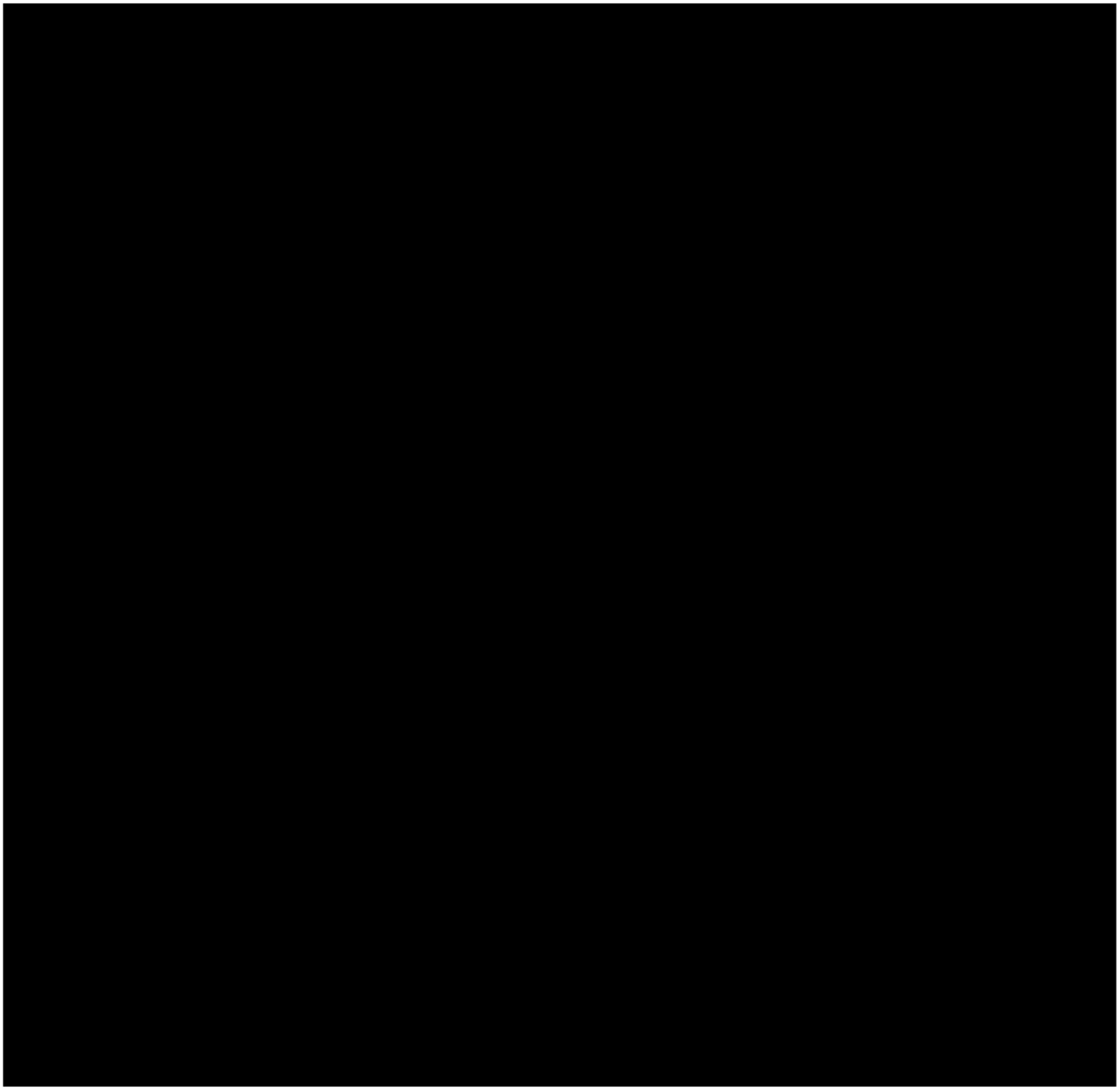
Revision History

Date	Reason for Update	Section Updated
10AUG2022	Original Version 1.0	NA
03FEB2023	Amendment Version 2.0	1. 8. Analysis Sets Added the following categories under • Systemic Agents: ○ Oral/systemic corticosteroids for >5 days; removed "before 8 week visit" ○ Oral PDE4 inhibitors used for atopic dermatitis (e.g., roflumilast, apremilast), or other conditions if not on stable dose for period prior to and over course of the study ○ Oral/systemic retinoids (e.g.,alitretinoin), if not on a stable dose for period prior to and over course of the study ○ Other injected monoclonal antibodies with potential impact on AD (omalizumab) ○ Oral/systemic antihistamines for ≥3 days when used for skin conditions ○ Oral/systemic antibacterials for ≥3 days when used for skin conditions ○ Other investigational drug • Topical Agents: ○ Topical antihistamines for ≥3 days when used for skin conditions ○ Topical antibacterials limited to gentamicin and neomycin ○ Other investigational drug 2. 10.4 Handling of Dropouts or Missing Data • Added a note to clarify example SAS code for multiple imputation. • Added a sentence to clarify that unscheduled visits will be included in the LOCF analysis.

Date	Reason for Update	Section Updated
		• Added a sentence to clarify handling more than one PP_NRS records collected on the same day. 3. 11.1 Primary Efficacy Analyses • Tipping point analysis: ○ Added a sentence that alternative approaches will be utilized if computational issues are encountered due to a large number of combinations. 4. 11.2 Secondary Efficacy Analyses • Added a sentence that for PP-NRS, if any day of the 7-day period used to compute the average weekly PP-NRS score is on or after the date of the intercurrent event, then the response will be considered a failure for the estimand analysis starting at that visit. 5. 13.1 Extent of Exposure • Clarified language around calculation of ○ Number of doses administered ○ Percent compliance • Removed: ○ 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. 6. 13.4 Clinical Laboratory Evaluation • Added "by visit" for Changes from baseline in abnormality status 7. APPENDIX C: LIST OF TABLES, LISTINGS, AND FIGURES Updated TOC per shell

Approval

Upon review of this document, including the table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable.



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LIST OF ABBREVIATIONS

Term	Description
AD	atopic dermatitis
ADaM	Analysis Dataset
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ATC	Anatomical/Therapeutic/Chemical
BMI	body mass index
BQL	below the quantification limit
BSA	body surface area
%BSA	percent of total body surface area
[redacted]	[redacted]
CSR	clinical study report
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
Dermavant	Dermavant Sciences, Inc.
DBP	diastolic blood pressure
[redacted]	[redacted]
[redacted]	[redacted]
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
EOT	end of treatment
[redacted]	[redacted]
ICH	International Council for Harmonisation
ITT	Intent-to-Treat
LOCF	last observation carried forward
LTS	Local Tolerability Scale
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputations
NRS	Numeric Rating Scale
OC	observed cases
OL-LTE	Open-Label, Long-Term Extension study
PK	Pharmacokinetic(s)
[redacted]	[redacted]
PP	Per-Protocol
PP-NRS	peak pruritus-numeric rating scale (daily itch score)
[redacted]	[redacted]

Term	Description
PT	preferred term
QC	quality control
QD	once daily
RTF	rich text format
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TF	Treatment Failure
TLF	tables, listings, figures
VAS	visual analog scale
vIGA-AD™	validated Investigator Global Assessment for Atopic Dermatitis
WHO-Drug Global	World Health Organization Global Drug Dictionary

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Dermavant Sciences, Inc.'s (Dermavant) Protocol DMVT-505-3101 [A Phase 3 Efficacy and Safety Study of Tapinarof for the Treatment of Moderate to Severe Atopic Dermatitis in Children and Adults]. The purpose of this plan is to provide specific guidelines for the statistical analyses. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the Statistical Analysis Plan (SAP):

- Protocol, Version 4.0, 09AUG2022
- Annotated case report form (CRF), Version 4, 01JUN2022
- Data management plan, Version 2, 24JUN2022

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of tapinarof cream, 1% once daily (QD) compared with vehicle control in subjects with atopic dermatitis (AD).

3.2 Secondary and Exploratory Objectives

The secondary and exploratory objectives of the study are as follows:

- To further characterize the efficacy of tapinarof cream, 1% QD compared with vehicle control over time
- To evaluate the safety and tolerability of tapinarof cream, 1% QD in subjects with AD
- To describe the effect of tapinarof cream, 1% QD on AD symptom severity and the associated impact on daily activities and attitudes in subjects with AD
- To evaluate plasma concentrations of tapinarof in subjects with AD

4. STUDY DESIGN AND PLAN

This is a double-blind, randomized, vehicle-controlled, Phase 3, multicenter study to evaluate the efficacy and safety of topical tapinarof cream, 1% compared with vehicle cream in children and adult subjects (ages 2 and above) with AD.

Following a 30-day screening period, eligible subjects will be randomized at a 2:1 ratio to receive QD treatment with tapinarof cream, 1% or vehicle cream for 8 weeks. Subjects will return to the clinic at Weeks 1, 2, 4, and 8 for efficacy and safety assessments. Additionally, subjects will be contacted by phone at Weeks 3 and 6 to assess adverse events (AEs) and

concomitant medications, to review study drug administration instructions, and to confirm subject's continued participation in this study.

Study drug will be dispensed and applied during the clinic visits and will be administered at home between clinic visits as instructed by site personnel.

Subjects or their caregivers will be instructed to apply study drug QD to all affected areas, including newly appearing lesions and lesions/areas that improve during the study. Subjects or their caregivers will apply sufficient study drug to cover completely each lesion with a thin layer of study drug and will record the time of study drug application and daily itch score (PP-NRS) in a daily diary provided by the study site. Subjects are allowed, but not required, to treat scalp lesions with study drug; however, efficacy analyses will not include assessment of AD in this area. Subjects and/or caregivers will be advised to maintain the approximate dosing time chosen at the beginning of the study for their full study participation. Nonmedicated emollients that do not contain salicylic acid may be used on nonlesional skin, but the subject (or caregiver) should wait at least 30 minutes after applying study drug before applying nonmedicated emollients; emollients should not be applied to lesional skin during treatment. The same emollient should be used throughout the subject's participation in the study. At the phone contacts at Weeks 3 and 6, subjects or caregivers should be reminded to complete their daily diary and bring it with them to the next clinic visit.

Study drug application instructions will be reviewed at all post-randomization clinic visits and during any planned study phone calls. On clinic visit days, subjects and/or caregivers will be instructed/reminded on how to apply study drug (except during the final treatment/end-of-study visits). During the clinic visits, subjects or their caregivers will apply the daily dose of study drug while on-site under the supervision of site personnel after efficacy and safety assessments have been completed, with the exception of the local tolerability scale (LTS) at some visits (as outlined in the Schedule of Assessments [Protocol Table 1]). The time of the dose application and assessments will depend on the time of the clinic visit. Therefore, the timing of the clinic visit may lead to a change in the subject's chosen dosing time for that day.

At the end of the 8 weeks of assessments in this study, subjects will have the option to enroll in an Open- Label, Long-Term Extension (OL-LTE) study for an additional 48 weeks. Subjects who complete Visit 6/Week 8 but choose not to participate in the OL-LTE study or who fail to qualify for participation in the OL-LTE study will complete a Follow-up Visit (Visit 7/Week 9 visit) approximately 1 week after the end of treatment in this study. Subjects who withdraw from the study before Visit 6/Week 8 will complete an Early Termination Visit as their final visit and are not eligible for the OL-LTE study. The subjects who complete the Early Termination Visit must not complete a Follow-Up Visit.

Study duration for subjects who complete this Phase 3 study and who fail to qualify for participation in the OL-LTE study, or who qualify to participate in the OL-LTE study but elect not to enroll in that study is approximately 13 weeks in total. Study duration for subjects who complete this Phase 3 study and are eligible and decide to participate in the OL-LTE study is approximately 12 weeks in total.

Efficacy assessments will include the validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) score, percentage of total body surface area (%BSA) affected, Eczema Area and Severity Index (EASI), PP-NRS, [redacted] Safety assessments will include treatment-emergent adverse events (TEAEs), clinical laboratory tests, physical examination, vital signs, and electrocardiograms (ECGs) (in a subset of subjects), and investigator and subject/caregiver local tolerability assessments. PK will be assessed in a subset of subjects at Week 4 and Week 8.

Refer to Protocol Section 6 for descriptions of study procedures and assessments and the Schedule of Assessments (Protocol Table 1) for timing of procedures and assessments. The study schema is presented in Protocol Figure 2.

5. DETERMINATION OF SAMPLE SIZE

It is estimated that the proportion of subjects who will achieve a vIGA-AD™ score of 0 or 1 and at least a 2-grade reduction from Baseline to Week 8 will be 45% for subjects receiving tapinarof compared with 25% for subjects receiving vehicle control, based upon the Phase 2 results. With 400 subjects randomized in a 2:1 ratio (267 subjects receiving tapinarof, and 133 subjects receiving vehicle control), this will provide 97.2% power for statistical significance (2-sided $p < 0.05$). The power is calculated from a Fisher Exact sample size calculation. It is assumed that 15% of the subjects receiving tapinarof will be lost to follow-up by 8 weeks compared with 30% of the subjects receiving vehicle control. These subjects will be included in the primary analysis using the multiple imputation method.

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Council for Harmonisation (ICH) numbering convention will be used for all TLFs. Unless otherwise noted, all statistical testing will be 2-sided and will be performed at the 0.05 significance level. Tests will be declared statistically significant if the calculated p-value is <0.05.

Continuous variables will be summarized by presenting the number of observations, means, standard deviations, medians, minimums, and maximums.

Categorical variables will be summarized by presenting counts and percentages of subjects in corresponding categories. All possible categories as defined in the case report form (CRF) should be populated, even if they have zero counts. Percentages for missing values are omitted and do not account for the percent calculation of other categories. Percentages are based on the total category count excluding the missing category if not otherwise mentioned. In certain tables (e.g., TEAEs), the total number of subjects is used as denominator. Footnotes will specify the percent basis in those cases.

All summary tables will be presented by treatment. Baseline summaries will also include a total summary column.

Individual subject data obtained from the eCRFs, external vendors, central clinical laboratory, ECG laboratory, pharmacokinetic (PK) data, and any derived data will be presented by subject in data listings.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock.

Any analyses performed after breaking the blind (after database lock, for unblinded studies) will be considered post hoc and exploratory. Post hoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using Statistical Analysis System® (SAS®) software Version 9.4 or higher. Tables, listings, and figures will be presented in rich text format (RTF).

The process for SAS program validation and quality control (QC) for programs and outputs is documented in the Synteract working instruction "SAS programming quality control." Study-specific QC requirements can be found in Appendix B: SAS programming QC requirements.

7. NOTATION OF TREATMENT GROUPS AND VISITS

Notation of treatment groups

The following notation of **treatment groups** will be used throughout the report:

Full* Notation *(as used in the study protocol)	***Notation* Used Throughout All Tables, Listings, *and* Figures**
Tapinarof Cream 1% Vehicle	Tapinarof Cream 1% Vehicle Cream

Visit terminology

Visit	***Notation* Used Throughout All Tables, Listings, *and* Figures**
Screening, Days -30 through Day -1, Visit V1	Screening
Baseline, Day 1, Visit V2	Baseline
Week 1, Day 8, Visit V3	Week 1
Week 2, Day 15, Visit V4	Week 2
Week 4, Day 29, Visit V5	Week 4
Week 8, Day 57, Visit V6 (End of Treatment)	Week 8
Week 9, Day 64, Visit V7 (End of Study/Follow-up) [1]	Week 9

Note: phone calls to assess AEs and concomitant medications, to review study drug application procedures, and to confirm subject's continued participation in the study will occur on Week 3 (Day 22) and Week 6 (Day 43).

[1] Subjects who choose not to participate in the OL-LTE study or who fail to qualify for participation in the OL-LTE study will complete a Follow-up Visit (Week 9 visit) approximately 1 week after the end of treatment in this study.

Analysis visits

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
Week 1	8	Post first dose to Day 12
Week 2	15	Day 13 – Day 21
Week 4	29	Day 22 – Day 42
Week 8	57	Day 43 – Maximum (last day of treatment + 3 days, Day 59)
Week 9	64	>Maximum (last day of treatment + 3 days, Day 59)

8. ANALYSIS SETS

The safety population will be used for the safety analyses and will include all randomized subjects who receive at least 1 application of study drug. Treatment assignment will be based on the treatment received.

The following subject populations will be used for efficacy analyses:

- The intent-to-treat (ITT) population will include all randomized subjects. Treatment assignment will be based on the randomized treatment.
- The per-protocol (PP) population will exclude ITT subjects with protocol deviations or other events that may impact the interpretation of the primary efficacy endpoint, regardless of whether the deviation(s) is considered major or minor. Exclusion criteria for the Per-protocol population may include:
    - Failure to meet the enrollment inclusion/exclusion criteria
    - Specified use of prohibited concomitant medication

Systemic Agents:

- Oral/systemic corticosteroids for >5 days
- Oral PDE4 inhibitors used for atopic dermatitis (e.g., roflumilast, apremilast); or other conditions if not on stable dose for period prior to and over course of the study
- Any oral immunosuppressive medication including cyclosporine, Imuran (azathioprine), methotrexate, tacrolimus, any Janus kinase inhibitor
- Injected IL4/13 blocking biologic including lebrikizumab, dupilumab
- Oral/systemic retinoids (e.g.,alitretinoin), if not on a stable dose for period prior to and over course of the study
- Other injected monoclonal antibodies with potential impact on AD (omalizumab)
- Oral/systemic antihistamines for ≥3 days when used for skin conditions
- Oral/systemic antibacterials for ≥3 days when used for skin conditions
- Other investigational drug

Topical Agents:

- Topical immunomodulators on affected skin (other than transient <5 days focal treatment for AESI) including topical corticosteroids, topical calcineurin inhibitors (Elidel, Protopic), topical PDE4 inhibitor (crisaborole/Eucrisa), coal car containing products
- Topical emollients containing keratolytics (including salicylic acid, urea) on affected skin (other than transient ≤7 days focal treatment for AESI)
- Topical antihistamines for ≥3 days when used for skin conditions
- Topical antibacterials limited to gentamicin and neomycin
- Other investigational drug

- Failure to be compliant with treatment regimen (compliance < 80%)

- Inclusion of scalp in efficacy assessment (see protocol section 5.1.5)

Final determination of subject inclusion in the PP population will be made before unblinding. Treatment assignment will be based on the treatment received.

The PK population will be used for the PK analyses and will include all subjects who undergo plasma PK sampling and have evaluable concentration-time data for analysis. A sample that is below the quantification limit (BQL) of the assay is considered evaluable. Treatment assignment will be based on the treatment received.

9. STUDY POPULATION

9.1 Subject Disposition

Subject disposition information will be summarized for all subjects by treatment and overall. Summaries will include: the number of subjects screened, the number of enrolled (randomized) subjects, the number of subjects in each 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, and number of days in the study (defined as study completion/discontinuation date – treatment start date + 1).

In order to describe the impact of COVID-19 on current study, the following disposition events will be summarized in the tables separately:

- Subjects discontinued from the treatment/study as a result of a positive COVID-19 diagnosis.
- Subjects discontinued from the treatment/study due to other reasons related to COVID-19. This is excluding COVID-19 diagnosis but may include reasons such as site closure, travel restrictions, fear of infection, etc.
- Subjects with study visits altered (including modified in-clinic visit, virtual and phone visits) and missed due to COVID-19.

COVID-19 related protocol deviations will be summarized separately. The impact of COVID-19 (including protocol deviation, visit alteration, treatment/study discontinuation and diagnosis of COVID-19) will also be flagged at subject-level in a data listing. Subject profile will be used to compile all COVID-19 related information for affected subjects.

Also, all COVID-19 related symptoms and confirmed cases that occur during the study will be reported as AEs and included in the summaries.

9.2 Protocol Deviations

Major protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified before database lock and unblinding of individual subject treatment information. Major protocol deviations may include, but are not limited to:

- Randomized subjects who did not satisfy selected inclusion and exclusion criteria;
- Subjects who received the wrong treatment or an incorrect dose;
- Subjects who received an excluded concomitant treatment;
- Failure to have a Week 8 assessment within ±7-day visit window;
- Non-compliance with the dosing regimen. A subject will be considered 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.

Reasons for exclusion of a subject from the analysis and protocol violations (minor/major) will be listed.

All protocol deviations, including the deviation designation (major or minor), category, and indication of whether the deviation led to an exclusion of a subject from the PP population, will be presented in a data listing.

Protocol deviations will be summarized by deviation category and treatment group. In addition, COVID-19 related protocol deviations will be summarized separately.

9.3 Eligibility

Subjects not fulfilling any eligibility criteria will be presented in a data listing.

9.4 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.

Other baseline characteristics include height, weight, body mass index (BMI), vIGA-AD^{TM}, %BSA, EASI score, and PP-NRS.

Demographic and baseline characteristics will be summarized for the safety, ITT, and PP populations.

Medical history
The verbatim term of the medical history condition/event will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.0.

A summary table will be prepared by treatment and in total. The summary will show the system organ class (SOC) and preferred terms (PT) ordered by descending subject count in the total column by SOC and PT.

9.5 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms in the eCRFs will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and preferred names using the WHODrug global dictionary (Version B3 01MAR2021).

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 for each treatment group. 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 class and preferred name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than 1 medication per ATC class 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. Each summary will be ordered alphabetically by ATC by descending PT subject count within each ATC.

Prior AD Medications

All systemic (oral and injectable) medications used by the subject for treatment of AD prior to 30 days before the Screening visit will be collected. Prior AD medications will be summarized by frequency count and percent by treatment and overall.

10. EFFICACY ANALYSES

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

10.1 Efficacy Variables

The primary efficacy endpoint is proportion of subjects who achieve vIGA-AD™ score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline at Week 8.

Secondary efficacy endpoints include the following:

- Proportion of subjects with ≥75% improvement in EASI score from Baseline at Week 8
- Mean change in %BSA affected from Baseline at Week 8
- Proportion of subjects with ≥90% improvement in EASI score from Baseline to Week 8
- Proportion of subjects ≥12 years old with a Baseline PP-NRS score ≥4 who achieve ≥4-point reduction in the average weekly PP-NRS from Baseline at Week 8

Exploratory efficacy endpoints include the following:

- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

10.2 Baseline Values

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.

10.3 Adjustments for Covariates

The model for the primary, secondary, and exploratory efficacy analyses will include adjustments for the following covariates:

- Primary, secondary, and exploratory categorical endpoints analyzed using CMH test for proportions will be stratified by vIGA-AD[redacted] score at Baseline (vIGA-AD[redacted] scores of 3 or 4) and by age group (2-6 yrs, 7-11 yrs, 12-17 yrs, 18+ yrs)

- Continuous secondary and exploratory efficacy endpoints (excluding Functional Outcomes and Quality of Life Endpoint) analyzed using ANCOVA models will include baseline vIGA-AD™ score and age group as a categorical covariate and the baseline value as a continuous covariate (see Section 11.2 and Section 11.3).

10.4 Handling of Dropouts or Missing Data

Imputation of Missing Efficacy Data

The principal method for handling of missing data will be multiple imputation (MI). MI will be performed separately using estimand requirements (MI estimand) and without estimand requirements (MI non-estimand). MI estimand will be considered primary.

For the MI estimand analyses investigator assessments including vIGA-AD™, EASI, %BSA based on data not collected at in-person visits (e.g., due to COVID-19 considerations) will be set to missing. Multiple imputation will be done as described in more detail below. Afterwards, using the MI estimand dataset, subjects who prematurely discontinue treatment due to an AE or lack of efficacy and subjects who use a specified prohibited medication prior to Week 8 will be considered a treatment failure at the time of treatment discontinuation or the date of initiation of prohibited medications for the primary and dichotomized secondary endpoints. For the continuous secondary endpoint of change from baseline BSA, BSA value will be set to the baseline value for the treatment failures specified above. For the MI non-estimand analyses, all visit assessments (including in-clinic and not in-clinic) will be included. Treatment failures will not be implemented as described previously for the MI estimand analyses.

For both the MI estimand and MI non-estimand analyses, 100 imputations will be generated using PROC MI of SAS. Fully Conditional Specification (FCS) model using the regression method will be used with the response (e.g., vIGA-AD™ score) at prior post-baseline visits, baseline vIGA-AD™ score, baseline age group, baseline value of the corresponding endpoint (for endpoints other than vIGA-AD™ score), and treatment group as covariates. The ROUND, MINIMUM and MAXIMUM options will be utilized to ensure imputed values are within appropriate ranges and precision. The seed to be used in all MI models is 20230421.

Two sets of MI datasets (MI estimand and MI non-estimand) will be generated for the vIGA-AD™ scores, EASI scores, %BSA, and PP-NRS results separately. Response status (Yes, No) will be derived from the imputed scores in each MI dataset. Analysis of each primary and secondary outcome will then be performed for each of the relevant MI datasets. The results of the 100 analyses will be transformed into a normal statistic and combined into a single analysis using PROC MIANALYZE.

[redacted]

[redacted]

[redacted]

The imputation models may be modified based on the actual data if there is an issue in model convergence.

Sensitivity analyses of the primary and secondary endpoints will be performed using MI (non-estimand), last observation carried forward (LOCF), observed cases (OC) (i.e., no imputation), and imputing missing data as Treatment Failures (TF). Only missing data up to Week 8 will be imputed. Missing data at the Week 9 Follow-up visit will be summarized as OC only.

LOCF: The last observed value will be carried forward for any subsequent missing values. Baseline values will not be carried forward. Unscheduled visits will be included.

TF: missing data will be imputed as treatment failures for responder endpoint.

Missing functional outcomes, quality of life endpoints or safety endpoints will not be imputed.

Average weekly PP-NRS scores will be calculated for all nominal visits as the average of 7 daily post-baseline PP-NRS scores prior to and including the values assessed on the visit date. If daily PP-NRS scores are missing for more than 3 days in a 7-day period, the average weekly PP-NRS score will be set to missing. If two or more scores are reported on the same day, the maximum score on that day will be used.

10.5 Interim Analysis and Data Monitoring

No interim analysis is planned for this study.

10.6 Examination of Subgroups

The primary and all secondary efficacy endpoints will be summarized descriptively in each baseline vIGA-AD™ subgroup, study center, age cohort (2-6 yrs, 7-11 yrs, 12-17 yrs, and ≥18 yrs), sex, race (White, Asian, Black or African American and Other), duration of disease (<2yrs, 2-5 yrs, >5 yrs), prior AD medication, baseline %BSA affected (<10% and ≥10%), and country (US and Canada). The %BSA Affected continuous outcome will be further explored with summaries of change and % change in %BSA affected at Week 8, by body region. The implications of any significant heterogeneity on the assessment of overall efficacy will be explored.

10.7 Multiple Comparison/Multiplicity

Multiple comparisons of the secondary endpoints will be controlled using the Fixed-Sequence method. Hypotheses testing for the secondary efficacy endpoints will only be conducted if the primary efficacy endpoint has demonstrated statistical significance at 0.05 two-sided in favor of tapinarof. Testing of the secondary endpoints will be performed sequentially following the below pre-specified order (see details in Section 11.2) using the MI estimand analyses:

- Proportion of subjects with ≥75% improvement in EASI from Baseline at Week 8
- Mean change in %BSA affected from Baseline at Week 8
- Proportion of subjects with ≥90% improvement in EASI from Baseline at Week 8
- Proportion of subjects ≥12 years old with a Baseline PP-NRS score ≥4 who achieve ≥4-point reduction in the average weekly PP-NRS from Baseline at Week 8

Hypothesis testing for secondary endpoints will stop if statistical significance at 0.05 two-sided in favor of tapinarof is not observed.

10.8 Multicenter Studies

There will be approximately 60 study sites in the United States (US) and Canada.

The primary and secondary efficacy endpoints will be summarized by study site using descriptive statistics. Exploratory analyses of the primary and secondary endpoints may be performed to elucidate any identified sources of heterogeneity in the results.

11. METHODS OF EFFICACY ANALYSIS

11.1 Primary Efficacy Analyses

The primary estimand of interest is the composite estimand in a patient population offered treatment with tapinarof cream, 1% as compared to vehicle. Interest is focused on the treatment

effect measured by the ratio of response rates at Week 8. The primary efficacy endpoint for treatment effectiveness is proportion of subjects who achieve vIGA-AD™ score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline at Week 8. Subjects who prematurely discontinue treatment due to an AE or lack of efficacy and subjects who use a prohibited medication with significant impact on efficacy evaluations prior to Week 8 will be considered treatment failure as of the start of the intercurrent event. Discontinuing treatment due to adverse event or lack of efficacy will be based on data recorded on the End of Treatment eCRF. Analysis will be based only on data collected at in-person visits for investigator assessments.

Estimand Attribute	**Description**
Treatment	tapinarof cream, 1% compared to vehicle
Population	Intent-to-treat
Variable of interest	Proportion of subjects who achieve vIGA-AD™ score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline at Week 8
Intercurrent event handling	Subjects who prematurely discontinue treatment due to an AE or lack of efficacy and subjects who use a prohibited medication with significant impact on efficacy evaluations prior to Week 8 will be considered treatment failure. Investigator assessments will only include data collected at in-person visits.
Summary measure	Ratio of response rates at Week 8

The primary efficacy comparison will test the following hypotheses:

H_0: The proportion of subjects who achieve a vIGA-AD™ score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline at Week 8 is equal between tapinarof cream, 1% and vehicle cream;

H_1: The proportion of subjects who achieve a vIGA-AD™ score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline at Week 8 is different between the tapinarof cream, 1% and vehicle cream.

The primary efficacy endpoint will be analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by vIGA-AD™ score at Baseline (vIGA-AD™ scores of 3 or 4) and age group (2-6 yrs, 7-11 yrs, 12-17 yrs, 18+ yrs) based on the ITT population using the MI estimand approach.

- For each of the 100 multiple imputation datasets, the CMH option in PROC FREQ will calculate the adjusted estimate of the common relative risk of achieving a vIGA-AD™ score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline at Week 8 (tapinarof/vehicle) over all strata with the corresponding 95% confidence interval (CI).

- The logit-based version of the estimates and confidence bounds will be log-transformed and the SE of the estimate of the log (relative risk) will be back-calculated from the log (confidence bounds) by assuming an asymptotic normal distribution.

- The estimates of the log (relative risk) and their standard errors for all the multiple imputation datasets will be input to PROC MIANALYZE to test the null hypothesis that tapinarof is not different from vehicle. The p-value of the combined results will be reported for interpretation.

- PROC MIANALYZE will output an overall estimate of the log (relative risk) and 95% CI. These will be exponentiated to produce an overall estimate of the relative risk and 95% CI.

- The treatment difference in mean proportion of subjects who achieve a vIGA-AD^{TM} score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline at Week 8 will be computed along with the 95% CI.

Sensitivity analyses in the ITT population will be conducted in which missing values are not imputed (i.e., OC), are imputed as TFs, imputed using LOCF, or imputed using the MI non-estimand approach. For the MI non-estimand analyses, efficacy will be tested as described above for the MI estimand approach. For the other sensitivity analyses, efficacy will be tested using a CMH test stratified by vIGA-AD^{TM} score at Baseline and age group.

Additional sensitivity analyses of the primary endpoint (in addition to MI non-estimand, LOCF, OC, and TF as specified in section 10.4) will be done as follows:

- tipping point analysis

  A tipping point analysis will be done using vIGA-AD^{TM} observed cases data. All possible combinations of the number of imputed successes (vIGA-AD^{TM} score of clear (0) or almost clear (1) and at least a 2-grade reduction from Baseline at Week 8) by treatment group will be enumerated, accounting for baseline vIGA-AD^{TM} and age group. CMH p-values will be computed for each combination and results will be summarized and displayed in a tipping point plot. . If computational issues are encountered due to a large number of combinations, then alternative approaches will be utilized.

Supporting analyses of the primary endpoint will also be performed:

- in the PP population using the MI estimand dataset only.

11.2 Secondary Efficacy Analyses

The dichotomized secondary endpoints will follow the same composite variable strategy estimand (MI estimand) as the primary analysis of the primary endpoint.

For PP-NRS, if any day of the 7-day period used to compute the average weekly PP-NRS score is on or after the date of the intercurrent event, then the response will be considered a failure for the estimand analysis starting at that visit.

Mean change in %BSA will be analyzed with an ANCOVA with factor of treatment and age group*vIGA-AD^{TM} score as a categorical covariate and baseline %BSA as a continuous covariate. The age group*vIGA-AD^{TM} score covariate cohort is as follows:

age group:	vIGA-AD™ score	age group* vIGA-AD™ score cohort
2-6 yrs	3	1
2-6 yrs	4	2
7-11 yrs	3	3
7-11 yrs	4	4
12-17 yrs	3	5
12-17 yrs	4	6
≥18 yrs	3	7
≥18 yrs	4	8

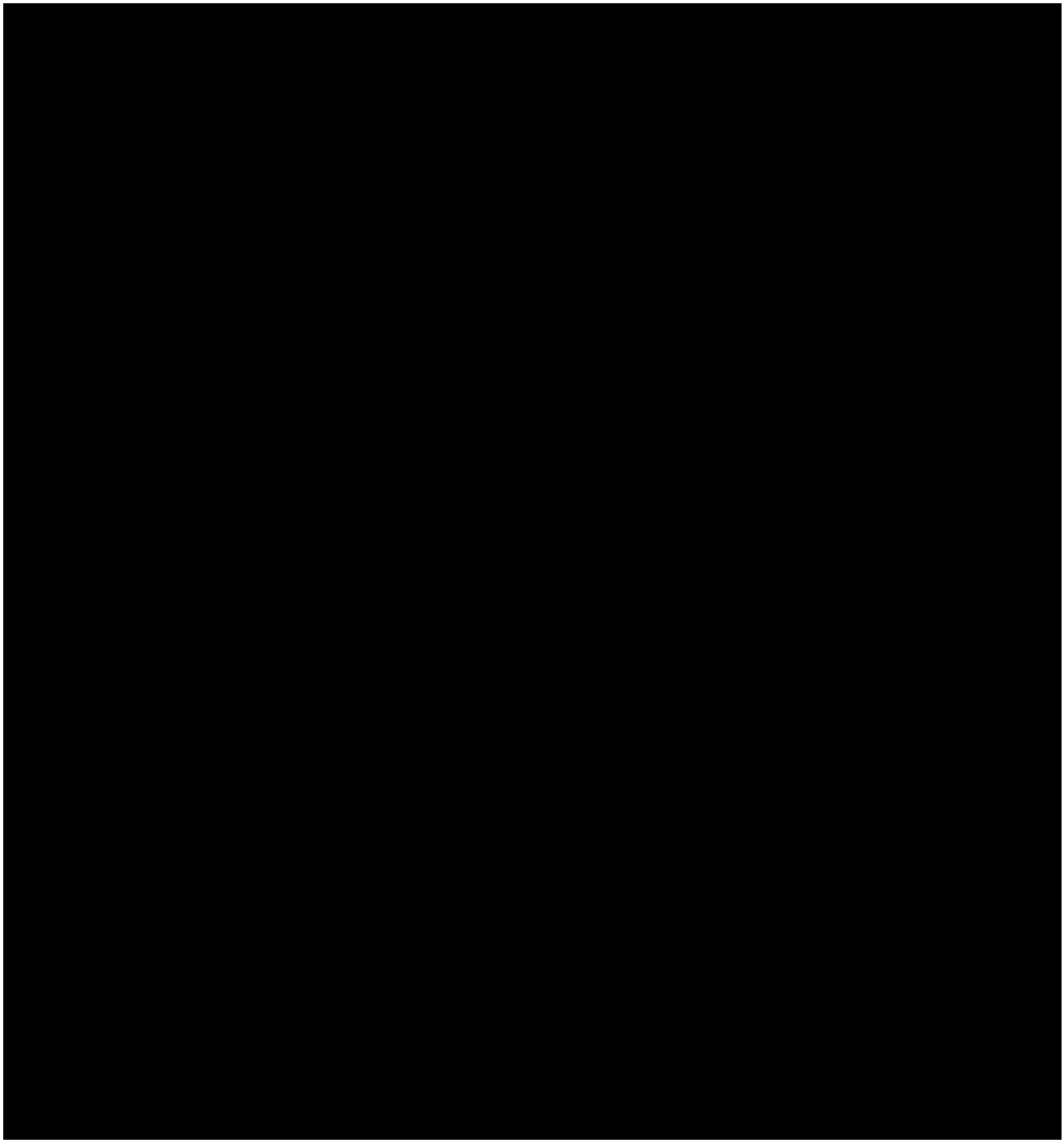
The standard MI procedures (Section 10.4) for ANCOVA will be followed. Least squared means of treatment difference (tapinarof – vehicle) along with the 95% CI will be reported. Change from baseline will be assigned to 0 in a manner corresponding to assignment of non-response for the dichotomized secondary endpoints for subjects who discontinue treatment due to an AE or lack of efficacy and subjects who use prohibited medication with significant impact on efficacy evaluations prior to Week 8.

The secondary efficacy endpoints will be tested sequentially using the MI estimand analyses. Testing will stop if non-significance (2-sided p ≥0.05) is observed as described in Section 10.7.

11.3 Exploratory Analyses

[redacted]

[redacted]



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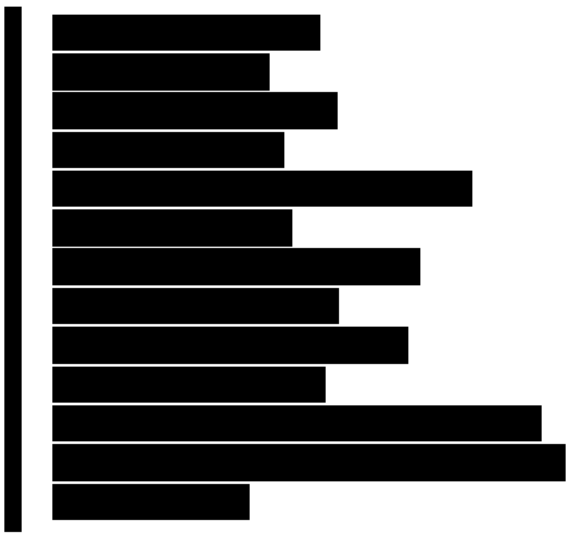

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12. PHARMACOKINETIC ANALYSES

All blood samples collected at Week 4 will be analyzed by the PK laboratory. Additionally, the PK laboratory will analyze Week 8 samples for subjects randomized to tapinarof cream, 1%.

12.1 Presentation of Plasma Concentrations

Individual plasma concentration results:

A raw data listing will be provided displaying the concentration as reported and the nominal and actual sampling times relative to start of dose administration. Results will be displayed using 3 significant digits. Listings will be sorted by treatment, subject, day, and time.

Summary statistics of plasma concentrations:

The plasma concentrations for each analyte will be summarized by treatment and the nominal time point at Week 4 and 8 (Days 29 and 57) using descriptive statistics (n, arithmetic mean, median, standard deviation (SD), minimum, and maximum. Additionally, plasma concentrations will be summarized by treatment group and nominal timepoint by (1) age cohort (2-6 yrs, 7-11 yrs, 12-17 yrs, and ≥18 yrs), (2) race (White, Asian, Black or African American and Other), (3) %BSA (<10% and ≥10%), and (4) plasma tapinarof concentrations divided by baseline %BSA affected.

Exploratory analyses may include relationships of plasma concentrations with patient demographics, efficacy parameters, and/or TEAEs.

13. SAFETY ANALYSES

All safety analyses will be based on the safety population. No formal comparisons will be made for safety data.

13.1 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 subject dose diary and the in-clinic dosing data. 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.

- Grams (g) of study drug administered, total and average per day. Drug administered is calculated as the summation of the difference between dispensed weight and returned weight for all returned tubes. Unreturned/unopened tubes will be assumed unused and will be included as 0 gram in amount drug used calculation.

- Percent compliance will be calculated as the (Number of Doses Administered) / (Number of Days Exposed) * 100.

- 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. .

13.2 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 such. Verbatim terms in the eCRFs will be mapped to SOCs and PTs using MedDRA (Version 24.0). The one exception will be the summary of Any AE which will include AEs not considered treatment-emergent. The summary of Any AEs will be reported in the Overall Summary of Adverse Events.

For subjects not rolling over to the OL-LTE study, all reported AEs will be included in the Double-Blind phase summaries. For subjects rolling over to the OL-LTE study, all AEs with an onset date on or before the Week 8 visit date will be included in the Double-Blind phase summaries.

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 8 visit for those who elect to participate in the OL-LTE study, or the Week 9 follow-up visit for those who fail to qualify for participation in the OL-LTE study, or who qualify to participate but ultimately elect not to enroll.

- 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 treatment and 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 leading to study discontinuation, and TEAEs related to study drug will also be listed separately. The following adverse events of special interest (AESIs) will be identified and listed separately: contact dermatitis, follicular event, and headache.

All AEs will be summarized by treatment as incidence rates of:

- Any AE

TEAEs will be summarized by treatment as incidence rates of:

- Any TEAE
- Any AESIs
- Any treatment-related TEAE
- Any TEAE leading to study drug discontinuation
- Any TEAE leading to study discontinuation
- Any SAE (non-Fatal)

- Any serious TEAE
- Death
- Treatment-related Serious TEAE
- Serious TEAE leading to study drug discontinuation
- Serious TEAE leading to study discontinuation
- TEAE (COVID-19) (i.e., positive COVID-19 diagnosis)

Individual PTs will be summarized by treatment according to the following:

- All TEAEs by SOC and PT in descending order of frequency for Tapinarof Cream 1% (also for treatment-related TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to study discontinuation and serious TEAEs)
- All TEAEs by SOC, PT, and maximum CTCAE grade
- All TEAEs by SOC, PT, and maximum causality (not related, related) to the study drug

In addition, TEAEs and serious TEAEs will be summarized by SOC (alphabetical order) and PT (descending order) for the following subgroups:

- Age (2-6 yrs, 7-11 yrs, 12-17 years, ≥18 years)
- Sex
- Race (White, Asian, Black or African American and Other)

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.

For treatment-emergent AESIs, summarization will be more extensive, reflecting the more detailed information collected. Information summarized will include number of events per subject, earliest onset day, duration (in days), causality, grade, and seriousness of AESIs, outcome, actions taken with study drug, assorted physical characteristics of the AESIs, and demographic/baseline characteristics and vIGA-AD™ status. Each type of AESI will be summarized separately. If a subject has more than one treatment-emergent occurrence of an AESI, the subject's maximum duration, highest levels of causality and seriousness, maximum grade and generally the most extreme level of each characteristic will be summarized. If an AESI is ongoing at time of study completion/discontinuation, it will not be included in the duration summary.

A Kaplan-Meier figure will be generated for each treatment-emergent AESI of time to first event. Subjects not experiencing the AESI will be censored at the date of study completion or discontinuation.

For purposes of CT.gov reporting, two additional summaries of AEs by SOC, PT and treatment group will be done as follows:

- including only PTs >= 1% (in either treatment group)
- including only PTs >= 5% (in either treatment group)

Each of these two summaries will include a total row summarizing the number of subjects with at least one of the PTs that meet the corresponding threshold.

13.3 Local Tolerability Scale (LTS) Scores

Local tolerability scale scores will be summarized with frequency counts and percent by treatment and visit for subject (or caregiver) overall assessment for burning/stinging and for itching (scores from 0=None to 4=Strong/Severe) and Investigator overall assessment for dryness, erythema, and peeling (scores from 0=No irritation to 4=Very Severe) separately. Additionally, observed values and change from baseline will be summarized by treatment and visit.

Local tolerability scale scores and change from Baseline scores at the sensitive areas (face, neck, skin folds, axilla, inframammary, anal crux, and genitalia) where study drug is applied will be summarized by visit, area, and treatment group for Investigator overall assessment, as well as listed by subject and anatomical site.

13.4 Clinical Laboratory Evaluation

Laboratory values will be classified as normal, low, or high based on normal ranges supplied by the laboratory. Changes from baseline in abnormality status will be summarized using shift tables by visit.

For quantitative laboratory measures, observed values and changes from baseline will be summarized descriptively by visit and treatment group.

13.5 Vital Signs

Vital signs (systolic and diastolic blood pressure [SBP and DBP], pulse rate, and body temperature) will be summarized using descriptive statistics at baseline and at each post-baseline time point. Changes from baseline will also be summarized.

Vital sign values in adults (≥18 yrs) will be classified as normal, low, high, based on reference ranges as per below. Subjects with markedly abnormal changes will be listed and tabulated separately.

	Absolute Values			Change (Absolute) from Baseline	
	Low	Normal	High	Abnormal Change	Markedly Abnormal Change
SBP	<90 mmHg	90-140 mmHg	>140 mmHg	≥20 mmHg	≥40 mmHg
DBP	<50 mmHg	50-90 mmHg	>90 mmHg	≥10 mmHg	≥20 mmHg
Pulse	<50 bpm	50-100 bpm	>100 bpm	≥10 bpm	≥30 bpm

Blood pressure in children (<18 yrs) will be classified as normal or elevated based on reference ranges as per Table below. Subjects with markedly abnormal changes will be listed and tabulated separately.

		Absolute Values		Change (Absolute) from Baseline	
Age		Normal	Elevated	Abnormal Change	Markedly Abnormal Change
2-6 yrs old	SBP	<105 mmHg	≥105 mmHg	≥20 mmHg	≥30 mmHg
	DBP	<67 mmHg	≥67 mmHg	≥10 mmHg	≥20 mmHg
7-11 yrs old	SBP	<110 mmHg	≥110 mmHg	≥20 mmHg	≥30 mmHg
	DBP	<74 mmHg	≥74 mmHg	≥10 mmHg	≥20 mmHg
12-17 yrs old	SBP	<120 mmHg	≥120 mmHg	≥20 mmHg	≥30 mmHg
	DBP	<80 mmHg	≥80 mmHg	≥10 mmHg	≥20 mmHg

Pulse in children (<18 yrs) will be classified as low, normal, or high based on reference ranges as per Table below. Subjects with abnormal (low or high) values will be listed and tabulated separately.

	Absolute Values		
	Low	Normal	High
2-10 yrs old	<60 bpm	60-140 bpm	>140 bpm
11-17 yrs old	<50 bpm	50-100 bpm	>100 bpm

13.6 Physical Examination

Physical examination results will be included in data listings only.

13.7 Electrocardiogram

The ECG data analysis will be conducted based on methodology recommended in the ICH E14 guideline (International Council for Harmonisation, 2005)[9].

Overall interpretation results for ECG will be summarized using shift tables (Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant) comparing baseline to end of treatment (Week 8). Descriptive statistics at baseline and at each post-baseline time point as well as changes from baseline will be summarized for each ECG parameter.

In addition, a categorical summary of abnormal corrected QT interval (QTc) values will be presented. At each time point, the number of subjects with QTc according to Fridericia's formula, QTcF and QTc according to Bazett's formula (QTcB) values of >450 ms, >480 ms, and >500 ms will be presented. At each post-baseline time point, the number of subjects with change from baseline values in QTcF and QTcB of >30 ms and >60 ms will be presented.

14. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

Not applicable. There are no changes to the protocol-specified analyses.

15. REFERENCES

1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6 [redacted]

[redacted]

[redacted]

9 US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythimic Potential for Non-Antiarrhythmic Drugs. Food and Drug Administration; October 2005. Available from https://www.fda.gov/media/71372/download

16. APPENDICES

APPENDIX A: PRESENTATION OF DATA AND PROGRAMMING SPECIFICATIONS

General

- Specialized text styles, such as bold, italics, borders, shading, and superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as nonprintable control characters, printer-specific, or font-specific characters, will not be used on a table, figure, or data listing.
- Hexadecimal character representations are allowed (e.g., μ, □, ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes must be used sparingly and must add value to the table, figure, or data listing.

Tables

- 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. If raw data has more than 2 decimal places, the same rule will be applied as the raw data with 2 decimal places. For MI tables with categorical endpoint, mean success %, median, min and max will be presented to 1 decimal place. Standard error will be presented to 2 decimal places.
- Percentages will be presented to the tenths place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will have zero percentages displayed. Results of one hundred percentages and zero percentages will have the same representation in tables as other percentages.
- Lower and upper CI values must be presented to 1 decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25%, 75%) must be presented to 1 decimal place more than the raw/derived data.
- For all inferential analyses, *P* values will be rounded to 4 decimal places (or at the highest level of precision) with a leading zero (0.0001). *P* values less than 0.0001 will be presented as "<0.0001."
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source **table number**(s) if applicable (in case aggregated results like mean or median are plotted), or the source listing(s) (in case individual responses are plotted), and/or source dataset(s) (e.g., ADaM).

- "PROGRAM SOURCE: ...\\xx.sas, RUN DATE: DDMMYY hh:mm".

Figures

- Legends will be used for all figures with more than 1 variable or item displayed. Treatment group sizes (n=xx) will be included, as appropriate.
- Figures will be in black and white but can be in color to add value to the clarity and readability of a figure. Lines must be wide enough to see the line after being copied.
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source listing number(s) and/or source dataset(s) (e.g., ADaM).
  - "PROGRAM SOURCE: ...\\xx.sas, RUN DATE: DDMMYY hh:mm".

Listings

- If not otherwise specified, all data listings will be sorted by treatment, subject number, visit, and date/time, as appropriate.
- All date values will be presented in a SAS date (e.g., YYYY-MM-DD) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.
- The last footnote will be
  - "PROGRAM SOURCE: ...\\xx.sas, RUN DATE: DDMMYY hh:mm".

Standard Calculations

Variables requiring calculation will be derived using the following formulas:

- **Days –** A duration expressed in days between 1 date (date1) and another later date (date2) is calculated using the formulas noted below:

  duration in days = date2 – date1 + 1
- **Months –** A duration expressed in months is calculated using the INTCK function of SAS as follows: months=intck('month','date1'd,date2'd, 'continuous').
- **Years –** A duration expressed in years between one date (date1) and another later date (date2) is calculated as follows:
  duration in years = intck('year', 'date1'd, 'date2'd, 'continuous').
- **Age –** Age at time of informed consent, reported on the CRF
- **Height –** Height entries made in inches (in) are converted to centimeters (cm) using the following formula:
  height (cm) = height (in) × 2.54.
- **Weight –** Weight entries made in pounds (lb) are converted to kilograms (kg) using the following formula:
  weight (kg) = weight (lb)/2.2046.
- **Temperature –** Temperature entries in degrees Fahrenheit are converted to degrees centigrade using the following formula:
  temp (degrees centigrade) = 5/9 × [temp (degrees Fahrenheit) – 32].

- **Body Mass Index (BMI) –** BMI is calculated using height (cm) and weight (kg) using the following formula:
  BMI (kg/m^2) = weight (kg)/ [[height (cm)/100]^2].
- **Change from baseline –** Change from baseline will be calculated as:
  Change = post-baseline value – baseline value.
- **Percent change from baseline –** Percent change from baseline will be calculated as:
  Percent change from baseline = (post-baseline value – baseline value)/baseline value × 100.

APPENDIX B: SAS PROGRAMMING QC REQUIREMENTS

Derived datasets are independently reprogrammed by a second programmer. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study Analysis Dataset (ADaM) Specifications provided to Dermavant at study conclusion.

Tables are independently reprogrammed by a second programmer for numeric results.

Listings are checked for consistency against corresponding tables, figures, and derived datasets.

Figures are checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.

The entire set of TLFs is checked for completeness and consistency prior to its delivery to Dermavant by the lead biostatistician and a senior level, or above, reviewer.

APPENDIX C: [redacted]

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DMVT-505-3101_SAPText_v2.0

Final Audit Report 2023-02-22

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