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Statistical Analysis Plan

Dermavant Sciences, Inc.

DMVT-505-3103

An Open-Label, Long-Term Extension Study to Evaluate the Safety and Efficacy of Tapinarof Cream 1% in Subjects with Atopic Dermatitis

Protocol Version: 2.0 16JUN2021

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Version	Date
1.0	21APR2023

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.

Signature / Date
[redacted] Apr 22, 2023
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Apr 24, 2023

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LIST OF ABBREVIATIONS

Abbreviation	Full Notation
AD	atopic dermatitis
ADaM	Analysis Dataset
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomical/Therapeutic/Chemical
BMI	body mass index
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
DBP	diastolic blood pressure
Dermavant	Dermavant Sciences, Inc.
[redacted]	[redacted]
[redacted]	[redacted]
EASI	Eczema Area and Severity Index
EOS	End of Study
EOT	End of Treatment
ICH	International Council for Harmonisation
[redacted]	[redacted]
ITT	Intent-to-Treat
LOCF	last observation carried forward
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
OC	observed cases
OL-LTE	Open-Label, Long-Term Extension study
PK	Pharmacokinetic(s)
[redacted]	[redacted]
PP-NRS	peak pruritus-numeric rating scale (daily itch score)
[redacted]	[redacted]
PT	preferred term
QC	quality control
QD	once daily

Abbreviation	Full Notation
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
TLFs	Tables, listings, and 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 DMVT-505-3103 [An Open-Label, Long-Term Extension Study to Evaluate the Safety and Efficacy of Tapinarof Cream 1% in Subjects with Atopic Dermatitis]. 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 2.0, 16JUN2021
- Annotated case report form (CRF), Version 1.0, 09SEP2021.
- Data management plan, Version 1, 08OCT2021.

3. STUDY OBJECTIVES

- To evaluate the safety and tolerability of tapinarof cream, 1% in subjects with atopic dermatitis (AD)
- To evaluate the efficacy of tapinarof cream, 1% over an extended period of time in subjects with AD
- To describe the effect of tapinarof cream, 1% on AD symptom severity and the associated impact on daily activities and attitudes in subjects with AD

4. STUDY DESIGN AND PLAN

This is an open-label, long-term multicenter, study to evaluate the safety and efficacy of topical tapinarof cream, 1% in subjects with AD. Subjects in this study will have either: a) completed treatment with tapinarof or vehicle in one of two Phase 3 pivotal safety and efficacy studies, DMVT-505-3101 or DMVT-505-3102, and rolled over into this study; b) completed treatment with tapinarof in the Phase 2 maximal use PK study, DMVT-505-2104, and rolled over into this study; or c) enrolled directly into this study. This study will consist of up to 48 weeks of treatment and a 1-week safety follow-up period.

At the completion of the Week 8 visit of study DMVT-505-3101 or study DMVT-505-3102 or the Day 28 visit of study DMVT-505-2104 (Baseline [Day 1] in this study), all eligible subjects will be offered enrollment in this open-label, long-term extension (OL-LTE) study. Approximately 125 additional pediatric subjects ages 2 to <18 years who are not eligible for participation in the Phase 3 pivotal studies (DMVT-505-3101 or DMVT-505-3102) will be enrolled directly into this OL-LTE study. Study visits during the treatment period for all subjects will occur every 4 weeks (±3 days). Unscheduled visits may occur, as needed. Subjects who withdraw from the study before Week 48 will return to the study site for an Early Termination

visit. The total duration of subject participation in this study will be approximately 49 weeks for rollover subjects (Baseline to Follow-Up) and approximately 53 weeks for direct-enrolling subjects (Screening to Follow-Up).

Rollover subjects in this study will begin treatment based on their validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™) score from the final visit in one of the three aforementioned studies (DMVT-505-3101, DMVT-505-3102, or DMVT-505-2104). Subjects entering with a vIGA-AD™ ≥1 will receive treatment with tapinarof cream, 1% once daily (QD) until they achieve a vIGA-AD™ score of 0, at which time treatment will be discontinued and subjects monitored for maintenance of disease control (i.e., the extent of the remittive effect). If/when disease worsening occurs, as evidenced by a flare to vIGA-AD™ ≥2, treatment will then be re-initiated and continued until a vIGA-AD™ of 0 is achieved. Subjects entering with a vIGA-AD™ of 0 will have treatment discontinued beginning at the Baseline visit and will be monitored for maintenance of the remittive effect. If/when disease worsening occurs, as evidenced by a vIGA-AD™ ≥2, treatment will then be re-initiated and continued until a vIGA-AD™ of 0 is achieved. This treatment and re-treatment pattern of use will be continued until the end of the study (i.e., subjects may receive study treatment up until the Week 48 visit).

Subjects enrolling directly into this study will receive treatment QD with tapinarof cream, 1% beginning at Baseline and continue treatment until they achieve a vIGA-AD™ score of 0, at which time treatment will be discontinued and subjects monitored for maintenance of the remittive effect. If/when disease worsening occurs, as evidenced by a flare to vIGA-AD™ ≥2, treatment will be re-initiated and continued until a vIGA-AD™ of 0 is achieved. This regimen of treatment and re-treatment will continue until the end of the study (i.e., subjects may receive study drug up until the Week 48 visit).

Study drug will be dispensed to subjects or their caregivers, applied during the clinic visits, and applied 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 until a vIGA-AD™ of 0 is achieved. Once a vIGA-AD™ of 0 is achieved, the treatment period ends. If/when disease worsening occurs, and treatment is re-initiated at a vIGA-AD™ of ≥2, all lesions currently present and any new lesions that occur during the new treatment period should be treated.

Subjects or their caregivers will apply sufficient study drug to cover each lesion completely 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 on the scalp. At the first clinic visit, if applicable, subjects and/or caregivers will be instructed to maintain the approximate dosing time for the daily application of study drug. At the phone contact at Week 2, 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 visit). 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 (except for Local Tolerability Scale [LTS] at Week 4 through Week 44). 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.

Safety assessments will include Adverse Events (AEs), clinical laboratory tests, physical examination, vital signs, and [redacted]. Efficacy assessments will include vIGA-AD™ score, percent of body surface area (%BSA) affected, Eczema Area and Severity Index (EASI), Peak Pruritus-Numeric Rating Scale (PP-NRS), [redacted]

Refer to Protocol Section 6 for descriptions of study procedures and assessments and Protocol Section 7 for timing of procedures and assessments.

5. DETERMINATION OF SAMPLE SIZE

The sample size of this study is based on the International Council for Harmonisation (ICH) E1A guideline on extent of population exposure to assess clinical safety for drugs intended for long term treatment of non-life-threatening conditions. Up to 961 subjects will be enrolled in this study across all regions, including up to 836 rollover subjects from studies DMVT-505-3101, DMVT-505-3102, and DMVT-505-2104 and approximately 125 subjects directly enrolling into this study.

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The ICH numbering convention will be used for all TLFs. The efficacy and safety results from this study will be summarized descriptively. There will be no statistical testing.

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 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., treatment-emergent adverse events [TEAE]), the total number of subjects is used as denominator. Footnotes will specify the percent basis in those cases.

Data will be summarized by the following categories: received tapinarof treatment in pivotal study; received vehicle treatment in pivotal study; total pivotal; received tapinarof treatment in maximal use study; enrolled directly; and overall total.

Individual subject data obtained from the CRFs, external vendors, central clinical laboratory, 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 before database lock.

All analyses and tabulations will be performed using SAS® software Version 9.4 or higher. Tables, listings, and figures will be presented in RTF format.

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%, rolling over from DMVT-505-3101 or DMVT-505-3102	Tapinarof Cream 1% (Pivotal)
Vehicle Cream, rolling over from DMVT-505-3101 or DMVT-505-3102	Vehicle Cream (Pivotal)
Tapinarof Cream 1% and Vehicle Cream (Pivotal)	Total (Pivotal)
Tapinarof Cream 1%, rolling over from DMVT-505-2104	Tapinarof Cream 1% (2104)
Tapinarof Cream 1%, enrolling directly into DMVT-505-3103	Tapinarof Cream 1% (Direct-Enroll)
Tapinarof Cream 1%	Total (Overall)

Visit terminology

Visit	*Notation* Used Throughout All Tables, Listings, *and* Figures
Screening, Days -30 to Day -1, Visit V0	Screening
Baseline, Day 1, Visit V1	Baseline
Week 4, Day 29 (±3 days), Visit V2	Week 4
Week 8, Day 57 (±3 days), Visit V3	Week 8
Week 12, Day 85 (±3 days), Visit V4	Week 12
Week 16, Day 113 (±3 days), Visit V5	Week 16
Week 20, Day 141 (±3 days), Visit V6	Week 20
Week 24, Day 169 (±3 days), Visit V7	Week 24
Week 28, Day 197 (±3 days), Visit V8	Week 28
Week 32, Day 225 (±3 days), Visit V9	Week 32
Week 36, Day 253 (±3 days), Visit V10	Week 36
Week 40, Day 281 (±3 days), Visit V11	Week 40
Week 44, Day 309 (±3 days), Visit V12	Week 44
Week 48, Day 337 (±3 days), Visit V13 (End of Treatment)	Week 48
Week 49, Day 344 (±3 days), Visit V14 (End of Study/Follow-up)	Week 49

Note: A phone call to review study drug application instructions, if applicable, and to record AEs and concomitant medication use will occur on Week 2, Day 15 (±3 days).

Analysis visits

Study days are measured from baseline (Visit 1) in the extension study. Study days corresponding to measurements are calculated as:

- Assessment date – date of baseline (Visit 1) + 1 if assessment date is on or after the date of baseline (Visit 1)
- Assessment date – date of baseline (Visit 1) if assessment date is before the date of baseline (Visit 1)

Efficacy and safety endpoints will be summarized according to the nominal visit as assigned by the investigator except for assessments collected on early termination visits. Early termination visit will be assigned based on the last nominal visit across all procedures and assessments and re-numbered to the last nominal visit number + 1. For example, if a subject attended Visit 1 (Baseline), Visit 2 (Week 4), Visit 3 (Week 8) and then early terminated, the early termination visit will be re-numbered and analyzed as Visit 4 (Week 12).

Unscheduled visits will not be re-numbered and will not be included in OC summaries but will be included in listings. Unscheduled visits will be included in the LOCF imputation by using

target day listed in the Visit Terminology table; for missing visits LOCF values will be based on scheduled and unscheduled visits occurring on or before target day.

8. ANALYSIS SETS

The following subject population will be used for safety and efficacy analyses:

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

9. STUDY POPULATION

9.1 Subject Disposition

Subject disposition information will be summarized and will include: the number of enrolled subjects, the number of subjects who apply any study medication, the number of subjects who complete the study and who withdraw from the study (together with reasons for withdrawal). The number of subjects whose drug was permanently withdrawn or interrupted due to AE, vIGA-AD™ score or other reasons will also be summarized over the entire study and by visit.

The number of days in the study, defined as the duration between date of study completion / discontinuation (or date of last visit if the study completion/discontinuation date is missing) and the date of Visit 1, will be summarized using descriptive statistics. A figure with Kaplan-Meier curves will also be generated to illustrate this information.

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.

Previous COVID-19 diagnosis and previous/on-study COVID-19 vaccination, and 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

Protocol deviations will be summarized by deviation category (major, minor) and will be listed by subject. In addition, COVID-19 related protocol deviations will be summarized separately.

9.3 Eligibility

Subjects not fulfilling any eligibility criteria (i.e., screen failures) will be presented in a data listing. Screen failure reasons for direct-enrolling subjects will be summarized by frequency in a table.

9.4 Demographic and Baseline Characteristics

Demographic variables include age, sex, ethnicity, race, and Fitzpatrick skin type. For subjects rolling over into the OL-LTE study, age will be based on age at time informed consent was signed in the pivotal or maximal use studies. Age for direct-enrolling subjects will be based on age at time informed consent was signed in the OL-LTE study.

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

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.

Medical history will be summarized descriptively. The summary will show the system organ class (SOC) and preferred terms (PT) sorted alphabetically by SOC followed by descending frequency preferred terms in the Total (Overall) column.

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 WHO-Drug Global dictionary (Version B3 01MAR2021).

Prior Medications

For rollover subjects, prior medications are those that were still being used within 30 days before Visit 1 (Baseline), and with a stop date prior to Visit 1. These medications will have been documented in the parent studies, and therefore, will not be presented in this study. For direct-enrolling subjects, prior medications are those that were still being used within 30 days before Screening (Visit 0), and with a stop date prior to first dose of study drug.

For direct-enrolling subjects, it is necessary to exclude previous medications that were stopped more than 30 days prior to Screening. Since the medication stop dates are sometimes partial dates, the following rules for medication stop dates will be used to distinguish between previous medications that will not be summarized (those stopping more than 30 days prior to Screening) and medications that will be summarized as Prior or Concomitant medications.

- If only year was recorded, and it is before the year of Screening Date – 30 days, it is a previous medication that will not be summarized; if year is same or after the year of Screening Date – 30 days, it will be summarized as a Prior or Concomitant Medication.
- If day is missing, but month and year are before those of the Screening Date – 30 days, it is a previous medication that will not be summarized; if month and year are the same as, or after, those of the Screening Date – 30 days, it will be summarized as a Prior or Concomitant Medication.
- If start date is after Screening Date – 30 days, it will be summarized as a Prior or Concomitant Medication.

Prior medications for direct-enrolling subjects will be summarized by WHO ATC class (level 2) and preferred name. The summary 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 summarization, a subject is counted once if he/she reported one or more medications at that level. The summary will be sorted alphabetically by ATC class followed by descending frequency preferred name. Prior medications for direct-enrolling subjects will be listed by subject.

Prior Systemic 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 reported for direct-enrolling subjects. Prior systemic AD medications for direct-enrolling subjects will be summarized by frequency count and percent.

Concomitant Medications

Concomitant medications are those medications that started on or after Visit 1 or medications that started before Visit 1 and continued until on or after baseline (Visit 1) for rollover subjects and continued on or after date of first dose for direct-enrolling subjects. 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 for rollover subjects, the following rules for medication 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.

To distinguish prior vs concomitant medications for direct-enrolling subjects, the following rules for medication stop dates will apply:

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

Concomitant medications will be listed by subject. Concomitant medications that are ongoing as of the end of the previous studies will be identified in the same listing.

Concomitant medications will be summarized by WHO ATC class and preferred name. Subjects may have more than one concomitant medication per ATC class and preferred name. At each level of summarization, a subject is counted once if he/she reported one or more medications at that level. The summary will be sorted alphabetically by ATC class followed by descending frequency preferred name in the Total (Overall) column.

10. EFFICACY ANALYSES

The efficacy analysis will be based on the ITT population.

10.1 Efficacy Variables

Efficacy endpoints

[redacted]

[redacted]

For subjects entering the study with a vIGA-AD™ score ≥1:

- Proportion of subjects who achieve vIGA-AD™=0 at least 1 time on or before Week 48
- [redacted]
- [redacted]

For subjects entering the study with a vIGA-AD™ score ≥2:

- Proportion of subjects who achieve vIGA-AD™=0 or 1 at least 1 time on or before Week 48
- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted] change and percent change from Baseline in %BSA affected by visit (OC and LOCF)
- [redacted]
- [redacted] change and percent change from Baseline in EASI score by visit (OC and LOCF)
- Proportion of subjects with ≥50% improvement in EASI score from Baseline by visit (OC and LOCF)
- Proportion of subjects with ≥75% improvement in EASI score from Baseline by visit (OC and LOCF)
- Proportion of subjects with ≥90% improvement in EASI score from Baseline by visit (OC and LOCF)
- Mean change in average weekly PP-NRS score from Baseline at each study visit (OC and LOCF)
- Proportion of subjects with a Baseline PP-NRS score ≥4 who achieve ≥4-point reduction in the average weekly PP-NRS from Baseline at each study visit (OC and LOCF)

[redacted]

[redacted]

[redacted]

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

10.2 Baseline Values

For subjects rolling over from DMVT-505-3101 or DMVT-505-3102 studies, baseline is defined as the assessment collected at Visit 6 (Week 8) in the pivotal study. If Visit 6 (Week 8) assessment is missing, then Visit 5 (Week 4) will be used as the baseline. If Visit 5 (Week 4) assessment is still missing, the baseline value will be considered as missing. For PP-NRS, baseline is defined as the assessment collected at Visit 6 (Week 8) in the pivotal study. If Visit 6 (Week 8) assessment is missing, then the last PP-NRS at home assessment will be used as the baseline.

For subjects rolling over from DMVT-505-2104 study, baseline is defined as the assessment collected at Visit 4 (Day 28) in the PK study. If Visit 4 (Day 28) assessment is missing, then Visit 3 (Day 8) will be used as the baseline. If Visit 3 (Day 8) assessment is still missing, the baseline value will be considered as missing. [redacted] For PP-NRS, baseline is defined as the assessment collected at Visit 4 (Day 28) in the PK study. If Visit 4 (Day 28) assessment is missing, then the last PP-NRS at home assessment will be used as the baseline.

For subjects rolling over from DMVT-505-3101, DMVT-505-3102 or DMVT-505-2104 studies, if there are multiple records on the same visit, use the one with later date as the baseline.

For subjects enrolling directly into DMVT-505-3103 study, baseline is defined as the last non-missing value recorded before the first dose of study drug.

Unscheduled visits will not be used in the determination of baseline values.

10.3 Adjustments for Covariates

No adjustments for covariates are planned for this study.

10.4 Handling of Dropouts or Missing Data

Efficacy endpoints will be summarized by visit using OC. Additionally, efficacy endpoints will be summarized by visit using LOCF to impute missing data. LOCF will include scheduled and unscheduled visits. Baseline values will not be carried forward.

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

An interim analysis will be performed to review safety data after at least 100 pediatric subjects (<18 years of age) have reached 48 weeks of potential active study drug treatment, inclusive of active study drug treatment in one of three parent (i.e., pivotal and maximal use) studies. All summaries will be produced for interim analysis.

The final analysis will be conducted after study completion (i.e., the last subject's last visit) and database lock.

10.6 Examination of Subgroups

For the following efficacy outcomes:

1. Proportions of subjects who achieve vIGA-AD^{TM}=0 at least 1 time during the study (for subjects entering the study with a vIGA-AD^{TM} score ≥1):
2. [redacted]
3. vIGA-AD^{TM} scores at Week 48 (LOCF)

4. [redacted] change and percent change from Baseline in %BSA affected at Week 48 (LOCF)
5. [redacted] change and percent change from Baseline in EASI score at Week 48 (LOCF)

Subgroup analyses will be generated for the following groupings:

- Baseline vIGA-AD™
- Age (2-6 yrs, 7-11 yrs, 12-17 yrs, ≥18 yrs)
- Sex
- Race (White, Asian, Black or African American, and Other)
- Baseline %BSA affected (<10%, 10%-<20%, 20%-<30%, ≥30%)
- Duration of disease (<2 yrs, 2-5 yrs, >5 yrs)
- Prior Systemic AD Medication
- Country (USA and Canada)

Race subgroup "Other" includes "American Indian or Alaska Native", "Native Hawaiian or other Pacific Islander" and "Multiple Races Checked",

10.7 Multiple Comparison/Multiplicity

No adjustments for multiplicity will be made in this study.

10.8 Multicenter Studies

This is multicenter study, with up to approximately 135 sites in the US and Canada participating in the study. Up to 961 subjects will be enrolled in this study across all regions, including up to 836 rollover subjects from studies DMVT-505-3101, DMVT-505-3102, and DMVT-505-2104 and approximately 125 subjects directly enrolling into this study.

Efficacy endpoints will be summarized by country.

11. METHODS OF EFFICACY ANALYSIS

11.1 Efficacy Analyses

All efficacy parameters will be summarized based on the ITT population. Summaries of efficacy endpoints by visit will be performed using OC and/or LOCF methods.

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

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

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12. PHARMACOKINETIC ANALYSES

No pharmacokinetic analysis is planned for this study.

13. SAFETY ANALYSES

All safety analyses will be based on the ITT population. Definition of baseline values is outlined in section 10.2.

13.1 Extent of Exposure

Subjects will be characterized by a series of treatment periods as defined in Section 10.1. These treatment period definitions are based on attainment of specified vIGA-AD™ values.

The following exposure and compliance parameters will be summarized descriptively:

- Total expected number of days exposed, calculated as the sum of number of days over all treatment periods.
- Total number of doses administered within treatment periods, calculated from the subject dose diary including in-clinic dosing and summed over all treatment periods. If a subject returns no diary records, then the number of home doses is assumed to be 0. If a subject has no clinic visits where study drug was administered, then the number of clinical doses is assumed to be 0.
- Percent compliance will be calculated as the (total number of doses administered within treatment periods) / (total expected 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.

In addition, the following exposure parameters will be summarized descriptively for the entire study (regardless of vIGA-AD™ status):

- Total number of doses administered, calculated from the subject dose diary and in-clinic dosing. If a subject returns no diary records, then the number of home doses is assumed to be 0. If a subject has no clinic visits where study drug was administered, then the number of clinical doses is assumed to be 0.
- Grams (g) of study drug administered. 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 grams in the amount drug used calculation. Average grams of study drug administered per dose will be calculated as the total grams / total number of doses administered. Subjects that had no diaries returned will not have average grams per dose reported.

13.2 Adverse Events

All AE summaries will be restricted to TEAEs. For rollover subjects, all AEs reported in this study will be considered as TEAEs except for those AEs resolved prior to the Visit 1 date in this study. For direct-enrolling subjects, all AEs that start after the first dose of study drug will be

considered a TEAE. Verbatim terms in the eCRFs will be mapped to PTs and SOCs using MedDRA, Version 24.0.

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 Visit 1 date, while the known month and year match the month and year of the Visit 1 date, the date of Visit 1 will be used as the new estimated date.

- 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.

- 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.

- If the start date or end date is completely missing, duration will not be calculated.

For AEs ongoing at the end of the previous studies, duration will be computed using the DMVT-505-3103 Visit 1 date as the AE start date.

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 TEAEs will be listed by subject, detailing the verbatim term given by the investigator, PT, SOC, onset date, end date, ongoing at the end of parent studies (Y/N), duration (days), CTCAE grade, outcome, relationship to study drug, action taken with study drug, other action taken to treat the event, AE of special interest (AESI) (Y/N), seriousness and criteria for seriousness.

AEs resolved prior to the Visit 1 date, Serious TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to study discontinuation and TEAEs related to study drug will also be listed separately. The following AESIs will be identified and listed separately: contact dermatitis, follicular event, and headache.

The frequency and percent of subjects with AEs will be summarized as incidence rates of:

- Any AE

The frequency and percent of subjects with TEAEs will be summarized as incidence rates of:

- Any TEAE
- Any TEAE excluding those ongoing at the end of the previous studies
- Any TEAE ongoing at the end of the previous studies
- Any treatment-emergent AESIs
- Any treatment-emergent AESIs excluding those ongoing at the end of the previous studies
- Any treatment-emergent AESIs ongoing at the end of the previous studies
- Any treatment-related TEAE
- Any TEAE leading to study drug discontinuation
- Any TEAE leading to study discontinuation
- Any serious TEAE
- Death
- Treatment-related serious TEAE
- Serious TEAE leading to study drug discontinuation
- Serious TEAE leading to study discontinuation
- TEAE (COVID-19)

TEAEs will be sorted alphabetically by SOC and decreasing PT frequency in the Total (Overall) group for the following:

- All TEAEs
- All TEAEs by maximum CTCAE grade

- All TEAEs by maximum causality (not related, related) to the study drug
- All TEAEs excluding those ongoing at the end of the previous studies
- All TEAEs ongoing at the end of the previous studies
- All treatment-related TEAEs
- All TEAEs leading to study discontinuation
- All TEAEs leading to study drug discontinuation
- All serious TEAEs
- All serious TEAEs leading to study discontinuation
- All serious TEAEs leading to study drug discontinuation

All TEAEs and all serious TEAEs will also be summarized by SOC (alphabetical order) and PT (descending order) for the following subgroups:

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

TEAEs by maximum CTCAE grade, TEAEs by maximum causality, TEAEs leading to study drug discontinuation and TEAEs leading to study discontinuation, will be summarized by SOC (alphabetical order) and PT (descending order) for the Age subgroup.

Furthermore, TEAEs will be categorized by day of onset among the following 4 categories:

- ≤12 weeks
- >12 to ≤24 weeks
- >24 to ≤48 weeks
- >48 weeks.

For each of these categories, TEAEs will be summarized by SOC in alphabetical order and PT in descending order of frequency. TEAEs ongoing at the end of the previous studies will be considered in the first category (i.e., day of onset ≤12 weeks).

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 to 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, assorted physical characteristics of the AESIs, and demographic/baseline characteristics and vIGA-AD™ status of the subjects experiencing them. 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 was ongoing at end of study (EOS), it will not be included in the duration summary. AESIs ongoing at the end of previous studies will also be included in the summary.

A Kaplan-Meier figure will be generated for each AESI of time to first event for events starting during the study. Time to first onset will be computed as Onset Date of First Occurrence – Date of Visit 1 + 1 if onset date is on or after visit 1 date. Otherwise, time to first onset will be computed as Onset Date of First Occurrence – Date of Visit 1. Subjects not experiencing the AESI will be censored at the date of study completion or discontinuation. AESIs ongoing at the end of the previous studies will not be included.

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13.4 Clinical Laboratory Evaluation

All clinical laboratory (hematology, clinical chemistry, and urinalysis) values will be listed by treatment group and subject. The reference normal ranges and reference range indicators (e.g., high, low, normal) will be supplied by the central laboratory and displayed in the data listings. Values outside the normal range for chemistry and hematology laboratory parameters will be

flagged. Change from baseline in abnormality status will be summarized using shift tables by visit. For quantitative measures, observed values and change from baseline in clinical laboratory values will be summarized descriptively by visit.

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

14. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

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

15. REFERENCES

1 [redacted]

2 [redacted]

[redacted]

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7 [redacted]

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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, α, 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.
- 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 (i.e., 0.0%) displayed if the denominator of the percentage is greater than 0. Categories with zero counts will be displayed as '0' without percentage if the denominator of the percentage is 0. Results of one hundred percent and zero percent will have the same decimal accuracy in tables as other percentages.
- Percentiles (e.g., 25%, 75%) must be presented to 1 decimal place more than the raw/derived data.
- 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 datatset(s) (e.g., ADaM).
  - "PROGRAM SOURCE: ...\\xx.sas, DATA CUT-OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

Figures

- Legends will be used for all figures with more than 1 variable or item displayed.
- 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 datatset(s) (e.g., ADaM).
  - "PROGRAM SOURCE: ...\\xx.sas, DATA CUT-OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".

Listings

- If not otherwise specified, all data listings will be sorted by sequence/treatment (pivotal/PK/direct enrolling), center, subject number, visit, and date/time, as appropriate.
- All date values will be presented in a SAS date (e.g., 29AUG2001) 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, DATA CUT-OFF DATE: DDMMMYYYY, 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 will be 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.

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DMVT 3103 SAP Signoff

Final Audit Report 2023-04-24

Created:	2023-04-22
By:	[redacted]
Status:	Signed
Transaction ID:	CBJCHBCAABAAhu2w0SRjB0UiH4k_ZqJFum7mWlWQ-WZr

"DMVT 3103 SAP Signoff" History

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