Statistical Analysis Plan

Dermavant Sciences GmbH

DMVT-505-2104

Open-Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Pediatric Subjects with Extensive Atopic Dermatitis

Protocol Version/Date: 2.0 16JUN2021

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Version	Date
1.0	08SEP2022

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
ATC	Anatomical/Therapeutic/Chemical
BMI	body mass index
BQL	below the quantification limit
BSA	body surface area
%BSA	percent of total body surface area
CSR	clinical study report
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
Dermavant	Dermavant Sciences, Inc.
DBP	diastolic blood pressure
EASI	Eczema Area and Severity Index
EOS	end of study
EOT	end of treatment
ICH	International Council for Harmonisation
ITT	Intent-to-Treat
LTS	Local Tolerability Scale
MedDRA	Medical Dictionary for Regulatory Activities
OC	observed cases
OL-LTE	Open-Label, Long-Term Extension
PK	Pharmacokinetic(s)
PP-NRS	Peak Pruritus-Numeric Rating Scale
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
TLF	tables, listings, figures

Term	Description
vIGA-AD™	validated Investigator Global Assessment for Atopic Dermatitis
WHODrug 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-505-2104 [Open-label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Pediatric Subjects with Extensive 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. 3, 13MAY2022
- Data management plan, Version # 2, 24JUN2022

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objectives of the study are as follows:

- To evaluate the safety and tolerability of tapinarof cream, 1% once daily (QD) in pediatric subjects ages 2 to 17 years old with extensive atopic dermatitis (AD)
- To evaluate the pharmacokinetics (PK) of tapinarof cream, 1% QD in pediatric subjects ages 2 to 17 years old with extensive AD

3.2 Secondary Objectives

The secondary objective of the study is to assess the efficacy of tapinarof cream, 1% QD in pediatric subjects ages 2 to 17 years old with extensive AD.

4. STUDY DESIGN AND PLAN

This is a Phase 2a, multicenter, open-label, safety, tolerability and PK study in pediatric subjects ages 2 to 17 years old with AD. The study will consist of 3 phases: Screening (up to 30 days), Treatment (27 days), and Follow-up (approximately 7 days).

At Day 1 (Baseline), eligible subjects and/or their caregiver(s) will be instructed on how to apply tapinarof cream, 1% while under the supervision of site personnel in the clinic and have collection of PK samples to assess systemic absorption. During the treatment period, subjects and/or their caregiver(s) will apply tapinarof cream, 1% to affected areas once a day for 27 days, including newly appearing lesions and lesions/areas that improve during the study. Subjects or 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 (Peak Pruritus-Numeric Rating Scale [PP-NRS]) in a daily diary provided by the study site. (Note that 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 will return to the clinic on Days 8 and 28 for study assessments. On clinic visit days, subjects and/or their caregiver(s) will apply study drug under the supervision of site personnel and instructed/reminded on how to apply study drug (except during the final treatment/end-of-study visits). Additionally, subjects will be contacted by phone at Day 15 to assess adverse events (AEs) and concomitant medications, to review study drug administration instructions, confirm subject's continued participation in this study, and reminded to complete their daily diary and bring it with them to the next clinic visit.

Study drug will be dispensed and applied to subjects during the clinic visits and will be administered at home between clinic visits as instructed by site personnel. 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; emollients should not be applied to lesional skin during treatment. The same emollient should be used throughout the subject's participation in the study.

Study drug application instructions will be reviewed at all post baseline clinic visits and during the planned study phone call. 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.

On Day 28 of this study, a final PK sample will be collected, and subjects will have the option to enroll in a separate open-label long-term extension (OL-LTE) safety study for an additional 48 weeks. Subjects who choose not to participate in the OL-LTE safety study or who fail to qualify for participation in the OL-LTE safety study will complete a Follow-up Visit (Day 35) approximately 7 days after the end of treatment in this study. Subjects who withdraw from the study before Day 28 will complete an Early Termination Visit as their final visit and are not eligible for the OL-LTE safety study. Subjects that complete an Early Termination Visit will not complete a Follow-up visit.

Study duration for subjects who complete this study and who fail to qualify for participation in the OL-LTE safety study, or who qualify to participate in the OL-LTE safety study but elect not to enroll in that study is approximately 9 weeks in total. Study duration for subjects who complete this study and are eligible and decide to participate in the OL-LTE safety study is approximately 8 weeks in total.

Efficacy assessments will include validated Investigator Global Assessment for Atopic Dermatits (v-IGA-AD^{TM}) score, % body surface area (%BSA) affected, eczema area and severity index (EASI), and PP-NRS. Safety assessments will include AEs, clinical laboratory tests, physical examination, vital signs, and local tolerability scale (LTS) assessments.

Pharmacokinetics will be assessed at Days 1 and 28. The screening blood sample will be used for baseline PK if the subject is enrolled. Blood samples for PK should not be collected from any anatomic site where study drug has been applied in order to minimize potential contamination.

Refer to protocol Section 6 for descriptions of study procedures and assessments and protocol Section 7 for the Schedule of Assessments (Table 1) for timing of procedures and assessments.

5. DETERMINATION OF SAMPLE SIZE

Approximately 36 subjects ages 2 to 17 years old will be enrolled in the study with approximately 12 subjects, and a minimum of 10 subjects, enrolled into each of the three following age cohorts: 2-6 years old, 7-11 years old, 12-17 years old.

There is no formal statistical hypothesis planned and the sample size is mainly based on feasibility and an estimated number of subjects needed to address the objectives of the study.

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.

All study data will be summarized by age group (2-6 years old, 7-11 years old, and 12-17 years old) and overall using descriptive statistics.

Categorical endpoints 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., AEs), the total number of subjects is used as denominator. Footnotes will specify the percent basis in those cases.

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

Individual subject data obtained from the eCRFs, external vendors (e.g., central clinical laboratory data, 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 database lock will be considered post-hoc and exploratory. Post-hoc analyses will be labeled as such on the output and identified in the CSR.

All TLFs will be programmed 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%	Tapinarof Cream 1%

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 4, Day 28, Visit V4 (End of Treatment)	Week 4
Week 5, Day 35, Visit V5 (End of Study/Follow-up)	Week 5

Note: A phone call 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 2 (Day 15).

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, PK, 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 18
Week 4 (End of Treatment)	28	Day 19 – Maximum (last day of treatment + 3 days, Day 31)

Analysis Visit	Target Day	Analysis Visit Window
Week 5 (End of Study)	35	>Maximum (last day of treatment + 3 days, Day 31)

8. ANALYSIS SETS

The safety population will include all enrolled subjects who receive at least 1 application of study drug. Subjects will be analyzed as treated. The safety population will be used for efficacy and safety analyses.

The PK population will include all subjects who undergo plasma PK sampling and have at least one evaluable concentration-time data available for analysis. A sample that is below the quantification limit (BQL) of the assay is considered evaluable. Subjects will be analyzed as treated.

The number of subjects screened, number enrolled, and the number of subjects in each population will be summarized.

9. STUDY POPULATION

9.1 Subject Disposition

Subject disposition information will be summarized and will include the number of subjects completing the treatment phase of the study, the number of subjects enrolling in the OL-LTE safety study, the number of subjects completing the study through follow-up and primary reason for discontinuation.

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

Protocol deviations will be summarized by deviation category (major, minor). COVID-19 related protocol deviations will be summarized separately. Additionally, protocol deviations will be presented in a data listing.

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™, %BSA, EASI score, and PP-NRS.

Demographic and baseline characteristics will be summarized for the safety population. In addition, demographic and baseline characteristics will be listed by subject.

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 in descending order based on subject count by system organ class (SOC) and preferred term (PT).

Atopic dermatitis history, cardiovascular risk factors, liver disease family history, previous COVID-19 diagnosis, and previous on-study COVID-19 vaccination will be summarized descriptively.

Medical history will be listed by subject.

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

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

- If only year was recorded, and it is before Baseline year, it is a prior medication; if year is same or after Baseline year, 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 by descending order of incidence of ATC class and preferred name within each ATC class.

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 performed based on the safety population.

10.1 Efficacy Variables

Efficacy endpoints include the following:

- Change in vIGA-AD™ score from Baseline at each study visit,
- Proportion of subjects who have a vIGA-AD™ score of clear or almost clear (0 or 1) and at least a 2-grade reduction from Baseline at each study visit,
- Proportion of subjects with ≥50% improvement in EASI score from Baseline at each study visit,
- Proportion of subjects with ≥75% improvement in EASI score from Baseline at each study visit,
- Proportion of subjects with ≥90% improvement in EASI score from Baseline at each study visit,
- Mean change and percent change in EASI score from Baseline at each study visit,
- Mean change and percent change in %BSA affected from Baseline at each study visit,
- Mean change and percent change in %BSA x vIGA-AD™ from Baseline at each study visit
- 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,
- Proportion of subjects ≥12 years old with a Baseline PP-NRS score ≥4 who achieve a ≥4-point reduction in the average weekly PP-NRS from Baseline at each study visit,

- Proportion of subjects 2 to <12 years old with a Baseline PP-NRS score ≥4 who achieve a ≥4-point reduction in the average weekly PP-NRS from Baseline at each study visit,
- Mean change in average weekly PP-NRS score from Baseline at each study visit.

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

Not applicable.

10.4 Handling of Dropouts or Missing Data

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.

Handling of partial or missing start and end dates for AEs can be found in Section 13.2.

No other missing data will be imputed.

10.5 Interim Analysis and Data Monitoring

No formal interim analyses will be performed; however, the Dermavant study team may review PK and safety data on an ongoing basis. This includes an analysis of the PK data after 25% of the subjects (n=9) have completed the study to re-assess the PK sampling scheme with the potential to eliminate the 5-hour post-dose blood draw. If required, changes to the protocol will be made through a protocol amendment.

10.6 Examination of Subgroups

Efficacy endpoints will be summarized by age group (2-6 yrs, 7-11 yrs, and 12-17 yrs) and overall.

10.7 Multiple Comparison/Multiplicity

Not applicable.

10.8 Multicenter Studies

There will be approximately 12 study sites in the United States (US) and Canada. Efficacy data will not be summarized by site; however, study sites will be identified in data listings.

11. METHODS OF EFFICACY ANALYSIS

11.1 Efficacy Analyses

All efficacy analyses will be performed based on the safety population. The efficacy endpoints will be summarized descriptively by age group (2-6 yrs, 7-11 yrs, and 12-17 yrs) and overall.

Categorical endpoints include:

- Proportion of subjects who have a vIGA-AD™ score of clear or almost clear (0 or 1) and at least a 2-grade reduction from Baseline at each study visit,
- Proportion of subjects with ≥50% improvement in EASI score from Baseline at each study visit,
- Proportion of subjects with ≥75% improvement in EASI score from Baseline at each study visit,
- Proportion of subjects with ≥90% improvement in EASI score from Baseline at each study visit,
- 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,
- Proportion of subjects ≥12 years old with a Baseline PP-NRS score ≥4 who achieve a ≥4-point reduction in the average weekly PP-NRS from Baseline at each study visit,
- Proportion of subjects 2 to <12 years old with a Baseline PP-NRS score ≥4 who achieve a ≥4-point reduction in the average weekly PP-NRS from Baseline at each study visit,

Continuous endpoints include:

- Change in vIGA-AD™ score from Baseline at each study visit,
- Mean change and percent change in EASI score from Baseline at each study visit,
- Mean change and percent change in %BSA affected from Baseline at each study visit,
- Mean change and percent change in %BSA x vIGA-AD™ from Baseline at each study visit
- Mean change in average weekly PP-NRS score from Baseline at each study visit by age group.

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

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

12. PHARMACOKINETIC ANALYSES

All pharmacokinetic analyses will be performed using a validated installation of Phoenix WinNonlin®, Version 8.1 or above (Certara, Princeton, NJ USA) as part of a 21 CFR Part 11 compliant database system (Phoenix Knowledgebase Server "PKS") and all the analyses will be stored on the PKS, with an audit trail for all the steps capturing the changes needed to finish the analysis.

Concentrations of tapinarof and tapinarof sulfate will be determined in plasma samples using a validated bioanalytical method. Raw data will be archived at the bioanalytical site. From the plasma concentration time data on Day 1 (1, 3-, and 5-hours post-dose), the following primary PK parameters will be determined, if data permit: AUC_{0-t}, C_{max}, $C\tau$, T_{max}, and T_{last}.

Analyses of the PK data will be performed after 25% of the subjects (n=9) have completed the study to re-assess the PK sampling scheme with the potential to eliminate the 5-hour post-dose blood draw. If required, changes to the protocol will be made through a protocol amendment. This analysis will be performed by Dermavant and is not considered to be a formal PK analysis.

12.1 Data Handling

Blood samples will be collected at Screening (to serve as the Baseline pre-dose sample), on Day 1 at 1, 3, and 5-hours post-dose and a single pre-dose sample on Day 28.

The raw plasma concentration data will be handled as follows:

For summary tables and figures for plasma concentrations:

1. The planned sampling time will be used in summary tables and the actual sampling times will be used for all figures of individual concentrations.
2. All concentration values < lower limit of quantification (BQL) will be set to zero.
3. Missing values will not be replaced.

For determination of PK metrics:

1. Actual sampling time will be used.
2. Concentration values <BQL before T_{max} will be set to zero. Therefore, a subject with BQL values for the entire sampling period will have a C_{max} of zero.
3. Concentration values <BQL that occur after a measurable concentration and followed by a value above the BQL will be set to missing.
4. Concentration values <BQL that occur at the end of the collection interval (after the last quantifiable concentration) will be set to missing.
5. Missing values will not be replaced.

12.2 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 (time since last dose). Results will be displayed using 3 significant digits.

Summary statistics of plasma concentrations:

The plasma concentrations for each analyte (i.e., tapinarof, tapinarof sulfate) will be summarized by nominal time point on Day 1 and Day 28 using descriptive statistics (n, arithmetic mean, standard deviation (SD), coefficient of variation (CV) % of arithmetic mean, median, minimum, maximum, geometric mean, and CV % for the geometric mean). The number of plasma concentrations that are BQL will be summarized by subject and the number and percentage of plasma concentrations that are BQL will be summarized overall.

Results will be displayed using 3 significant digits.

The CV % for the geometric mean will be calculated using the following formula:

$$CV\ (\%) = 100 * \sqrt{e^{SD^2} - 1}$$

where SD = standard deviation of the natural-log transformed data.

Figures:

Individual and mean concentration-time profiles on Day 1 will be provided on linear and semilogarithmic scales and may be presented with or without error bars. For individual concentration-time profiles, the actual sampling times will be used. Mean concentration-time profiles will be provided by age group and overall.

Overlaid individual and mean concentration-time plots on Day 1 for tapinarof and tapinarof sulfate will be provided in linear and semi-log scales.

Figures will be provided for the following relationships:

- Baseline %BSA of disease (x-axis) and Day 1 C_{max} (y-axis)
- Baseline %BSA of disease (x-axis) and Day 1 AUC_{0-t} (y-axis)
- Average grams of study drug administered per day (x-axis) and Day 1 C_{max} (y-axis)
- Average grams of study drug administered per day (x-axis) and Day 1 AUC_{0-t} (y-axis)
- Day 1 C_{max} (x-axis) and Day 1 C_{max} normalized by BSA (y-axis)
- Day 1 AUC_{0-t} (x-axis) and Day 1 AUC_{0-t} normalized by BSA (y-axis)

12.3 Determination and Analysis of PK Parameters

Full precision concentration data and actual sample times will be used for the determination of all PK parameters.

Raw plasma concentrations for the derivation of pharmacokinetic parameters will be handled as described in Section 12.1.

The following PK parameters will be derived, based on available data:

- **C_{max}** (pg/mL) – maximum observed concentration
- **T_{max}** (hr) – time of the maximum observed concentration
- **Cτ** (pg/mL) – last quantifiable concentration determined directly from individual concentration-time data
- **T_{last}** (hr) – time of the last quantifiable concentration
- **AUC_{0-t}** (pg•hr/mL) – area under the concentration-time curve from time zero to the last quantifiable concentration, calculated using a linear trapezoidal rule that includes summation from the time of the first measurable concentration to the time of the last measurable concentration as follows:

$$AUC_{0-t} = \sum_{i=1}^{n-1}\left[\frac{C_{i+1}+C_i}{2}(t_{i+1}-t_i)\right]$$

Where C_i is the *i*-th sample, t_i is the time of the *i*-th sample from dosing, and n is the number of available samples up to and including the final quantifiable concentration.

AUC values will be estimated using the linear-up, log-down method. A minimum of 3 data points are required for determination of an AUC.

The PK parameters as listed above will be obtained by non-compartmental analysis.

Individual PK parameters:

A raw data listing will be provided displaying the individual PK parameters. Results will be displayed using 3 significant digits.

Summary statistics of PK parameters:

Pharmacokinetic parameters (except T_{last} and Cτ) will be summarized using descriptive statistics (n, arithmetic mean, SD, CV % for the arithmetic mean, median, minimum, maximum, geometric mean, and CV % for the geometric mean). The geometric mean and CV % for the geometric mean will not be calculated for Tmax. Results will be displayed using 3 significant digits.

Summary statistics of PK parameters will be determined by age group and overall. PK parameters of C_{max} and AUC_{0-t} will also be normalized to %BSA at Baseline by dividing each parameter by cm^2 of BSA of disease. For this calculation, 1% BSA is equal to 185 cm^2.

13. SAFETY ANALYSES

All safety analyses will be based on the safety population.

13.1 Extent of Exposure

The following exposure and compliance parameters will be summarized descriptively:

- 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 including in-clinic doses. 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 (date of last dose – date of first dose +1 – number of missed doses) / (date of last dose – date of first dose + 1) * 100. Number of missed doses will be based on data from the summary missed doses form.

- Subject compliance, defined as ≥80.0% 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 treatment-emergent AEs (TEAEs), which are defined as those AEs that occurred after dosing and those pre-existing AEs (prior to first application of study drug) 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. 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.

Verbatim terms in the eCRFs will be mapped to SOCs and PTs using MedDRA (Version 24.0).

For subjects not rolling over to the OL-LTE safety study, all reported AEs will be included in the open-label maximal use summaries. For subjects rolling over to the OL-LTE safety study, all

AEs with an onset date on or before the Week 4 visit date will be included in the open-label maximal use summaries.

Imputation of Start and End Dates of Adverse Event

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 4 visit for those who elect to participate in the OL-LTE safety study, or the Week 5 Follow-up Visit for those who fail to qualify for participation in the OL-LTE safety 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 subject, detailing the verbatim term given by the Investigator, the SOC, PT, onset date, end date, common terminology criteria for adverse events (CTCAE) grade, outcome, relationship to study drug, action taken with study drug, other action taken to treat the event, seriousness, and criteria for seriousness. Serious AEs (SAEs), TEAEs related to study drug, TEAEs leading to study drug discontinuation, and TEAEs leading to study discontinuation will also be listed separately. The following adverse events of special interest (AESIs) will be identified and listed separately: contact dermatitis, follicular events, and headache.

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

- Any AE

TEAEs will be summarized as incidence rates of:

- Any TEAE
- Any treatment-related TEAE
- Any TEAE leading to study drug discontinuation
- Any TEAE leading to study discontinuation
- Any TEAE by maximum CTCAE Grade
- Any treatment-related TEAE by maximum CTCAE Grade
- Death
- Any treatment-emergent AESIs
- Any serious TEAEs

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^{TM} 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.

13.3 Local Tolerability Scale (LTS) Scores

Local tolerability scale scores will be summarized with frequency counts and percent by visit (through Week 4/End of Treatment [EOT]). 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 descriptively by visit and area 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.

For quantitative laboratory measures (chemistry and hematology), observed values and changes from baseline 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.

Blood pressure 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 mm Hg	≥105 mm Hg	≥20 mm Hg	≥30 mm Hg
	DBP	<67 mm Hg	≥67 mm Hg	≥10 mm Hg	≥20 mm Hg
7-11 yrs old	SBP	<110 mm Hg	≥110 mm Hg	≥20 mm Hg	≥30 mm Hg
	DBP	<74 mm Hg	≥74 mm Hg	≥10 mm Hg	≥20 mm Hg
12-17 yrs old	SBP	<120 mm Hg	≥120 mm Hg	≥20 mm Hg	≥30 mm Hg
	DBP	<80 mm Hg	≥80 mm Hg	≥10 mm Hg	≥20 mm Hg

Pulse 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.

14. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

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

15. REFERENCES

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 (eg, 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.
- Throughout the data cleaning process, all attempts will be made to avoid missing values for TEAE relationship and severity. If either or both are missing, no imputation will be performed.

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 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 (ie, to the same number of decimal places as the mean).
- Percentiles (eg, 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) (eg, ADaM).
  - “PROGRAM SOURCE: ...\\xx.sas, DDMMYY hh:mm”.

Figures

- Legends will be used for all figures with more than 1 variable or item displayed. Subject count (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 datatset(s) (eg, ADaM).
  - "PROGRAM SOURCE: ...\\xx.sas DDMMYY hh:mm".

Listings

- If not otherwise specified, all data listings will be sorted by subject number, visit, and date/time, as appropriate.
- All date values will be presented in a SAS date (eg, 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (eg, 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 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 –** will be reported in EDC based on informed consent date
- **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

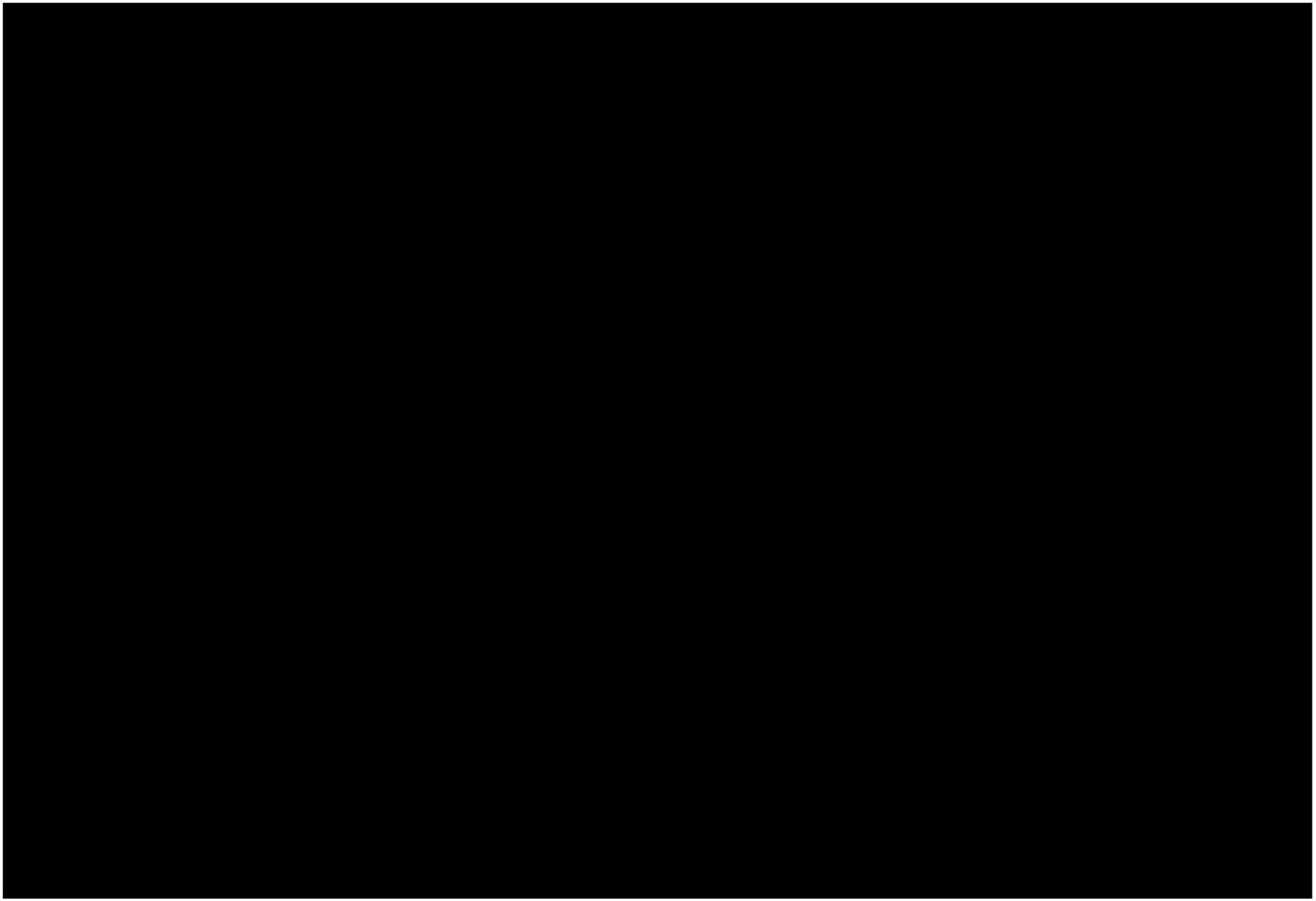
Derived datasets are independently reprogrammed by a second programmer. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study Analysis Dataset (ADaM) Specifications provided to Dermavant at study conclusion.

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

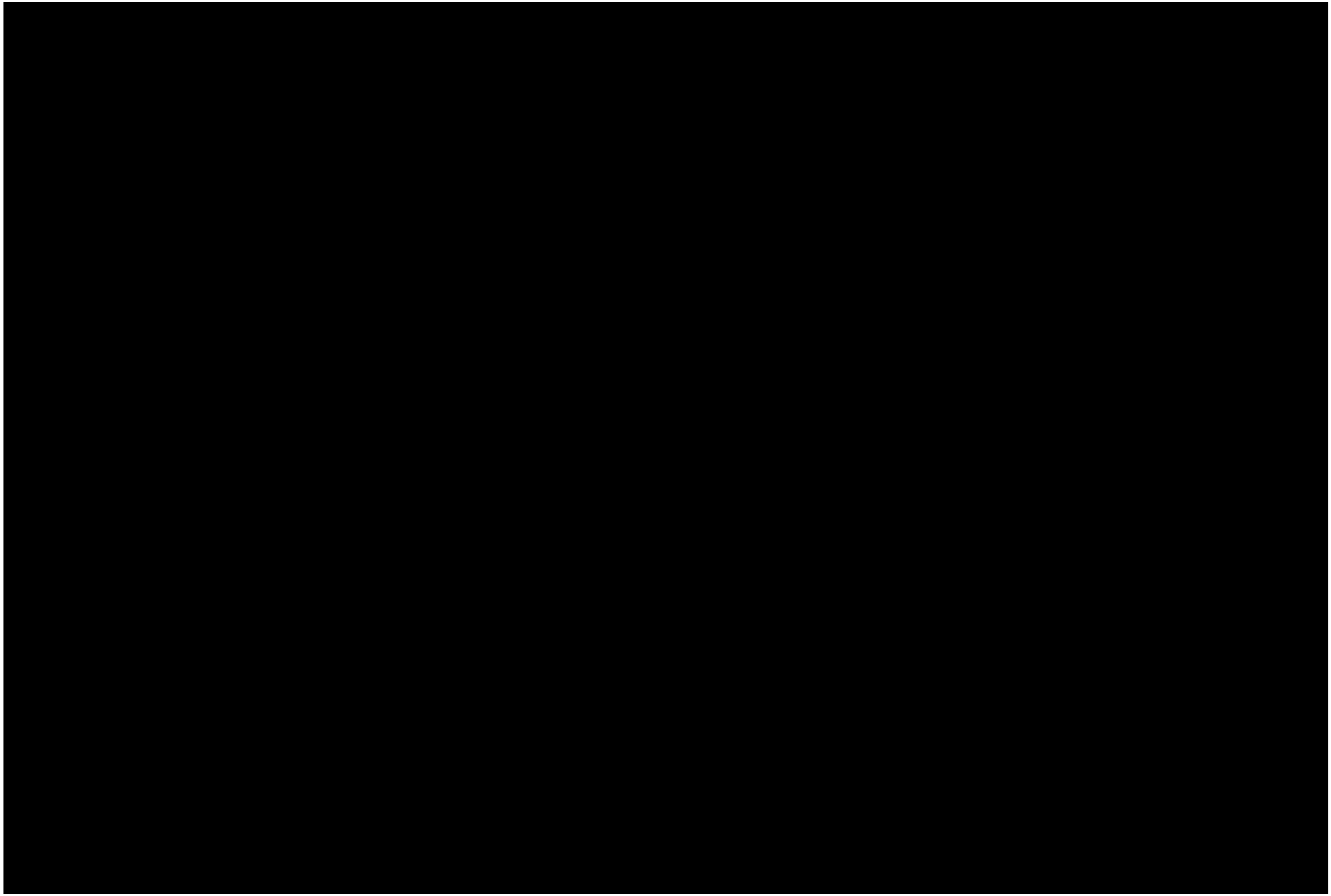
Listings are checked for consistency against corresponding tables, figures, and derived datasets.

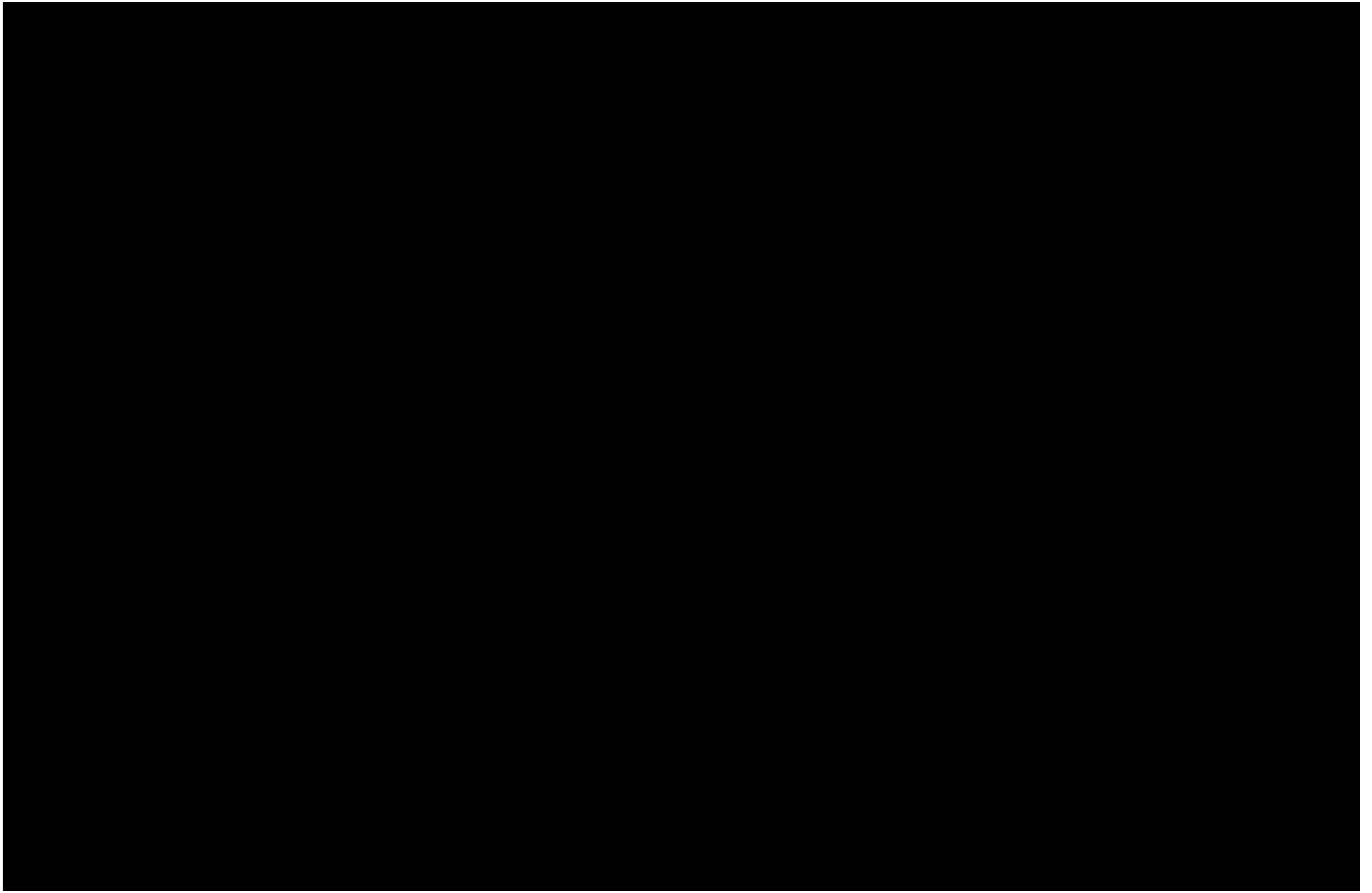
Figures are checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.

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.



[redacted]





[redacted]