[redacted]

Statistical Analysis Plan

Dermavant Sciences GmbH

DMVT-505-2002

Open-Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Adults with Extensive Plaque Psoriasis

Protocol Version: Original, 26-April-2019

Sponsor: Dermavant Sciences GmbH
[redacted]

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Version 1	14-January-2020
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SAP Revision Log

SAP Section	Brief Description of Revision	Date of Revision
11	Number of concentrations required for computation of AUC	06-FEB-2020
11	Methods of imputation for BQL data	06-FEB-2020

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]	
[redacted]	2/6/2020

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List of Abbreviations and Definitions of Terms

Term	Description
%BSA	percent body surface area
AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
AhR	aryl hydrocarbon receptor
ALT	alanine aminotransferase
Anti-HBc	anti-hepatitis B core antigen
AST	aspartate aminotransferase
$AUC_{0-\tau}$	area under the plasma concentration vs time curve in one dosing interval
BMI	body mass index
BP	blood pressure
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FSH	follicle-stimulating hormone
[redacted]	[redacted]
HBC	hepatitis C virus
HBsAg	hepatitis B surface antigen
Hep	hepatitis
HIV	human immunodeficiency virus

Term	Description
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	Institutional Review Board
IV	intravenous(ly)
LS	least squares
LTS	Local Tolerability Scale
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PK	pharmacokinetic(s)
PND	postnatal day
QTcF	QT interval corrected with Fridericia's formula
RBC	red blood cell(s)
SAE	serious adverse event
TEAE	treatment-emergent adverse event
t_{max}	time of maximum plasma concentration
$t_{1/2}$	elimination half life
ULN	upper limit of normal
UV	ultraviolet
WBC	white blood cell(s)
WOCBP	women of childbearing potential

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Dermavant Sciences GmbH Protocol DMVT-505-2002 [Open-Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Adults with Extensive Plaque Psoriasis]. The purpose of this plan is to provide specific guidelines from which the statistical analyses will proceed. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY DOCUMENTS

The following study documents were used for the preparation of the SAP:

- Protocol version 1.0, dated 26-April-2019
- Annotated electronic case report form (eCRF), version 1.4, dated 22-Jul-2019

3. STUDY OBJECTIVES

3.1 Primary Objectives

- To evaluate the safety and tolerability of tapinarof cream, 1% in adult subjects with extensive plaque psoriasis
  Associated endpoints including:
  - Frequency and severity of adverse events (AEs) (local and systemic)
  - Laboratory and biomarker values
  - Vital signs
  - Electrocardiograms (ECGs)
  - Mean Local Tolerability Scale (LTS) scores by visit

- To evaluate the pharmacokinetics (PK) of tapinarof cream, 1% in adult subjects with extensive plaque psoriasis
  Associated endpoints including:
  - Tapinarof and tapinarof sulfate (metabolite) plasma PK parameters on Day 1 and Day 29, if data permit, including: area under the plasma concentration vs time curve in one dosing interval ($AUC_{0-\tau}$), maximum plasma concentration (C_{max}), time of maximum plasma concentration (t_{max}) and elimination half-life ($t_{1/2}$).

3.2 Secondary Objectives

- To exclude clinically relevant effects of tapinarof cream, 1% on QT interval corrected by Fridericia's formula (QTcF)
  Associated endpoints including:
  - Analysis of change from Baseline in QTcF (ΔQTcF) at each post-treatment time point on the sampling day with the higher C_{max} (Day 1 or Day 29)

- Concentration-QTc analysis investigating the relationship between tapinarof plasma concentration and ΔQTcF, if data permit

- To assess the efficacy of tapinarof cream, 1% in adult subjects with extensive plaque psoriasis
  Associated endpoints including:
  - Mean change from Baseline to Day 29 in Physician Global Assessment (PGA), Psoriasis Area and Severity Index (PASI), and percent body surface area (%BSA)

3.3 Exploratory Objective

- [redacted]

4. STUDY DESIGN AND PLAN

This is a Phase 2a, multicenter, open-label study to evaluate the safety and PK of topical tapinarof cream in adults with extensive plaque psoriasis. The study will consist of 3 phases: Screening (up to 34 days), Treatment (29 days), and Follow-up (7 to 10 days).

At Day -1, eligible subjects will be enrolled into the study. During the treatment period beginning on Day 1 (Baseline), subjects will apply tapinarof cream, 1% to affected areas once a day for 29 days. Subjects will return to the clinic on Days 2, 15, 29, and 30 for study assessments and will receive a phone call on Days 8 and 22. Subjects will return to the clinic for a follow-up visit 7 to 10 days after the Day 29 visit. On clinic visit days, subjects will apply the study drug under the supervision of site personnel, after assessments have been completed. Full PK profiles and Holter monitoring will be collected on Day 1 and Day 29 (with corresponding 24-hour time points collected on Day 2 and Day 30, respectively). Limited PK sampling will be performed on Day 15. Pre-treatment, time-matched Holter monitoring will be conducted on Day -1 and the morning of Day 1.

Study drug will be dispensed to subjects during the clinic visits and will be administered at home between clinic visits as instructed by site personnel. Subjects will be instructed to apply study drug once daily to all affected areas, including newly appearing plaques and plaques/areas that improve during the study. Subjects 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 in a daily diary provided by the study site. Note that subjects are allowed, but not required, to treat palms, fingernails, soles, toenails, and scalp plaques with study drug. If a subject chooses to treat

plaques on palms, fingernails, soles, toenails, and/or scalp, they should do so for the entirety of the treatment period from Day 1 to Day 29. Subjects will be instructed to apply study drug in the morning throughout the entirety of their participation in the study. At the phone contacts at Day 8 and Day 22, subjects 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-baseline clinic visits. On clinic visit days, subjects will be instructed/reminded on how to apply study drug (except during the final treatment/end-of-study visits). During the clinic visits, subjects will apply the daily dose of study drug while on-site under the supervision of site personnel, after other assessments have been completed.

Subjects who withdraw from the study before Day 30 will complete an Early Termination Visit. Study duration for subjects who complete this study is approximately 10 weeks in total. Refer to the study protocol for further details (Section 6 for descriptions of study procedures and assessments and Section 7 and the Schedule of Assessments [Table 1] for timing of procedures and assessments).

Treatment Groups and Duration

All subjects will receive tapinarof cream, 1% for 29 days with once daily application.

A subject will be considered to have completed the study when he/she completes all required procedures/visits for the 29-day treatment phase.

5. DETERMINATION OF SAMPLE SIZE

This study will be conducted to evaluate the safety and PK of tapinarof cream, 1% in adult subjects with extensive plaque psoriasis. There is no formal statistical hypothesis testing 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.

Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories. Percentages are based on the number of non-missing results unless otherwise mentioned. Percentages showing a rate relative to the total number of subjects in this group are given in special tables (e.g., AE tables). Footnotes will specify the percent basis in those cases.

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

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.

Unless otherwise specified, the Baseline value for each variable is the last non-missing value prior to the initiation of study drug. No imputations will be made for missing values. Summaries will be based on observed data only. Unscheduled visits will not be summarized but will be included in the listings.

Conventions for handling partial dates and missing dates for AEs and prior and concomitant medications are given below. Listings will present the dates in their original format (without any imputation).

Missing or Incomplete Dates for Adverse Events and Concomitant Medications

Imputation of Start and End Dates of Adverse Events and Concomitant Medications

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. For AEs, the AE will be considered as a 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.
- 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. For an AE, if the year of start is the same or greater than the year of the first dose date, the AE will be considered as treatment emergent.
- 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 treatment emergent.

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) will be calculated using the following formula:
  Duration in days = date2 – date1 + 1
- **Body mass index (BMI)** – BMI will be 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.

7. ANALYSIS SETS

Safety Analysis Set

All subjects who receive at least 1 application of study drug will be included in the safety analysis set. Subjects will be analyzed as treated.

PK Analysis Set

All subjects who have at least 1 application of study drug and have at least 1 evaluable PK assay result will be included in the PK analysis set. A value that is below the limit of quantification is considered evaluable.

QT/QTc Analysis Set

The QT/QTc analysis set will include all subjects in the safety analysis set with measurements at Baseline as well as on-treatment with at least 1 post-dose time point with a valid ΔQTcF value.

PK/QTc Analysis Set

The PK/QTc analysis set will include all subjects who are in both the QT/QTc and PK analysis sets with at least 1 pair of post-dose PK and QTcF data from the same time point.

8. STUDY POPULATION

8.1 Subject Disposition

Subject disposition information will be summarized using the safety analysis set. The summary will include: the number of subjects in each analysis set, the number of subjects completing the study, and the primary reason for discontinuation.

8.2 Protocol Deviations

Major protocol deviations that could potentially affect the efficacy or safety conclusions of the study will be identified prior to database lock.

A listing of all protocol deviations including the deviation designation (major or minor) and deviation category will be presented in a data listing.

8.3 Eligibility

A listing of subjects not fulfilling any eligibility criteria will be created.

8.4 Demographic and Baseline Characteristics

Demographic variables include age, sex, ethnicity, race, height, weight, and body mass index (BMI). Age will be calculated in years relative to the informed consent date. Baseline characteristics include physician global assessment (PGA), percent body surface area affected (%BSA), and psoriasis area and severity index (PASI) score.

Demographic and baseline characteristics as well as medical history will be summarized using the safety analysis set. In addition, demographic and baseline characteristics as well as medical history will be listed by subject.

9. EFFICACY ANALYSES

All efficacy analyses will be performed based on the safety analysis set. The secondary study endpoints include mean change from Baseline at Day 29 in PGA, %BSA, and PASI. Descriptions of these endpoints can be found in Protocol Appendix 1 and 2.

The PGA, %BSA, and PASI will be summarized using descriptive statistics at Baseline and Day 29. Change and percent change from Baseline to Day 29 will be summarized descriptively including 95% confidence intervals and analyzed with a one sample t-test.

The one sample t-test will test the following hypotheses:

H_0: The mean change or percent change from baseline to day 29 in efficacy endpoint is equal to 0;

H_1: The mean change or percent change from baseline to day 29 in efficacy endpoint is not equal to 0;

SAS code examples:

```
proc ttest data=DATAset sides=2 alpha=0.05 h0=0;
     var CHG;       *PCHG-for Percentage Change*;
run;
```

CHG = Change from Baseline to Day 29. PCHG = Percentage change from Baseline to Day 29.

In addition to the above, the percent of subjects with treatment success at Day 29 will be summarized. Treatment success is defined as at least a 2-grade improvement from Baseline in PGA as well as a PGA score of clear or almost clear (score of 0 or 1) at Day 29. Percent of subjects with 1-point improvement and percent of subjects with 2-point improvement from Baseline at Day 29 will also be summarized.

In addition, Physician Global Assessment (PGA), Percent Body Surface Area (%BSA) Assessment and Psoriasis Area and Severity Index (PASI) Assessment will be listed by subject.

10. SAFETY ANALYSES

The safety analysis set will be used in the analysis of safety and biomarker data. Data will be listed by subject and summarized. No formal statistical comparisons will be made for safety data. Unless otherwise noted, baseline is defined as the last non-missing value recorded prior to the first dose of study drug.

10.1 Interim Analysis and Data Monitoring

There are no planned interim analyses for this study. The Sponsor may review PK data in an ongoing basis during the study.

10.2 Extent of Exposure and Measurement of Treatment Compliance

The extent of exposure to study drug will be summarized by the number of applications, number of missed applications and compliance with study treatment. A subject will be considered compliant with the dosing regimen if the subject applied 80% to 120% of the total number of expected doses during the treatment period. The expected number of doses during the treatment period is 29.

Dosing information will be presented in listings and will include the tube dispense and return weights as well as dates and time of study drug administration.

10.3 Prior and Concomitant Medications

Prior and concomitant medication verbatim terms in the eCRFs will be mapped to anatomical/therapeutic/chemical class and preferred names using the WHODrug Global B3 (version 01MAR2019).

- Prior medications are defined as medications with a stop date before the date of the first dose of study drug.

- Concomitant medication are medications with a start date on or after the date of first dose of study drug administration or are medications started before study drug administration and ended after study drug administration.

Prior and concomitant medications will be summarized 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.

10.4 Adverse Events

Treatment-emergent AEs (TEAEs) are defined as those AEs that occurred on or after the date of first dosing and those existing AEs that worsened during the study. Verbatim terms in the eCRFs will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) (version 22.0).

For this study, AEs of particular clinical importance will be reported as AESIs in the eCRFS to include: Contact dermatitis, Folliculitis and Headache which could be found from eCRF pages AESI Contact Dermatitis, AESI Folliculitis and AESI Headache, respectively. These AEs will not be summarized separately but rather will be included in the summaries described below.

Each AE summary will be summarized by system organ class and preferred term and ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries will include the following:

- Overall summary of AEs that contain an overview of each item below.
- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and highest severity. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported 1 or more events. Adverse events with missing severity will be considered severe for this summary.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to study drug (Related/Not Related). At each level of subject summarization, a subject is classified according to the closest relationship if the subject reported 1 or more events. Adverse events with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs leading to discontinuation of study drug by MedDRA system organ class and preferred term.

AEs, SAEs, AESIs and AEs of action taken with study treatment as drug discontinued will be presented in data listings.

10.5 Clinical Laboratory Evaluation

Laboratory assessments (chemistry, hematology and urinalysis) and serologic biomarker tryptase assessment will be summarized using descriptive statistics at Baseline and at each post-baseline time point of collection (see Table 1 Schedule of Events in the protocol). Change from Baseline will also be summarized.

Shift tables for laboratory assessments with low-normal-high at baseline versus low-normal-high at follow-up for the continuous laboratory assessments will be summarized to include low to low, low to normal, low to high, normal to low, normal to normal, normal to high, high to low, high to normal, and high to high at Day 29 and at follow-up (7-10 days after Day 29 or ET).

In addition, laboratory and [redacted] assessments will be listed by subject.

[redacted]

10.6 Vital Signs

Vital signs will be summarized using descriptive statistics at Baseline and at follow-up including change from Baseline. Additionally, shifts in vital sign assessments will be summarized to include the shift categories identified under laboratory assessments (Section 11.5) as well as abnormal change from Baseline and markedly abnormal change from Baseline.

Abnormal Flags will be determined as follows:

- Systolic Blood Pressure: Low= <90 mmHg; Normal= 90-140 mmHg; High= >140 mmHg;
- Diastolic Blood Pressure: Low= <50 mmHg; Normal= 50-90 mmHg; High= >90 mmHg;
- Heart Rate: Low=<50 bpm; Normal=50-100 bpm; High=>100 bpm;

Abnormal change from baseline will be determined as follows:

- Systolic Blood Pressure >=20 mmHg
- Diastolic Blood Pressure >=10 mmHg
- Heart Rate >=10 bpm

Markedly abnormal change from baseline will be determined as follows:

- Systolic Blood Pressure >=40 mmHg
- Diastolic Blood Pressure >=20 mmHg
- Heart Rate >=30 bpm

A listing of vital signs will also be presented.

10.7 Local Tolerability Scale

Local tolerability scale (LTS) overall score for dryness, erythema, and peeling will be summarized using descriptive statistics at Baseline and at Days 15 and 29 as will the number and percent of subjects who apply study drug to the following sensitive areas: face, neck, skin folds, axilla, inframammary, anal crux, and genitalia. If 5 more subjects treat a sensitive area(s) at any time during the treatment period, LTS scores will be summarized at Baseline and Days 15 and 29 for that specific area(s).

In addition, LTS scores will be listed by subject overall and by sensitive area as applicable.

10.8 Physical Examination

Nicotine usage assessed at Baseline and pregnancy test results at Screening, Baseline, and Follow-up will be presented in listings.

10.9 Cardiodynamic Assessments (Continuous Holter Monitoring)

ECG data from Baseline and while on study treatment will be collected using a 12-lead Holter monitor. ECG data will be summarized in tables, presented graphically in figures and listed in data listings by [redacted] The final [redacted]-signed SAP including mock TFLs can be found in Appendix D.

11. PHARMACOKINETIC ANALYSES

Unless otherwise specified below, missing sampling or concentration values should not be imputed, but left missing in the calculation of derived PK parameters. If the actual sampling time is missing, but a valid concentration value has been measured, the scheduled protocol time will be used for the calculation of derived PK parameters. A missing pre-dose value will be set to 0 for the PK calculations corresponding to an observation at dosing time.

All pharmacokinetic (PK) analyses and generation of the tables, figures, and listings (TFLs) will be performed using a validated installation of Phoenix WinNonlin® version 8.1 ([redacted]) as part of a 21 CFR Part 11 compliant database system (Pharsight Knowledge Database "PKS").

Blood samples for the analysis of tapinarof and its metabolite, tapinarof sulfate, will be collected pre-dose and post dose on Day 1 and Day 2 (Visits 3 and 4) as well as Day 29 and Day 30 (Visits

6 and 7) at 1, 2, 3, 4, 5, 8, 12, and 24 hours after dosing. On Day 15 (Visit 5), samples will be collected pre-dose and at 2- and 4-hours post dose (±10 mins). Samples collected outside the pre-determined intervals will be flagged and footnoted.

PK data from the PK population will be presented in listings. Plasma concentrations will be summarized using descriptive statistics. The number of plasma samples that were BQL will be summarized by subject and overall.

PK parameter estimates for tapinarof and its metabolite tapinarof sulfate on Day 1 and Day 29 will be calculated using non-compartmental analysis (NCA) of the plasma concentration versus time data utilizing actual sample collection time. NCA will be conducted using validated PK data analysis software (Phoenix WinNonlin version 8.1). AUC values will be estimated using the linear up-log down method. A minimum number of 3 data points are required for determination of AUC. The apparent first-order terminal elimination rate constant (λ_z) will be calculated as the negative of the slope from linear regression of the semi-log concentration-time curve during the terminal phase. The apparent first-order terminal elimination half-life, $t_{1/2}$, will be calculated as $0.693/ \lambda_z$. A minimum of three descending concentration-time points, excluding the Cmax, above the lower limit of quantification (LLOQ) will be used in the estimation of the terminal phase rate constant (λ_z), for the determination of the terminal half-life ($t_{1/2}$). PK parameter estimates are listed in Table 1, other parameters can be added, if data permits.

PK parameters Cmax and $AUC_{0-\tau}$ will also be normalized to %BSA treated by dividing each parameter by cm^2 of body surface area of disease. For this calculation, 1% BSA is equal to 185 cm^2.

Imputation of BQL data should be addressed as follows:

- If a BQL value occurs in a profile before the first measurable concentration, it will be assigned a value of zero concentration. Therefore, a subject with BQL values for the entire dosing interval will have a Cmax of zero.
- If a BQL value occurs after a measurable concentration in a profile and is followed by a value above the lower limit of quantitation (LLOQ), then BQL should be treated as 'missing'.
- If a BQL value occurs at the end of the collection interval (after the last quantifiable concentration) it will generally be treated as 'missing'
- If two BQL values occur in succession after Cmax, the profile will be deemed to have terminated at the first BLQ value and any subsequent concentrations will be omitted from pharmacokinetic calculations and individual plots, which are to reflect data that were used in the NCA, but will be maintained in concentration-time tables and plots of mean data

BQL values will be treated as zero for summary statistics tables or mean figures.

On a case by case basis, it may be necessary to exclude individual PK concentration values for the calculation of derived PK parameters because they are erroneous, abnormal or appear

implausible to the pharmacokineticist in charge of the analysis. Any excluded data will be flagged in the individual data listings. The reason for exclusion will also be documented. If the exclusion has a meaningful impact on the overall interpretation of the results, then it will be discussed.

Table 1: PK Parameters and Definitions

Parameter	Description of Parameter
C_{max}	The maximum observed concentration of tapinarof and its metabolite tapinarof sulfate measured after dosing
T_{max}	Time at which the Cmax is observed.
$AUC_{0-\tau}$	The area under the tapinarof and its metabolite tapinarof sulfate concentration versus time curve from time zero to the end of the dosing period
$t_{1/2}$	Apparent first-order terminal elimination half-life of tapinarof and its metabolite tapinarof sulfate

Individual PK parameter estimates from non-compartmental analysis, sorted by Day, will be listed for all individuals and will include tapinarof and its metabolite tapinarof sulfate.
PK parameters for tapinarof and its metabolite tapinarof sulfate will be summarized separately and will include the count, mean, geometric mean, standard deviation, CV%, median, min, max and geometric CV% range.

Individual Day 1 and Day 29 time-concentration graphs for tapinarof and its metabolite tapinarof sulfate will be provided for each subject in both linear and semi-log scales. Actual sampling times will be used for individual plots. Overlaid individual concentration-time plots by Day for tapinarof and its metabolite tapinarof sulfate will be provided in linear and semi-log scale. Mean concentration-time graphs by Day for tapinarof and its metabolite tapinarof sulfate will be provided in both linear and semi-log scales.

12. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

Note the following modifications and/or clarifications to the methodology specified in the protocol:

- The following efficacy summaries were added to Section 10 to include the primary endpoint of treatment success used in Phase 3 psoriasis studies as well as a summary of the percent of subjects with 1-grade and 2-grade improvement from Baseline at Day 29.
    - The percent of subjects with treatment success at Day 29 will be summarized. Treatment success is defined as at least a 2-grade improvement from Baseline in PGA as well as a PGA score of clear or almost clear (score of 0 or 1) at Day 29.

- Dosing compliance will be determined for each subject and summarized descriptively. A subject will be considered compliant with the dosing regimen if the subject applied 80% to 120% of the total number of expected doses during the treatment period. The expected number of doses during the treatment period is 29.

- Drug-related AEs will be summarized overall and by maximum severity.

13. REFERENCES

Not applicable

14. APPENDICES

Appendix A: Presentation of Data and Programming Specifications

General

- Specialized text styles, such as bold, italics, borders, shading, 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

- Formal organization of tabulations may be changed during programming, if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than 1 variable may be split into several 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.
- 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 not have zero percentages displayed.
- Lower and upper confidence interval values must be presented to 1 decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25%, 75%) must be presented to 1 decimal place more than the raw/derived data.
- For all inferential analyses, *P* values will be rounded to 4 decimal places (or at the highest level of precision) with a leading zero (0.0001). *P* values less than 0.0001 will be presented as "<0.0001."
- The last footnotes will be
  - "Source: xxx", where xxx indicates the source **table number**(s) if applicable (in case aggregated results like mean or median are plotted) or the source listing(s) (in case individual responses are plotted) and/or source dataset(s) (e.g., ADaM).
  - "PROGRAM SOURCE: ...\\xx.sas, DATA CUT OFF DATE: DDMMMYYYY, RUN DATE: DDMMYY hh:mm".
    where extract date is the date stamp of the data snapshot used.

Figures

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

Listings

- Formal organization of the listing may be changed during programming, if appropriate, e.g., additional variables may be included, change in the column order, or the listing may be split into multiple parts due to space constraints.
- If not otherwise specified, all data listings will be sorted by sequence/treatment, 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".
    where extract date is the date stamp of the data snapshot used.

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 Specifications provided to the client 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 the client by the lead biostatistician and a senior level, or above, reviewer.

Appendix C: List of Tables, Figures, and Listings

The following proposal for Sections 14 and 16.2 is completed according to ICH E3 guidelines. The ICH heading numbers and descriptions are in **bold**. Minor changes from this planned index do not need to be amended in the SAP.

Formal organization of tabulations may be changed during programming, if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than 1 variable may be split into several tables.

TABLES, FIGURES AND LISTINGS

ICH Table Number	Table Title
14	**TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT**
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14.1.2	Demographic Characteristics (Safety Analysis Set)
14.1.3	Baseline Characteristics (Safety Analysis Set)
14.1.4	Medical History (Safety Analysis Set)
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14.2	**Efficacy data**
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14.2.1.2	Physician Global Assessment (PGA) – Summary Statistics Including Change and Percent Change from Baseline (Safety Analysis Set)
14.2.2	Percent Body Surface Area (%BSA) - Summary Statistics Including Change and Percent Change from Baseline (Safety Analysis Set)
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14.3	**SAFETY DATA**
14.3.1	**Extent of Exposure, Dose Information, and Compliance**
14.3.1	Extent of Exposure and Study Drug Compliance (Safety Analysis Set)

ICH Table Number	Table Title
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14.3.2.1.3	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity (Safety Analysis Set)
14.3.2.1.4	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Closest Relationship to Study Drug (Safety Analysis Set)
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14.3.4.1.2	Summary of Clinical Laboratory Results, Shift from Baseline – Hematology (Safety Analysis Set)
14.3.4.2.1	Summary of Clinical Laboratory Results, Change from Baseline - Chemistry (Safety Analysis Set)
14.3.4.2.2	Summary of Clinical Laboratory Results, Shift from Baseline – Chemistry (Safety Analysis Set)
14.3.4.3.1	Summary of Clinical Laboratory Results, Change from Baseline - Urinalysis (Safety Analysis Set)
14.3.4.3.2	Summary of Clinical Laboratory Results, Shift from Baseline – Urinalysis (Safety Analysis Set)
14.3.4.4.1	[redacted]
14.3.5.1.1	Summary of Vital Signs - Change from Baseline (Safety Analysis Set)
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14.3.5.2.2.2	Local Tolerability Scale Assessments, Sensitive Areas Treated - Neck (Safety Analysis Set)
14.3.5.2.2.3	Local Tolerability Scale Assessments, Sensitive Areas Treated – Skin Folds (Safety Analysis Set)
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ICH Listing Number	Listing Title
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16.2.9.4.4	<Listings from [redacted]>
16.2.9.4.5	<Listings from [redacted]>
16.2.9.6	Individual Sampling Times and Concentrations of Tapinarof and Tapinarof Sulfate
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14.2.17	Mean (±SD) Tapinarof and Tapinarof Sulfate Concentration vs. Nominal Time on Day 1 (Linear scale) (PK Analysis Set)
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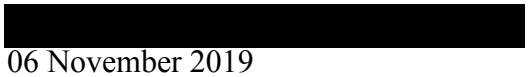
Appendix D: Statistical Analysis Plan for ECG Data

Statistical Analysis Plan

Open-Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Adults with Extensive Plaque Psoriasis

Protocol: DMVT-505-2002

Sponsor: Dermavant Sciences GmbH

Version: Final 1.0
Authors: 
Date: 06 November 2019

[redacted]

Revision History

Version	Issue Date	Author(s)	Description
Draft 0.1	14 August 2019	[redacted]	Initial version for review.
Draft 0.2	27 August 2019	[redacted]	Revised version.
Draft 0.3	25 September 2019	[redacted]	Revised version.
Final 1.0	06 November 2019	[redacted]	Final Version.

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1 Abbreviations

Abbreviation	Term/Description
BA	Bland-Altman
bpm	Beats per minute
CI	Confidence interval
C_{max}	Maximum plasma concentration
Δ	Change-from-baseline
ECG	Electrocardiogram
EPQT	Expert Precision QT analysis technique (formerly High Precision QT)
HR	Heart rate
LOESS	Locally weighted scatter plot smoothing
LS	Least squares
ms	Millisecond
PK	Pharmacokinetic(s)
PR	PR interval of the ECG
Q-Q	Quantile-quantile
QRS	QRS interval of the ECG
QT	QT interval of the ECG
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
RR	RR interval of the ECG
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
TQT	Thorough QT

[redacted]

2 Introduction

This statistical analysis plan (SAP) was developed after review of the protocol DMVT-505-2002 (Version 1.0 dated 26 April 2019) for the study "Open-Label Maximal Use Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Tapinarof Cream, 1% in Adults with Extensive Plaque Psoriasis" and the [redacted] contract/proposal. This document defines the populations to be analyzed and provides full details of the statistical analyses, data displays, and algorithms to be used for data derivations to aid in the production of the statistical output and the statistical section of the cardiac safety report in regard to electrocardiogram (ECG) and concentration-QTc analyses. Relevant subject characteristics as well as the electrocardiographic parameters that will be evaluated are described along with the specific statistical methods.

3 Study Design

This is a Phase 2a, multicenter, open-label study to evaluate the safety and pharmacokinetics (PK) of topical tapinarof cream in adults with extensive plaque psoriasis. The study will consist of 3 phases: screening (up to 34 days), treatment (29 days), and follow-up (7-10 days).

At Day −1, eligible subjects will be enrolled into the study. During the treatment period beginning on Day 1 (baseline), subjects will apply tapinarof cream, 1% to affected areas once a day for 29 days. Subjects will return to the clinic on Days 2, 15, 29, and 30 for study assessments and will receive a phone call on Days 8 and 22. Subjects will return to the clinic for a follow-up visit 7-10 days after the Day 29 visit. On clinic visit days, subjects will apply the study drug under the supervision of site personnel, after assessments have been completed. Full PK profiles and Holter monitoring will be collected on Day 1 and Day 29 (with corresponding 24-hour time points collected on Day 2 and Day 30, respectively). Limited PK sampling will be performed on Day 15. Pre-treatment, time-matched Holter monitoring will be conducted on Day −1 and the morning of Day 1.

Subjects who withdraw from the study before Day 30 will complete an early termination visit. Study duration for subjects who complete this study is approximately 10 weeks in total.

4 Cardiodynamic ECG Assessment

Continuous Holter recordings will be performed on Days −1, 1, 2, 29, and 30.

On Day −1, a Holter monitor will be attached for approximately 13 hours to collect pre-treatment, time-matched ECG data. Digital 12-lead ECGs will be extracted from the continuous recording at time points corresponding to time points on Day 1 and Day 29.

On Day 1 and Day 29, a Holter monitor will be attached 1 hour prior to dosing and for 12 hours post-dose. Digital 12-lead ECGs will be extracted at the same time points as PK samples, i.e., pre-dose and at 1, 2, 3, 4, 5, 8, and 12 hours post-dose.

[redacted]

On Day 2 and Day 30, a Holter monitor will be attached for 1 hour prior to the 24-hour post-dose PK time point to allow for extraction of 12-lead ECGs corresponding to the 24-hour post-dose PK time point.

Subjects will rest in a supine or semi-recumbent position for at least 10 minutes before and 5 minutes after each time point for ECG extraction. All ECG extractions will be performed immediately before the PK sample is drawn, when applicable.

All Holter/ECG data will be collected using M12R continuous 12-lead digital recorders and the M12A Enterprise Holter System Client (Global Instrumentation, LLC, Manlius, New York, USA). The equipment will be supplied and supported by [redacted]

ECG intervals will be measured by the core laboratory in a blinded manner using the Expert Precision QT technique (EPQT) (see Appendix A for more details). The ECG database will be locked before any statistical analysis is undertaken.

4.1 Cardiodynamic ECG Objectives

For the purpose of this analysis plan, objectives related to ECG assessment are described.

4.1.1 Primary Objective

The secondary objective of the study and the primary ECG objective is to exclude clinically relevant effects of tapinarof cream, 1% on the QTc interval using the Fridericia method (QTcF) in adult subjects with extensive plaque psoriasis.

4.1.2 Secondary Objective

The exploratory objective of the study and the secondary ECG objective is to [redacted]

4.2 Cardiodynamic ECG Endpoints

4.2.1 Primary Endpoint

The secondary endpoints of the study and primary ECG endpoints are change-from-baseline QTcF (ΔQTcF) at each post-treatment time point on the sampling day with the higher C_{max} (Day 1 or Day 29) and, if data permit, concentration-QTc analysis investigating the relationship between tapinarof plasma concentration and ΔQTcF.

4.2.2 Secondary Endpoints

[redacted]

[redacted]

- [redacted]

5 Statistical Methods

5.1 General Methodology

All statistical analyses will be performed using the statistical software SAS for Windows Version 9.4 or higher (SAS Institute, Inc., Cary, NC). In all calculations, zero will be substituted for concentrations below the quantification limit of the assay. Data collected from all enrolled subjects will be presented in data listings. Both absolute values and change-from-baseline values for each subject will be given where applicable. All continuous data will be listed with the same precision as will be presented in the database. Data listings will be sorted by subject ID and time point. Missing values will be represented by an empty cell and no imputation will be made.

Continuous data will be summarized using descriptive statistics including number of subjects (n), mean, median, standard deviation (SD), standard error (SE), 90% confidence interval (CI), minimum, and maximum by treatment and time point. Mean and median values will be rounded to the nearest tenth, or to the first non-zero decimal. SD, SE, and CI will be rounded to the nearest hundredth, or to 1 digit more than the nearest non-zero digit. For the concentration-QTc analysis, 3 significant digits will be kept for the effect estimates. *P* values will be reported with 4 digits and *P* values less than 0.0001 will be reported as < 0.0001. Categorical data will be summarized 2 ways, by subject and by time point. Subject data will be summarized using the count of distinct subjects that fall into the category and the percentage of the total number of subjects. Time point data will be summarized using the count of time points at which the assessments fall into the category and the percentage of the total number of time points at which assessments are performed. Percentages will be rounded up or down to the nearest tenths decimal place. Counts (either number of subjects or number of time points) for each treatment group will be used as the denominator in the calculation of percentages unless otherwise specified.

5.2 Analysis Sets

The analysis set for cardiodynamic ECG assessment are defined as follows (Table 1).

Table 1 Analysis sets for cardiodynamic ECG assessment

Analysis Set	Definition
Safety Analysis Set	All subjects enrolled in the study who receive at least 1 dose of study drug (tapinarof). Subjects will be analyzed as treated.
PK Analysis Set	All subjects who have at least 1 application of study drug and have at least 1 evaluable PK assay result. A value that is below the limit of quantification is considered evaluable.
QT/QTc Analysis Set	All subjects in the Safety analysis set with measurements at baseline as well as on-treatment with at least 1 post-dose time point with a valid

[redacted]

Analysis Set	Definition
	ΔQTcF value. The QT/QTc analaysis set will be used for the by-time point and categorical analyses of the cardiodynamic ECG parameters.
PK/QTc Analysis Set	All subjects who are in both the PK and QT/QTc analysis sets with at least 1 pair of post-dose PK and QTcF data from the same time point. The PK/QTc analysis set will be used for the concentration-QTc analysis.

5.3 Baseline

Time-matched baseline will be derived from measurements on Day −1 and the morning (pre-dose) of Day 1 for all continuous ECG parameters. For T-wave and U-wave, baseline includes any findings observed in any replicates from the time point that constitute time-matched baseline derived from Day −1 measurements.

5.4 QT Correction Methods

The QT and RR value for each beat will be used for HR correction. Replicate ECGs will be extracted in up to 10 replicates from each nominal time point prespecified in the protocol. The median value from each extracted replicate from evaluable beats will be calculated, and then the mean of all available medians (minimum 3 medians) from a nominal time point will be used as the subject's reportable value at that time point.

The Fridericia's correction QTcF is defined as $QTcF = QT/RR^{1/3}$.

6 Analysis

The Study Day to be used for all analyses (including by-time point analysis, categorical analysis, concentration-QTc analysis, and method bias sensitivity analysis) in this SAP will be either Day 1 or Day 29, depending on which day the highest mean C_{max} is observed. Based on the PK of tapinarof, it is expected that the highest mean C_{max} is observed on Day 1 and in such case, the analysis will be performed with data from all subjects on Day 1.

If tapinarof C_{max} is observed on the Day not chosen for the analysis, as described above, in a substantial proportion of subjects, , a sensitivity analysis may be performed using the concentration-QTc model from data on both days. The geometric mean C_{max} values for tapinarof on Day 1 and Day 29 will be determined, respectively, and the population point estimate and its 2-sided 90% CI for the predicted ΔQTcF interval at the geometric mean C_{max} will be obtained.

6.1 By-Time Point Analysis (Primary Analysis)

The QT/QTc analysis set on the selected Study Day, as described above, will be used for the by-time point analysis of cardiodynamic ECG parameters. The analysis for QTcF will be based on a linear mixed-effects model with ΔQTcF as the dependent variable; time (i.e., post-baseline time point on the

[redacted]

Study Day: categorical), treatment (tapinarof), and time-by-treatment interaction as fixed effects. An unstructured covariance matrix will be specified for the repeated measures at post-baseline time points within subjects. If the model with an unstructured covariance matrix fails to converge, other covariance matrices such as compound symmetry and autoregressive will be considered. From this analysis, the least squares (LS) mean and 2-sided 90% CI for ΔQTcF will be calculated at each post-baseline time point on the Study Day. If the upper bound of the 2-sided 90% CI lies below 10 ms for all post-baseline time points, tapinarof will be concluded not to have a clinically relevant effect on QT interval prolongation.

For HR, PR, and QRS intervals, the analysis will be based on the ΔHR, ΔPR, and ΔQRS, respectively. The same (by-time point analysis) model will be used as described for QTcF. The LS mean, standard error, and 2-sided 90% CI from the statistical modeling for change-from-baseline values will be listed in the tables and graphically displayed.

The SAS code for the by-time point analysis for QTcF is as follows.

[redacted]

6.2 Categorical Analysis

The QT/QTc analysis set on the Study Day will be used for the categorical analysis of cardiodynamic ECG parameters. Results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts and percentages for both number of subjects and number of time points on the Study Day.

A subject or time point will be determined as an outlier if the following criteria (which are assessed separately) are met for the ECG intervals (Table 2).

Table 2 Criteria for determining a subject or time point outlier

ECG interval	Categorical outlier criteria
QTcF	Treatment-emergent value of > 450 and ≤ 480 ms when not present at baseline (new onset)
	Treatment-emergent value of > 480 and ≤ 500 ms when not present at baseline (new onset)
	Treatment-emergent value of > 500 ms when not present at baseline (new onset)
	Increase of QTcF from baseline of > 30 and ≤ 60 ms
	Increase of QTcF from baseline > 60 ms

[redacted]

ECG interval	Categorical outlier criteria
PR	Increase of PR from baseline > 25% resulting in PR > 200 ms
QRS	Increase of QRS from baseline > 25% * resulting in QRS > 120 ms
HR	Decrease of HR from baseline >25% resulting in HR < 50 bpm
	Increase of HR from baseline >25% resulting in HR > 100 bpm

* In Section 10.4.3.3 of the protocol, it states a QRS increase from baseline >5%. This is an error in the protocol and it should be 25%.

All outliers will be summarized for each treatment group on the basis of incidence rates. If the subject experiences more than 1 episode of that event, then a subject will be counted only once for a particular outlier event. The total number of time points will be based on the number of observed time points across all subjects within a treatment group.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed, i.e., changes not present at baseline. For each category of T-wave morphology and of U-waves, the category will be deemed as present when observed in any replicates at the time point. For baseline, the category will be deemed as present when observed in any replicates from all time points that constitute baseline.

The T-wave morphology and U-wave presence categories are described as follows (Table 3).

Table 3 T-wave morphology and U-wave presence categories (assessed manually)

Category	Description
Normal T-wave (+)	Any positive T-wave not meeting any criterion below.
Flat T-wave	T-amplitude < 1 mm (either positive or negative), including flat isoelectric line.
Notched T-wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T-wave.
Biphasic	T-wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive/negative and negative/positive and polyphasic T-waves included).
Normal T-wave (-)	T-amplitude that is negative, without biphasic T-wave or notches.
Notched T-wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T-wave.
U-waves	Presence of abnormal U-waves.

[redacted]

The number and percentage of subjects in each treatment group having changes from baseline that represent the appearance of the morphological abnormality will be summarized. The total number of time points having a particular change category will be summarized in terms of number and percentage based on the number of observed time points across all subjects within a treatment group.

6.3 Concentration-QTc Analysis (Potential Exploratory Analysis)

A concentration-QTc analysis for tapinarof will be performed if a sufficient number of PK samples are above the lower limit of quantification to provide a PK profile, as defined in Section 13.1.2 of the SAP, for at least 50% of subjects.

The PK/QTc analysis set on the Study Day will be used in the potential exploratory concentration-QTc analysis. In this analysis, the relationship between tapinarof plasma concentrations and ΔQTcF will be investigated using a linear mixed-effects modeling approach with ΔQTcF as the dependent variable, time-matched tapinarof plasma concentration as the explanatory variable, a fixed intercept, and a random intercept and slope per subject, when applicable (Garnett et al).[1] The relationship between plasma concentrations of tapinarof sulfate (metabolite) and ΔQTcF will be investigatedif a sufficient number of PK samples are above the lower limit of quantification to provide a PK profile for tapinarof sulfate, as defined in Section 13.1.2 of the SAP, for at least 50% of subjects.

The geometric mean C_{max} values for tapinarof on the Study Day will be determined. The population point estimate and its 2-sided 90% CI for the ΔQTcF interval at the geometric mean C_{max} will be obtained.

The plot of the observed median-quantile tapinarof plasma concentrations and associated mean ΔQTcF (90% CI), together with the mean (90% CI) predicted ΔQTcF (as described by Tornøe et al[2]), will be used to evaluate the adequacy of the model fit to the assumption of linearity and the impact on quantifying the concentration-QTc relationship. For evaluation of the HR-corrected QT interval, a scatter plot and quantile plot of QTcF and RR intervals by treatment with a regression line and a linear mixed-effects line (90% CI), respectively, also will be produced. Additional exploratory analyses (via graphical displays and/or model fitting) will include accounting for a delayed effect (hysteresis, Section 6.3.1) and the justification for the choice of pharmacodynamic model (linear versus nonlinear, Section 6.3.2).

The SAS code for the concentration-QTc analysis is as follows.

[redacted]

6.3.1 Investigation of Hysteresis

Hysteresis will be assessed by graphical methods based on the LS mean of ΔQTcF for each post-baseline time point and the mean tapinarof plasma concentrations at the same time points. In addition, hysteresis plots will be given for LS mean ΔQTcF and the mean concentrations. If a QT effect (ΔQTcF) > 10 ms cannot be excluded in the by-time point analysis and if a delay between peak plasma levels and peak QT effect (ΔQTcF) in the plot (ΔQTcF versus tapinarof plasma concentration) of more than 1 hour is present, other concentration-QTc models such as a model with an effect compartment may be explored. With the provision stated above, hysteresis will be assumed if the curve of hysteresis plot shows a counterclockwise loop.

6.3.2 Appropriateness of a Linear Model

To assess the appropriateness of a linear model, normal Q-Q plots for the standardized residuals and the random effects, and plots of standardized residuals versus concentration and versus fitted values will be produced. The scatter plot of standardized residuals versus concentration by LOESS fitting (i.e., locally weighted scatter plot smoothing as described by Cleveland[3]) will also be produced with an optimal smoothing parameter selected by the Akaike information criterion with a correction.[4] In addition, a scatter plot of observed concentration and ΔQTcF with a LOESS smooth line with 90% CI and linear regression line will be provided to check the assumption of linear concentration-QTc relationship. If there is an indication that a linear model is inappropriate, additional models will be fitted, specifically an E_{max} model. The concentration-QTc analysis will then be repeated for the model found to best accommodate the nonlinearity detected.

6.4 Method Bias Sensitivity Analysis

The purpose of the Method Bias Sensitivity analysis is to ensure that the ECG measurement technique used by the central ECG laboratory, Expert Precision QT (EPQT), did not introduce bias at a level that would significantly affect the results.

The QT/QTc analysis set on the Study Day will be used for the Method Bias Sensitivity analysis. In this analysis the fully automated measurements from the iCOMPAS software will be compared to the results of the EPQT measurement technique, as described by Ferber et al.[5] In Bland-Altman (BA) plots, QTcF values from fully automated iCOMPAS measurements from the 5-minute time window will be subtracted from the QTcF values using EPQT at the same time point for each subject; obtained differences were displayed as a function of the mean of the two.[6] The relationship between the means and differences of the 2 methods will be investigated by robust regression using an M estimator, which reduces the impact of individual outlier values.[7] From the model, the fitted slope (hereafter called the BA slope) and associated 2-sided 95% CIs will be given to show the linear trends between the 2 variables. The BA slope indicates whether the observed difference between methods varies with the magnitude of the absolute QTcF value. A negative BA slope would indicate that the central ECG laboratory method (in this case, EPQT) measures relatively shorter QTcF intervals at prolonged levels than does the fully automated reference method (iCOMPAS), i.e., EPQT introduces a negative bias and may underestimate the QTcF prolongation.

The unit of BA slope is given as ms per QTcF range of 100 ms; a value of, for example, -10 ms per QTcF range of 100 ms is hereafter given as -0.10 ms. A bias exceeding -0.10 would indicate that EPQT has introduced a bias severe enough to negatively impact the result, potentially leading to false negative predictions using concentration-QTc analysis.[5]

6.5 Determination of Sample Size

This study will be conducted to evaluate the safety and PK of tapinarof cream, 1% in adult subjects with extensive plaque psoriasis. Approximately 20 subjects aged 18 to 75 years will be enrolled in the study. 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.

7 References

1. Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. [Published correction appears in *J Pharmacokinet Pharmacodyn*. 2018;45(3):399]. *J Pharmacokinet Pharmacodyn*. 2018;45(3):383-397.
2. Tornøe CW, Garnett CE, Wang Y, Florian J, Li M, Gobburu JV. Creation of a knowledge management system for QT analyses. *J Clin Pharmacol*. 2011;51(7):1035-1042.
3. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc*. 1979;74(368):829-836.
4. Hurvich CM, Simonoff JS, and Tsai CL. Smoothing parameter selection in nonparametric regression using an improved Akaike Information Criterion. *J R Stat Soc Series B Stat Methodol*. 1998;60(2):271-293.
5. Ferber G, Zhou M, Dota C, Garnett C, Keirns J, Malik M, Stockbridge N., and Darpo B. Can Bias Evaluation Provide Protection Against False-Negative Results in QT Studies Without a Positive Control Using Exposure-Response Analysis? *J Clin Pharmacol*. 2017;57(1):85-95.
6. Bland, JM, Altman, DG. Comparing methods of measurement: why plotting difference against standard method is misleading. *Lancet*. 1995;346(1982):1085-7.
7. Gervivi, D, Yohai, VJ. A class of robust and fully efficient regression estimators. *Ann Stat*. 2002;30(2):583-616.

8 Tables, Figures, and Listings

All tables 14.1.8-14.1.9, figures 14.2.4-14.2.13, and listings 16.2.3 will be provided separately for concentration-QTc analysis (1), and sensitivity analysis (2), when applicable, by using serial number 1-2 (such as Table 14.1.8.1 for concentration-QTc analysis, and Table 14.1.8.2 for sensitivity analysis, and so on).

[redacted]

8.1 Tables

Number	Title	Comments
14.1.1	Baseline values of ECG parameters with descriptive statistics	Number of subjects (n), mean, SD, 90% CI, median, minimum, and maximum from descriptive analysis will be given by treatment for each ECG parameter.
14.1.2	Absolute values of QTcF with descriptive statistics	n, mean, SD, SE, 90% CI, median, minimum, and maximum from descriptive statistics will be given by treatment and post-baseline time point.
14.1.3.1-14.1.3.4	Change-from-baseline QTcF, HR, PR, and QRS (ΔQTcF, ΔHR, ΔPR, and ΔQRS) at each time point	n, LS mean, SE, and 90% CI from the statistical modeling will be given by treatment and time point (Section 6.1).
14.1.4	QTcF outliers per absolute category	Number (%) of subjects and time points with QTcF > 450 and ≤ 480 ms, > 480 and ≤ 500 ms, or > 500 ms by treatment (Section 6.2).
14.1.5	QTcF outliers per change-from-baseline category	Number (%) of subjects and time points with ΔQTcF > 30 and ≤ 60 ms, or > 60 ms by treatment (Section 6.2).
14.1.6	Categorical analyses for HR, PR, and QRS	Number (%) of subjects and time points with ΔPR > 25% and PR > 200 ms at post-baseline; ΔQRS > 25% and QRS > 120 ms at post-baseline; HR decrease from baseline > 25% and HR < 50 bpm at post-baseline; and HR increase from baseline > 25% and HR > 100 bpm at post-baseline (Section 6.2).
14.1.7	T-wave morphology and U-wave presence across treatment groups: treatment-emergent changes	Number (%) of subjects and time points falling into each of the T-wave categories: Normal (+), Flat, Notched (+), Biphasic, Normal (-), Notched (-) as defined in Section 6.2.
14.1.8	Concentration-QTc analysis of tapinarof and associated ΔQTcF prolongation	Fixed-effect estimations and corresponding *P* values will be given (Section 6.3).
14.1.9	Predicted ΔQTcF interval at geometric mean peak tapinarof concentration	Section 6.3.
14.1.10	Summary of Bland-Altman plot parameters in the comparison between iCOMPAS and EPQT QTcF	Section 6.4.

8.2 Figures

Number	Title	Comments

14.2.1	Absolute QTcF across time points	Mean and 90% CI from descriptive analysis will be given by treatment.
14.2.2.1-14.2.2.4	Change-from-baseline QTcF, HR, PR, and QRS (ΔQTcF, ΔHR, ΔPR, and ΔQRS) across time point	LS mean and 90% CI from the statistical modeling will be shown by treatment (Section 6.1).
14.2.3.1	Scatter plot of QTcF versus RR by treatment	Scatter plots of QTcF and RR intervals by treatment with regression lines will be given (Section 6.3).
14.2.3.2	QTcF-RR quantile plot by treatment	QTcF-RR quantile plots (with quantiles) with linear mixed-effects line and 90% CI will be given (Section 6.3).
14.2.4	Mean tapinarof plasma concentrations over time	Section 6.3.
14.2.5	Joint plot of tapinarof plasma concentrations and ΔQTcF over time	Section 6.3.1.
14.2.6	Hysteresis plot of tapinarof plasma concentration and ΔQTcF connected in temporal order by dose	Section 6.3.1.
14.2.7.1	Scatter plot of observed tapinarof plasma concentrations and ΔQTcF (with LOESS and simple regression)	Scatter plot of ΔQTcF versus concentration with LOESS line and 90% CI and simple regression line (Section 6.3.2).
14.2.7.2	Scatter plot of observed tapinarof plasma concentrations and ΔQTcF (with linear mixed-effects regression)	Scatter plot of ΔQTcF versus concentration with linear mixed-effects regression line and 90% CI (Section 6.3).
14.2.8	Model-predicted ΔQTcF (mean and 90% CI) and observed ΔQTcF (mean and 90% CI) across deciles of tapinarof plasma concentrations	Section 6.3.
14.2.9	Predicted ΔQTcF interval at geometric mean peak tapinarof concentrations	Section 6.3.
14.2.10	Scatter plot of standardized residuals versus fitted values	Section 6.3.2.
14.2.11	Scatter plot of standardized residuals versus concentrations with LOESS	Section 6.3.2.
14.2.12	Normal Q-Q plot of standardized residuals	Section 6.3.2.
14.2.13	Normal Q-Q plots of the estimated random effects	Section 6.3.2.
14.2.14	Bland-Altman plot by treatment	Method Bias Sensitivity analysis (Section 6.4).
14.2.15	Bland-Altman plot: all treatments	Method Bias Sensitivity analysis (Section 6.4).

8.3 Listings

Number	Title	Comments
16.2.1.1-16.2.1.4	QTcF, HR, PR, and QRS intervals – absolute and change-from-baseline values	Section 6.1.
16.2.2	T-wave morphology and U-wave presence	Section 6.2.
16.2.3	ΔQTcF and time-matched tapinarof concentrations for each subject	Data for concentration-QTc analysis (Section 6.3).

[redacted]

9 Approvals

Appendix A: Expert Precision QT Analysis

Expert Precision QT analysis (formerly High Precision QT analysis) will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates (1 replicate consists of one 14 second ECG). Statistical quality control procedures will be used to review and assess all beats and identify "high" and "low" confidence beats using several criteria including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely)
- RR values exceeding or below certain thresholds (biologically unlikely)
- Rapid changes in QT, QTc, or RR from beat to beat

Placement of fiducials and measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates will be performed using the iCOMPAS software. All beats that are deemed "high confidence" will not be reviewed by an [redacted] ECG analyst. All low confidence beats will be reviewed manually by an [redacted] ECG analyst and adjudicated using pass-fail criteria. The beats found acceptable by manual review will be included in the analysis. The beats confirmed to meet fail criteria will not be included in the analysis.

For the purpose of measuring PR and QRS intervals and to assess T-wave morphology and presence of U-waves, the TQT Plus algorithm will select the 3 ECG replicates with the highest quality score from the ECG extraction window. These 3 ECGs will be analyzed using a semi-automated process to determine these parameters. If 3 consecutive usable beats cannot be identified in at least 2 of the 3 replicates, then all beats in all replicates will be reviewed for that time point using a manual analysis.

If manual analysis is required, then all beats in a minimum of 3 replicates will be reviewed using the iCOMPAS software. The [redacted] ECG analyst will review all usable beats in Lead II (or an alternate lead) for each replicate and will review and/or adjust the fiducial placements (onset of P, onset of Q, offset of S, and offset of T-wave that were electronically marked) of each waveform and also document the T-wave morphology and the presence of U-waves for each beat. A replicate will only be reported if it has 3 approved, usable beats.