Statistical Analysis Plan

A RANDOMIZED, VEHICLE-CONTROLLED, SAFETY AND EFFICACY STUDY OF EVO101 IN ADULT SUBJECTS WITH ATOPIC DERMATITIS

Sponsor	Evommune, Inc.
Product/Compound/Device	EVO101 Topical Cream, 0.1%
Phase of the study	2a

[redacted]

Statistical Analysis Plan

Protocol title: A RANDOMIZED, VEHICLE-CONTROLLED, SAFETY AND EFFICACY STUDY OF EVO101 IN ADULT SUBJECTS WITH ATOPIC DERMATITIS

Sponsor code: EVO101-AD001

[redacted] code: EPQ1001

Version number: Final 1.0

Date: 17-AUG-2023

	Name, Title, Affiliation	**Signature & Date**
Written by	[redacted]	
Reviewed by	[redacted]	
Reviewed by	[redacted]	
Reviewed by	[redacted]	
Approved by Sponsor representative	[redacted]	

[redacted]

Statistical Analysis Plan

Protocol title: A RANDOMIZED, VEHICLE-CONTROLLED, SAFETY AND EFFICACY STUDY OF EVO101 IN ADULT SUBJECTS WITH ATOPIC DERMATITIS

Sponsor code: EVO101-AD001

[redacted] code: EPQ1001

Version number: Final 1.0

Date: 17-AUG-2023

	Name, Title, Affiliation	**Signature & Date**
Approved by Sponsor representative	[redacted]	

Contents

1 Abbreviations

AD	Atopic Dermatitis
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
BMI	Body Mass Index
BSA	Body Surface Area
CMH	Cochrane Mantel- Haenszel
CSP	Clinical Study Protocol
CSR	Clinical Study Report
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
F	Fahrenheit
IC	Informed Consent
IGA	Investigator's Global Assessment scale
ITT	Intent-to-treat
LSR	Local Skin Reactions
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric Rating Scale
PD	Protocol Deviation
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cells
SAF	Safety
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLR	Toll-like receptor

WBC	White Blood Cells
WHO	World Health Organization

2 Document Version History

Version Number	Version date	Section(s) Updated	Change since previous version (with reason)
Draft 1.0	28-OCT-2022		Not applicable: Initial version
Draft 2.0	30-NOV-2022		Addressed comment from Evomunne
Draft 3.0	17-JAN-2023		Addressed comment from Evomunne and according to Protocol Amendment 2
Draft 4.0	12-MAY-2023	8.3.7 10.1	Added additional considerations for possible issues with the exposure and pruritus data
Draft 5.0	24-May-2023	3 6, 8.3.5, 8.3.6, 10.2 8.3.6	Changed Protocol version to Amendment 3 Changed testing to one-sided instead of two-sided. Updated corresponding sections accordingly. Changed procedure to analyze the following endpoints using MI: change from baseline to Week 8 in EASI, IGA and Pruritus NRS, and EASI-75 at Week 8
Draft 6.0	20-Jun-2023	8.3.5	Mi procedure changed to impute values at each visit instead of change or percentage change and changed method to analyze the binary outcome from Chi-square to Cochrane Mantel- Haenszel (CMH)
Draft 7.0	09-Aug-2023	8.3.5 8.3.6 10.1 10.3 8.3.1	Added additional summary statistics for the imputed data at Week 8 Added time window considerations for early withdrawal. Appendix 10.3 with the SAS code for pooled proportions Added derivation of date of first study drug application
Final 1.0	17-AUG-2023	8.3.5, 8.3.6	Added rule for MI and LOCF analyses: to consider only participant with baseline and at least one post-baseline assessment

3 Introduction

This Statistical Analysis Plan (SAP) is based on Clinical Study Protocol (CSP) Version Final, dated April 24, 2022, and Protocol Amendment number 3, dated May 11, 2023.

EVO101 is a novel, small molecule inhibitor of IRAK4, which is a critical mediator of the interleukin (IL)-1 family of cytokines and toll-like receptor (TLR) signaling in innate inflammation. [redacted]

4 Study Objectives and Endpoints

Objective	***Endpoint***
Primary	
The primary objective is to assess the safety, tolerability, and preliminary efficacy of EVO101 Topical Cream, 0.1%, applied twice daily, in adults with AD.	Safety will be assessed through: • Incidence of treatment-emergent adverse events (TEAEs) • Incidence of local skin reactions (LSRs) • Changes in clinical laboratory tests (Chemistry, Hematology and Urinalysis) from baseline to Week 8 and incidence of abnormal laboratory tests. • Changes in vital signs from baseline over time (to Week 2, 4 and 8) and incidence of anormal vital signs. • Changes in Electrocardiogram (ECG) parameters from baseline to Week 8 and incidence of abnormal overall ECG evaluation. • Incidence of abnormal physical examinations. Efficacy will be assessed through: • Mean percentage change from Baseline in EASI score at Week 8
Secondary	
Efficacy	
	• IGA response (≥2 point change from baseline) at Week 8. • Change from Baseline in IGA at Week 8. • Mean change from Baseline in BSA affected at Week 8
Pharmacokinetics	
The secondary Pharmacokinetics objective of this study will be to assess the pharmacokinetics of EVO101 Topical Cream, 0.1%, applied twice daily, in adults with AD	• Plasma levels of EVO101 at Baseline, Week 2 and 8

Objective	***Endpoint***
Exploratory	
Efficacy	
	• EASI-75 and EASI-90 from Baseline to Week 2, 4 and 8. • Mean change from Baseline in EASI at Weeks 2 and 4. • Proportion of subjects achieving an IGA score of 0 to 1 who have an improvement of ≥ 2 points from Baseline at Week 8. • Change from Baseline in IGA score at Weeks 2, 4 and 8. • Mean change from Baseline in the pruritus-NRS score at Weeks, 2, 4 and 8. • Mean and percentage change from Baseline in the pruritus-NRS score at Week 8. • Proportion of subjects achieving a 4-point improvement in the pruritus-NRS score from Baseline to Week 8. • Mean change from Baseline in BSA affected at Weeks, 2, 4 and 8.

5 Overall Study Design

The study is a randomized, double-blinded, vehicle controlled, parallel group study, designed to assess the safety, tolerability, and preliminary efficacy of EVO101 Topical Cream, 0.1%, in subjects with mild-to-moderate AD.

Approximately 118 adult subjects, ≥18 years of age will be enrolled into this trial. The duration of the study for each subject is expected to be approximately 12 weeks (up to 4 weeks screening, 8 weeks treatment) attending to the following visits: Screening (up to 30 days prior to Baseline), Baseline, Week 2, Week and Week 8 (Study Exit).

Subjects will be in generally good health and have a clinical diagnosis of mild-to-moderate AD for at least one year, an IGA score of 2 or 3, an EASI of 5-20, and an affected BSA of 4-12%. Subjects must be willing to discontinue any therapies for AD and refrain from using any topical or systemic agents for AD, other than the investigational product, during the trial.

[redacted]

6 Determination of Sample Size

[redacted]

7 Data Sets to be Analyzed

The following analysis sets will be used for the statistical analysis and presentation of data:

- The Intent-to-treat (ITT) population will consist of all randomized subjects.

- The Per-Protocol (PP) population will consist of the subset of the ITT population who
  - complete the Week 8 evaluation and have evaluable data for the EASI and IGA assessments at Week 8.
  - have no significant protocol deviations through the Week 8 visit.
- The Pharmacokinetic (PK) population will consist of all ITT subjects who have a pre-dose and at least one post-dose blood sample collected for plasma drug concentration analysis.
- The Safety (SAF) population will consist of all subjects who receive at least one confirmed dose of study drug.

The final criteria for the PP population, regarding the protocol deviations that warrant exclusion, will be determined during the pre-analysis review when all data on protocol deviations are available and before breaking the blind.

The ITT population is considered as the primary analysis dataset and will be used for all primary, secondary, and exploratory efficacy analyses. The primary endpoint and the secondary IGA responder and pruritus responder analyses will be repeated using the PP population (the analyses to be repeated in the PP population are specified in sections 8.3.5 and 8.3.6). In the efficacy analyses based on the ITT population, subjects will be included in the treatment arm to which they were randomized, and in the analyses based on the PP population, subjects will be included in the arm for which treatment was received.

Safety analyses will be performed using the safety population. In all safety analyses, subjects will be analyzed based on the actual treatment received.

PK analyses will be performed using PK population where subjects will be included in the treatment arm to which they actually received.

Disposition and Baseline demographics analyses will be performed using the ITT population.

Exposure to study drug will be summarized for the ITT and SAF populations.

8 Statistical and Analytical Plans

The planned tables, figures and listings are presented in section 9.

8.1 Changes from the Protocol

The SAP includes the following changes from the protocol. These changes provided additional details and clarify some of the definitions and analyses.

1. [redacted]

8.2 Pre-Analysis Review

A Pre-Analysis Review meeting will be held prior to database lock on blinded data. The objective of this meeting will be to review data and protocol deviations in order to finalize the analysis datasets. The assignment of subjects to the different analysis datasets will be completed during this meeting and documented before breaking the blind. In case any definition in this SAP needs to be changed because of this meeting, a new version of the SAP will be created and signed before the blind is broken. If only minor changes or handling of specific data issues are decided this will be documented in the form “Pre-Analysis Review - Statistics” and signed before the blind is broken. For this meeting some safety data listings will be provided by the data manager in addition to the following listings that will be prepared by the statistician:

- Subjects not meeting the eligibility criteria
- Subjects not completing the study
- Protocol deviations
- Subjects with no documented dose of study drug
- Study medication compliance
- Concomitant medication violations
- Main evaluable efficacy assessments by visit (evaluable data for: EASI, IGA, BSA and pruritus-NRS by visit)
- Preliminary subjects' classifications of analysis populations, as far as possible

8.3 Hypothesis and Statistical Methods

8.3.1 Definitions

Baseline	Baseline value refers to the last non-missing assessment made before or up to the date of the first study drug application at the screening or baseline visit. If not possible to obtain a baseline value from the specified visits the unscheduled assessment will be included in the derivation of baseline value. Baseline pruritus score is derived based on the prior 7 days of subject diary data, of which at least 4 of the 7 days must be completed.
Date of first study drug application	The date of first study drug application will be taken from ePRO. In case ePRO is not available, then the first available date will be taken from the drug accountability.
Relative day	The relative day of an event is derived as: Relative day = (Start date) - (Date of first study drug application) + 1 For events occurring or starting before the date of first study drug application the relative day is derived as: Relative day = (Start date) - (Date of first study drug application) In this way, there will be no Day 0. Day 1 is the same day as the day of first study drug application, and Day -1 is the day before. Relative day will be calculated only for the completed dates.

Treatment-emergent adverse event (AE)	Treatment-emergent is defined as any AE with an onset on or after the date of the first study drug application: TEAE if: (Start AE date) ≥ (Date of first study drug application) Derivation of the flag when missing or partial AE dates is specified in section 8.8. AEs reported on the same day as first drug administration, associated with abnormal physical examination findings and vital signs, will be identified and manually reviewed by the medical monitor to confirm if the AE(s) will be considered as a treatment-emergent event. Additionally, AE(s) reported same day as first drug administration associated with a skin reaction and indicated in the reported term (pre-dose or pre-administration) will not be considered as treatment-emergent.
Change from baseline to specific visit	Change from baseline to specific visit will be calculated as: Change to visit X = Value at visit X – Baseline value
Percentage of change from baseline to specific visit	Percentage of change from baseline to specific visit will be calculated as: Percentage of change to visit X = [(Value at visit X – Baseline value) / (Baseline value)] x 100

8.3.2 Summary Statistics

Appropriate descriptive statistics will be produced by treatment group according to the nature of the variable.

For continuous data, number of subjects, mean, standard deviation, median and range (minimum and maximum) will be presented.

For categorical data, frequency distributions and percentages for each category will be presented. Percentages will be given with 1 decimal place.

The number of subjects with missing data will be presented under the “Missing” category. Missing values will not be included in the denominator count when computing percentages. When continuous data are summarized, only the non-missing values will be used for computing summary statistics.

Summary statistics will be presented by treatment group and visit, as applicable.

8.3.3 Patient/Subject Data Listings

Data collected in the CRF will generally be listed in Appendix 16.2 (see Section 9.2). CRF check questions (e.g., reminders) will not be listed.

Listings will be sorted by randomized treatment group, actual treatment group, subject ID, visit and assessment time as applicable.

8.3.4 Demographic and Other Baseline Characteristics

The following summaries will be given by treatment group and in total. and will be based on the ITT population. For parameters where assessments are made at baseline and at other visits, baseline data will be presented together with the rest of the data in by-visit displays in the corresponding efficacy or safety section.

Subject disposition:

- Study disposition and discontinuation and reasons for withdrawal: number and percentage of subjects randomized, treated, completing and discontinued the study and reason for discontinuation
- Subject disposition in analysis data sets and reasons for exclusion: number and percentage of subjects in ITT, PP, PK and SAF population and reason for not inclusion in each population.
- Screen failures and reasons: All subjects who signed the informed consent (IC) and reason for screen failure.

Protocol deviations:

Protocol deviations (PDs) collected during the study will be classified by type and significance. Significant/Major PDs will be summarized presenting the number and percentage of subjects with at least one and the total number of deviations by type and deviation term. If a subject has more than one deviation by term, the subject will be only counted once and in addition the number of deviations will also be shown. The calculation of percentages will be based on the number of subjects within each treatment arm.

All PDs will be listed including the severity, type, and deviation term.

Demographic characteristics:

The following characteristics will be summarized as indicated in section 0 depending on the nature of the variable:

- Age (years)
- Age group: <65 years and ≥65 years
- Gender: Male and female
- Race: White, Asian, Black or African American, American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander
- Ethnicity: Hispanic or latino, Not hispanic or latino, Not reported and Unknown
- Height (m)

- Weight (kg)
- Body mass index (BMI) (kg/m^2)

Medical/surgical history:

Medical/surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

The number and percent of subjects reporting at least one medical/surgical history will be summarized. Summary will be presented by System Organ Class (SOC) and Preferred Term (PT). If a subject has more than one event per PT, the subject will only be counted once. The calculation of percentages will be based on the number of subjects within each treatment arm.

8.3.5 Primary Efficacy Analysis

The primary efficacy analysis will be conducted using an analysis of variance (ANOVA) model with the percentage change from Baseline to Week 8 in EASI score as the dependent variable and treatment group and the randomization stratification variable as factors. [redacted]

Missing data for raw EASI data will be imputed [redacted] Change from baseline, and percent change from baseline will then be calculated. The [redacted]

[redacted].

Additionally, a box plot will be created with the percentage of change from baseline as the y-axis and the treatment group as the x-axis.

The primary efficacy analysis will be performed on the ITT population. Derivation of the EASI score is described in appendix 10.1.

A sensitivity analysis of the primary endpoint will be conducted in the PP population. [redacted]

8.3.6 Secondary and Exploratory Analyses

The endpoints listed below will be analyzed based on the ITT population. [redacted]

Derivations of the following assessments are described in appendix 10.1.

The following summaries and analyses will be conducted:

EASI:

- Summary statistics at baseline, Week 2, Week 4 and Week 8 will be provided by each treatment group as well as for the change and percentage change from baseline. These analyses will also be conducted using the PP population.
- Number and percentage of subjects with EASI-75 at Week 2, Week 4 and Week 8 (defined as a subject with a percentage change from baseline <= - 75). These analyses will also be conducted using the PP population.
- Number and percentage of subjects with EASI-90 at Week 2, Week 4 and Week 8 (defined as a subject with a percentage change from baseline <= - 90).
- A listing with the visit, date of the assessment, score, change and percentage from baseline and the flags of EASI-75 and EASI-90.

IGA:

- Summary statistics at baseline, Week 2, Week 4 and Week 8 will be provided by each treatment group.
- Number and percentage of subjects with IGA response (≥2 points change from baseline (i.e., a change from baseline ≤ -2) at Week 8 and comparisons between treatments will be conducted in the ITT and PP populations.
- Number and percentage of subjects with IGA success (subjects with a score of 0 to 1 who have an improvement of ≥ 2 points, that means a change from baseline ≤ -2) from Baseline at Week 8 and comparison between treatments.
- A listing with the visit, date of the assessment, score, change from baseline and the flags of IGA response and IGA score of 0 to 1 who have an improvement of ≥ 2 points achievement.

BSA:

- Summary statistics at baseline, Week 2, Week 4 and Week 8 will be provided by each treatment group as well as for the change and the percentage change from baseline.
- Comparison between treatments for the change and percentage change from baseline to each visit.
- A listing with the visit, date of the assessment, value, change and percentage change from baseline.

Pruritus-NRS:

- For the assessment of pruritus-NRS:

  - Day 1 through Day 7 values will be based on the single assessments performed on each subject on that day.
  - Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7 and Week 8 values will be based on the average pruritus-NRS score of the 7 days prior to the visit date. Subjects with less than 4 values in the 7 days prior to the visit date will have that visit value considered missing.
- Summary statistics at baseline, Day 1, Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7 and Week 8 will be provided by each treatment group as well as the change and percentage of change from baseline.
- Comparison between treatments in the change and percentage change from baseline to each visit will be conducted in the ITT and PP populations.
- Number and percentage of subjects achieving a 4-point improvement in the pruritus-NRS score from Baseline to Week 8 in subjects who had an average maximum pruritus-NRS score of at least 4 at Baseline. Comparisons between treatments will be made in the ITT and PP populations.
- A listing with the visit, date of the assessment, score, change and percentage from baseline and the flags of 4-point improvement achievement.

Pharmacokinetics:

Plasma levels of EVO101 will be evaluated by:

- Summary statistics at baseline, Week 2, and Week 8 will be provided for the active treatment group.
- A listing with the visit, date of the assessment and value.

8.3.7 Exposure to Treatment

The extent of exposure to study drug in each treatment group will be summarized by total number of days of exposure, total number of applications, number of missed applications and number and percentage of subjects who are compliant. A subject will be considered compliant with the dosing regimen if the subject applied 80% to 120% of the expected number of applications while enrolled in the study. The compliance categories will be: <80%, [80%-120%] and >120%. Compliance will be summarized additionally as a quantitative variable.

Extent of exposure to study drug will be derived as:

Exposure (days) = (last study drug application date) – (first study drug application date) + 1

Compliance will be derived as:

Actual compliance (%) = (total number of applications / total number of expected applications as per protocol) x 100

Handling incorrect exposure data reported

Since the exposure data is collected by an ePRO, the following describes the possible issues that can be found and how to hand them for the analysis.

[redacted]

All the subjects with any of the described issues will be reviewed and confirmed during the DR meeting. Additionally, for subjects with exposure data as described in third issue it will be established a rationale to include/exclude them from PP population during the DR meeting.

8.3.8 Concomitant Medications and Therapy

All concomitant medications/therapies will be classified according to ATC level 3 group text and World Health Organization (WHO) Drug Dictionary preferred name. The medications will be classified into categories Prior and Concomitant based on start date and end date in relation to study drug exposure.

- Prior medication is defined as any medication/therapy strictly taken before the first study drug application.
- Concomitant medication is defined as any medication/therapy which the period between their start dates and end dates coincide with exposure to study drug.

The derivations will be as follows:

A medication will be considered a prior medication if one of the two following conditions are met:

- (End medication/therapy date) < (Date of first study drug application)

- (Start medication/therapy date) < (Date of first study drug application) and (End medication/therapy date) = Missing and "Ongoing" option is not ticked in the eCRF.

A medication will be considered as a concomitant medication if one of the two following conditions are met:

- (End medication/therapy date) ≥ (Date of first study drug application)
- "Ongoing" option is not ticked in the eCRF.

Derivation of the flag when missing or partial dates is specified in section 8.8.

The concomitant medications will be presented separately by prior and concomitant medications in two summary tables presenting the number and percentage of subjects with at least one occurrence for a preferred name. If a subject has more than one medication, the subject will only be counted once for each medication and timing category, on a preferred name level in each period. The calculation of percentages will be based on the number of subjects within each treatment arm based on the Safety population.

Additionally, a listing by subject for each period (prior and concomitant) will be presented for the SAF including the ATC 3 level, preferred name, reported name, start/end date, ongoing option, dose (units), route, frequency, indication, reason for medication and the associated AE as long as they are available.

8.3.9 Adverse Events

AEs will be coded using the MedDRA coding dictionary. Only TEAEs will be included in summary tables, while non-TEAEs will be listed separately.

The number and percentage of subjects reporting TEAEs will be tabulated by treatment arm as well as the total number of TEAEs. Summaries will be presented by SOC and PT, and further by severity and relationship to study drug. If a subject has more than one event per PT, the subject will be only counted once and in addition the number of events will also be shown. The calculation of percentages will be based on the number of subjects within each treatment arm in SAF population.

The relationship will be classified as "related" and "not related" for TEAEs. Serious AEs will be separately listed. When summarizing TEAEs by severity and relationship, each subject will be counted once within a SOC or a PT by using the event with the highest severity and greatest relationship within each classification.

[redacted]

The following summaries will be presented:

- Overview of treatment emergent adverse events by the following categories:

  - TEAEs
  - Serious TEAEs
  - Related TEAEs
  - Serious related TEAEs
  - TEAEs with CTCAE grade ≥ 3
  - TEAEs leading to study drug withdrawal
  - TEAEs leading to death
- TEAEs by SOC and PT
- TEAEs by PT
- TEAEs by intensity (CTCAE grade: 1, 2, 3, 4 or 5), SOC and PT
- Serious TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- Serious related TEAEs by SOC and PT
- TEAEs leading to study drug withdrawal by SOC and PT
- TEAEs leading to death by SOC and PT
- Local skin reactions TEAEs by SOC and PT

Additionally, two listings will be created for all AEs and serious AEs including the SOC, PT, reported term, start/end date, relative start/end date, AE duration, seriousness, intensity, relationship with the study drug, action taken with the study drug, outcome, application site flag and treatment-emergent flag.

8.3.10 Other Safety Assessments

All the analyses described below will be presented by treatment group and will be based on the SAF population. Percentages will be based on the available data within each treatment arm except for the shift table for which percentages will be based on the total number of subjects in each treatment arm.

[redacted]

Vital Signs

For all vital signs parameters [systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), temperature (ºF)] summary statistics will be provided at the following visits: Baseline, Week 2, Week 4 and Week 8. Additionally, Weight will be provided at baseline and Week 8.

For these parameters, the following summaries will be provided at each time-point:

- A summary table showing the values and the changes from baseline
- A summary table showing the number and percentage of subjects reporting “normal”, “abnormal, not clinically significant” and “abnormal, clinically significant” results
- A shift table presenting the number and the percentage of subjects in each bivariate category (baseline versus each post-baseline visit)
- Listing by subject including the parameter, visit, date of the assessment, the value, change from baseline and Normal/abnormal classification.

Clinical Laboratory Measurements

Analysis of clinical laboratory data will be performed for Hematology, Biochemistry and Urinalysis tests at the following visits: Baseline and Week 8.

The following laboratory tests will be summarized:

- Hematology: hematocrit, hemoglobin, red blood cells (RBC) count, white blood cells (WBC), percentage of Neutrophils, Lymphocytes, Monocytes, Eosinophils and Basophils, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), RBC morphology, Platelet count and Absolute of Neutrophils, Lymphocytes, Monocytes, Eosinophils and Basophils.
- Clinical chemistry: sodium, potassium, chloride, calcium, phosphorus, bicarbonate, uric acid, blood urea nitrogen, creatinine, total protein, albumin, total and direct bilirubin, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP) and non-fasting Glucose.
- Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocytes esterase, microscopic examination and urobilinogen.

For those parameters, the following summaries will be provided at each time-point:

- A summary table showing the values and the changes from baseline
- A summary table showing the number and percentage of subjects reporting “normal”, “abnormal, not clinically significant” and “abnormal, clinically significant” results

- A shift table presenting the number and the percentage of subjects in each bivariate category (baseline versus each post-baseline visit)
- 3 listings (hematology, chemistry and urinalysis) by subject including the parameter, visit, date of the assessment, value, change form baseline and Normal/abnormal classification.

Cardiac Assessments

For all ECG parameters [ECG Mean Heart Rate (beats/min), RR interval (msec), PR interval (msec), QRS duration (msec), QT interval (msec), QTcB interval (msec) and QTcF interval (msec)] summary statistics will be given at the following visits: Baseline and Week 8.

For those parameters, the following summaries will be provided at each time-point:

- A summary table showing the values and the changes from baseline.
- A summary table showing the number and percentage of subjects reporting “normal”, “abnormal, not clinically significant” and “abnormal, clinically significant” results for the overall interpretation.
- A shift table presenting the number and the percentage of subjects in each bivariate category (baseline versus each post-baseline visit) for the overall interpretation.
- Listing by subject including the parameter, visit, date of the assessment, the value, change from baseline, Normal/abnormal classification and any comments reported related to the result.

Physical Examination

For all body systems (general appearance, dermatological other than Atopic Dermatitis, head, ears, eyes, nose, throat, respiratory, cardiovascular, abdominal, neurological, musculoskeletal and lymphatic body system) collected in the physical examination)] summary statistics will be given at the following visits: Baseline and Week 8.

For those parameters, the following summaries will be provided at each time-point:

- A summary table showing the number and percentage of subjects reporting “normal”, “abnormal, not clinically significant” and “abnormal, clinically significant” results for the overall interpretation.
- A shift table presenting the number and the percentage of subjects in each bivariate category (baseline versus each post-baseline visit) for the overall interpretation.
- Listing by subject including the parameter, visit, date of the assessment, the value, change from baseline, Normal/abnormal classification and any comments reported related to the result.

COVID-19 and pregnancy tests

Listing by subject including the test, visit, date of the assessment and the result will be provided for Covid-19 and pregnancy tests.

8.4 Level of Significance, Multiple Comparisons and Multiplicity

[redacted].

For secondary efficacy endpoints, no adjustments for multiplicity will be applied.

8.5 Multicenter Studies

Not applicable.

8.6 Adjustment for Covariates

Covariates used for adjustment in the efficacy models are specified in the corresponding efficacy sections (8.3.5, 8.3.6).

8.7 Examination of Subgroups

Not applicable.

8.8 Handling of Dropouts and Missing Data

Adverse event

The following rules will be followed to determine treatment-emergent flag:

AE start date	AE stop date	TEAE rule
Known	Known, Partial or Missing	if AE start date < first study drug application date, then not TEAE if AE start date ≥ first study drug application date, then TEAE
Partial (missing day)	Known	if AE stop date < first study drug application date, then not TEAE if AE stop date ≥ first study drug application date and month and/or year of AE start date < first study drug application month and/or year, then not TEAE if AE stop date ≥ first study drug application date and month and/or year of AE start date ≥ first study drug application month and/or year, then TEAE
	Partial (missing day or missing month and day)	If month and/or year of AE start date < first study drug application month and/or year, then not TEAE If month and/or year of AE start date >= first study drug application month and/or year, then TEAE

Prior and concomitant medications

The following rules will be followed when partial or missing medication start and end dates:

Medication start date	Medication stop date	Prior and concomitant rule
Known, Partial (missing day or missing month and day) or Missing	Known	if stop date < first study drug application date, then prior if stop date ≥ first study drug application date, then concomitant
	Partial (missing day or missing month and day)	It's imputed stop date as latest possible date (only for the prior/concomitant calculation purpose): - if day missing then the day will be imputed to the last day of the month - if day and month missing then they will be imputed to December 31th After this imputation the rule will be: if stop date < first study drug application, then prior if stop date ≥ first study drug application, then concomitant
	Missing	if ongoing ticked as "Yes" then medication as concomitant if ongoing not ticked then: if start/imputed start date < first study drug application, then prior if start/imputed start date ≥ first study drug application, then concomitant

Efficacy endpoints

Handling of efficacy data is defined in sections 8.3.5 and 8.3.6.

8.9 Interim Analysis

No Interim analysis is planned for this study.

8.10 Data Monitoring Committee

No data monitoring is planned for this study.

8.11 References

Not applicable.

9 Tables, Listings and Figures Overview

The tables, figures and listing derived from the analyses described in this SAP will be allocated and numbered according to the ICH-E3 guidelines. The tables and figures will be displayed in 3 sections from section 14 of the CSR:

14.1 DISPOSITION, ANALYSIS POPULATIONS, BASELINE AND DISEASE HISTORY

14.2 EFFICACY DATA

14.3 SAFETY DATA

The listing will be part of the appendix 16 of the CSR.

9.1 Tables to be Produced for the Clinical Study Report

Title	Population	Key/Top Line Results
14.1.1.1 Study disposition and discontinuation and reasons for withdrawal	ITT	X
14.1.1.2 Analysis sets and primary reason for exclusion	ITT	X
14.1.1.3 Screen failures and reasons	All	
14.1.2.1 Major protocol deviations	ITT	
14.1.3.1 Demographic characteristics	ITT	X
14.1.4.1 Medical/Surgical history	ITT	
14.1.5.1 Prior medications	SAF	
14.1.5.2 Concomitant medications	SAF	
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
14.2.3.1 Pharmacokinetics: Absolute values by visit	PK	
14.3.1.1 Summary of Treatment Emergent Adverse Events	SAF	X
14.3.1.2 Treatment Emergent Adverse Events by System Organ Class and Preferred Term	SAF	X
14.3.1.3 Treatment Emergent Adverse Events by Preferred Term	SAF	X
14.3.1.4 Treatment Emergent Adverse Events by intensity and System Organ Class and Preferred Term	SAF	
14.3.1.5 Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term	SAF	X
14.3.1.6 Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term	SAF	
14.3.1.7 Serious related Treatment Emergent Adverse Events by System Organ Class and Preferred Term	SAF	
14.3.1.8 Treatment Emergent Adverse Events leading to study drug withdrawal by System Organ Class and Preferred Term	SAF	X
14.3.1.9 Treatment Emergent Adverse Events leading to death by System Organ Class and Preferred Term	SAF	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
14.3.3.1 Vital signs: Absolute values and changes from baseline	SAF	
14.3.3.2 Vital signs: Number of subjects (%) with abnormal values by visit	SAF	
14.3.3.3 Vital signs: Shift table from baseline versus each post-baseline visit of Normal/Abnormal values	SAF	
14.3.4.1 Hematology: Absolute values and changes from baseline	SAF	
14.3.4.2 Hematology: Number of subjects (%) with abnormal values by visit	SAF	

14.3.4.3 Hematology: Shift table from baseline versus each post-baseline visit of Normal/Abnormal values	SAF	
14.3.4.4 Chemistry: Absolute values and changes from baseline	SAF	
14.3.4.5 Chemistry: Number of subjects (%) with abnormal values by visit	SAF	
14.3.4.6 Chemistry: Shift table from baseline versus each post-baseline visit of Normal/Abnormal values	SAF	
14.3.4.7 Urinalysis: Absolute values and changes from baseline	SAF	
14.3.4.8 Urinalysis: Number of subjects (%) with abnormal values by visit	SAF	
14.3.4.9 Urinalysis: Shift table from baseline versus each post-baseline visit of Normal/Abnormal values	SAF	
14.3.5.1 ECG: Absolute values and changes from baseline	SAF	
14.3.5.2 ECG: Number of subjects (%) with abnormal values by visit	SAF	
14.3.5.3 ECG: Shift table from baseline versus each post-baseline visit of Normal/Abnormal values	SAF	
14.3.6.1 Physical examination: Number of subjects (%) with abnormal values by visit	SAF	
14.3.6.2 Physical examination: Shift table from baseline versus each post-baseline visit of Normal/Abnormal values	SAF	
14.3.7.1 Exposure and compliance data	SAF	X

9.2 Listings of Individual Subject Data and Other Information to be Produced for the Clinical Study Report

Title	Population	Key/Top Line Results
16.1.7 Randomization Scheme	RND	X
16.2.1.1 Study discontinuation and reasons for withdrawal	ITT	X
16.2.1.2 Screening failures including reasons for failure	All	
16.2.2 Protocol deviations	ITT	
16.2.3 Patient disposition in analysis data sets and primary reasons for withdrawal	ITT	X
16.2.4.1 Demographic data	ITT	X
16.2.4.2 Medical/Surgical history	ITT	
16.2.4.3 Prior medication and therapy	SAF	
16.2.4.4 Concomitant medication and therapy	SAF	
16.2.5.1 Extent of study drug administration compliance	SAF	X
16.2.6.1 EASI by visit	ITT	X
16.2.6.2 IGA by visit	ITT	X

16.2.6.3 BSA by visit	ITT	X
16.2.6.4 Pruritus-NRS by visit	ITT	X
16.2.6.5 Pharmacokinetic: Plasma levels of EVO101 by visit	PK	
16.2.7.1 Adverse events	SAF	X
16.2.7.2 Serious adverse events	SAF	
16.2.7.3 Deaths	SAF	
16.2.7.4 Local skin reactions	SAF	
16.2.8.1 Hematology	SAF	
16.2.8.2 Clinical Chemistry	SAF	
16.2.8.3 Urinalysis	SAF	
16.2.8.4 Covid-19 and Pregnancy tests by visit	SAF	
16.2.9 Vital Signs	SAF	
16.2.10 ECG values and interpretation	SAF	
16.2.11 Physical Examination by Body System	SAF	

10 Appendices

10.1 Definitions and Derivations of the efficacy assessment scores

Assessment	Derivation
EASI	EASI is used to assess the severity and extent of AD; it is a composite index with scores ranging from 0 to 72, with higher values indicating more severe and/or extensive disease. Four (4) body regions are analyzed: head and neck, trunk, upper extremities and lower extremities. The severity of disease in each region is evaluated using 5 clinical symptoms: Erythema, Edema/Papulation, Excoriation and Lichenification. The grade of the severity of each symptom uses a 0-3 scale: 0-None, 1-Mild, 2-Moderate and 3-Severe. An average score will be calculated. However, 0.5 will be not permitted: if a sign is present, it should be at least mild (1). Additionally, for each of the 4 regions of the body, the region area score will be recorded on a scale of 0 to 6: 0-0%, 1-[1-9%], 2-[10-29%], 3-[30-49%], 4-[50-69], 5-[70-89%] and 6-[90-100%]. Area score is the total percentage of skin affected with eczema for each body region. The severity score is calculated for each region of the body as the sum of the severity of the 4 different signs. For example: Severity score (Head and neck) = severity(Erythema) + severity(Edema/Papulation) + severity(Excoriation) + severity(Lichenification) Then for each region, the area score and the severity score will be multiplied. The following additional multiplies will also be used: - Head and neck: severity score x area score x 0.1 - Trunk: severity score x area score x 0.3 - Upper extremities: severity score x area score x 0.2 - Lower extremities: severity score x area score x 0.4 The final EASI will be the sum of the total scores for each region. The range of the score is from 0 to 72. All calculations defined above are automatically conducted in the eCRF. The value of EASI to be used for the analysis will be the corresponding EASI score in the visit schedule: Week 2, 4 and 8. The baseline value is defined in section 8.3.1. Note: If any severity score of a sign and/or region area score is missing, the EASI score will be not possible to calculate, and this will be considered as missing.

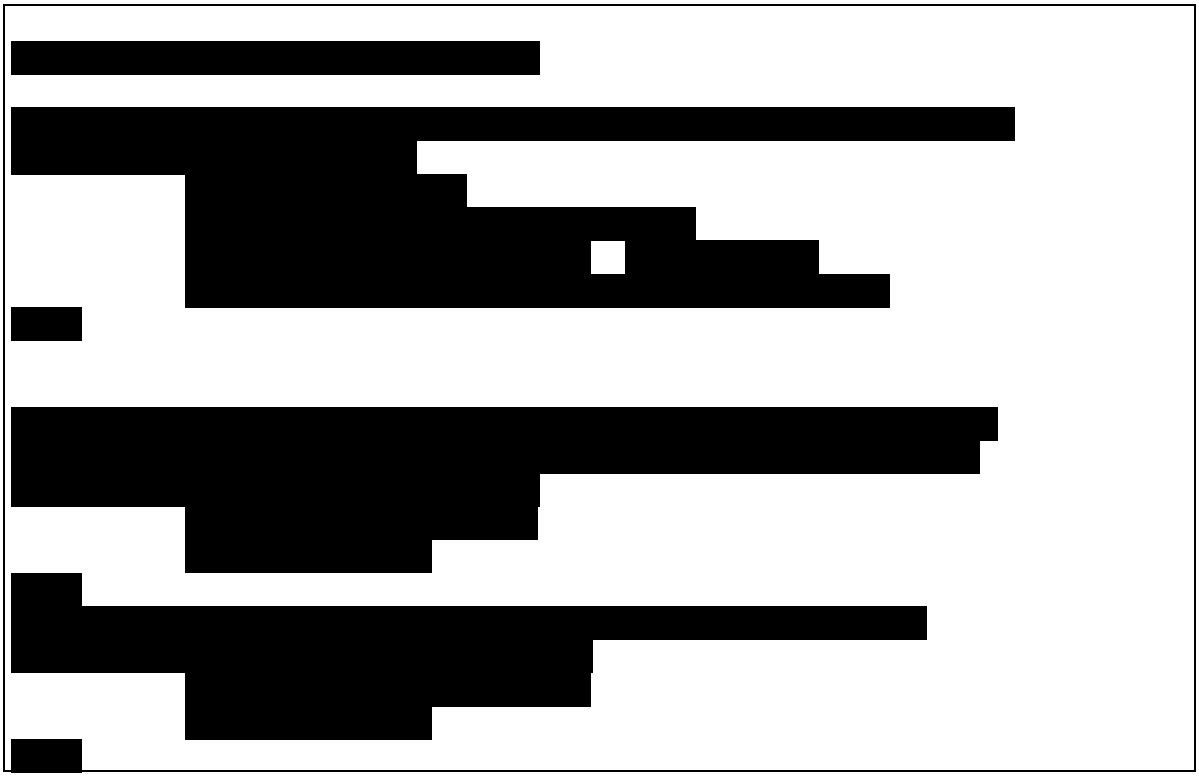
IGA	The investigator global assessment will be on a scale of 0 to 4: 0-Clear, 1-Almost clear, 2-Mild, 3-Moderate and 4-Severe. Note: No additional calculation will be needed for this assessment. The value of the IGA score to be used for the analysis will be the corresponding IGA score in the visit schedule: Week 2, 4 and 8. The baseline value is defined in section 8.3.1.
BSA	The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. BSA will be determined by the Investigator or designee using the subject palm = 1% rule. Note: No additional calculation will be needed for this assessment. The value of BSA percentage to be used for the analysis will be the corresponding BSA percentage in the visit schedule: Week 2, 4 and 8. The baseline value is defined in section 8.3.1**Error! Reference source not found.**.
Pruritus-NRS	Pruritus will be assessed using a Pruritus Numerical Rating Scale (NRS). The Pruritus NRS is an 11-point scale used by subjects to rate their worst itch severity over the past 24 hours with 0 indicating “No itch” and 10 indicating “Worst itch imaginable.” Subject assessments will be captured daily using an electronic diary. The value at each visit (Baseline, Week 1, Week 2, Week 3 Week 4, Week 5, Week 6, Week 7 Week 8) will be calculated as the mean of the values of the 7 previous days up to the corresponding visit. If there are less than 4 values in the prior 7 days, the value for that visit day will be set to missing. Values at each day (Day 1 through Day 7) will be the corresponding value collected in the day specified. The baseline value is defined in section 8.3.1. If more than one assessment is reported in the same day, then it will be taken that one with the worst severity following a conservative approach.

In the case of early withdrawals, a time window will be used for the efficacy assessments mentioned above, to reassign values to the correct visits using the days from baseline as follows.

Visit	Target day	Visit Window (days on treatment)
Visit 2	14	Days from Baseline ≤ 21
Visit 4	28	21 < Days from Baseline ≤ 42
Visit 8	56	42 < Days from Baseline

10.2 SAS code for multiple imputation of primary endpoint

[redacted]



10.3 SAS code for pooled proportions of secondary binary endpoints