STATISTICAL ANALYSIS PLAN

The ADRO Trial: An Adaptive, 2-Part, Phase 2 Clinical Trial Investigating the Safety and Efficacy of ADX-629 in Adults with Atopic Dermatitis

Sponsor: Aldeyra Therapeutics, Inc.

Protocol Number: ADX-629-ATD-001

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Statistical Analysis Plan Approval

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List of Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification
CI	Confidence Interval
CS	Clinically Significant
CSR	Clinical Study Report
DMP	Data Management Plan
eCRF	Electronic Case Report Form
HIPAA	Health Information Portability and Accountability Act
ICH	International Conference on Harmonisation
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NCS	Not clinically significant
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCORAD	Scoring Atopic Dermatitis
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol ADX-629-ATD-001, version 2.0 dated 11OCT2023.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the CSR.

2. Study Objectives

The primary objective of the ADX-629-ATD-001 clinical trial is to evaluate the safety of ADX-629 administered alone and in addition to standard-of-care in adults with atopic dermatitis. The secondary objective is to evaluate the activity and efficacy of ADX-629 administered alone and in addition to standard-of-care in adults with atopic dermatitis.

2.1 Study Variables

The efficacy variables are comprised of the following:

2.1.1 PRIMARY ENDPOINT

- Incidence and severity of treatment-emergent adverse events and serious adverse events

2.1.2 KEY SECONDARY ENDPOINT FOR EFFICACY:

- Proportion of subjects with an Investigator's Global Assessment score of 0 or 1 at Day 90

2.1.3 SECONDARY ENDPOINTS

- Proportion of subjects with an Investigator's Global Assessment score of 0 or 1 and ³ 2-grade improvement from Baseline (Day 1)
- Proportion of subjects achieving a ≥ 50%, 75%, and 90% improvement in the Eczema Area and Severity Index
- Proportion of subjects achieving ≥4 points improvement from Baseline (Day 1)in the peak pruritus numerical rating scale
- Time to AD flare-up (days), as defined by use of rescue medication
- Proportion of patients with a 4-point or more improvement in Patient Oriented Eczema Measure (POEM) total score at Day 90
- Percent change in High-density lipoprotein Cholesterol (HDL-C), Low-density lipoprotein Cholesterol (LDL-C), and triglycerides from Baseline (Day 1)
- Change from Baseline (Day 1) in the following:
    - IGA Score

- EASI Score
- Hamilton Depression Rating Scale (HAM-D) score
- Beck Anxiety Inventory (BAI) Score

2.1.4 EXPLORATORY ENDPOINT

- Change from Baseline (Day 1) in SCORAD (Scoring Atopic Dermatitis)

2.2 Statistical Hypotheses

This is a Phase 2a clinical trial to assess the safety, tolerability and activity of ADX-629 in adult subjects with atopic dermatitis. The primary endpoint is incidence and severity of treatment-emergent adverse events and serious adverse events. There are no formal statistical hypotheses.

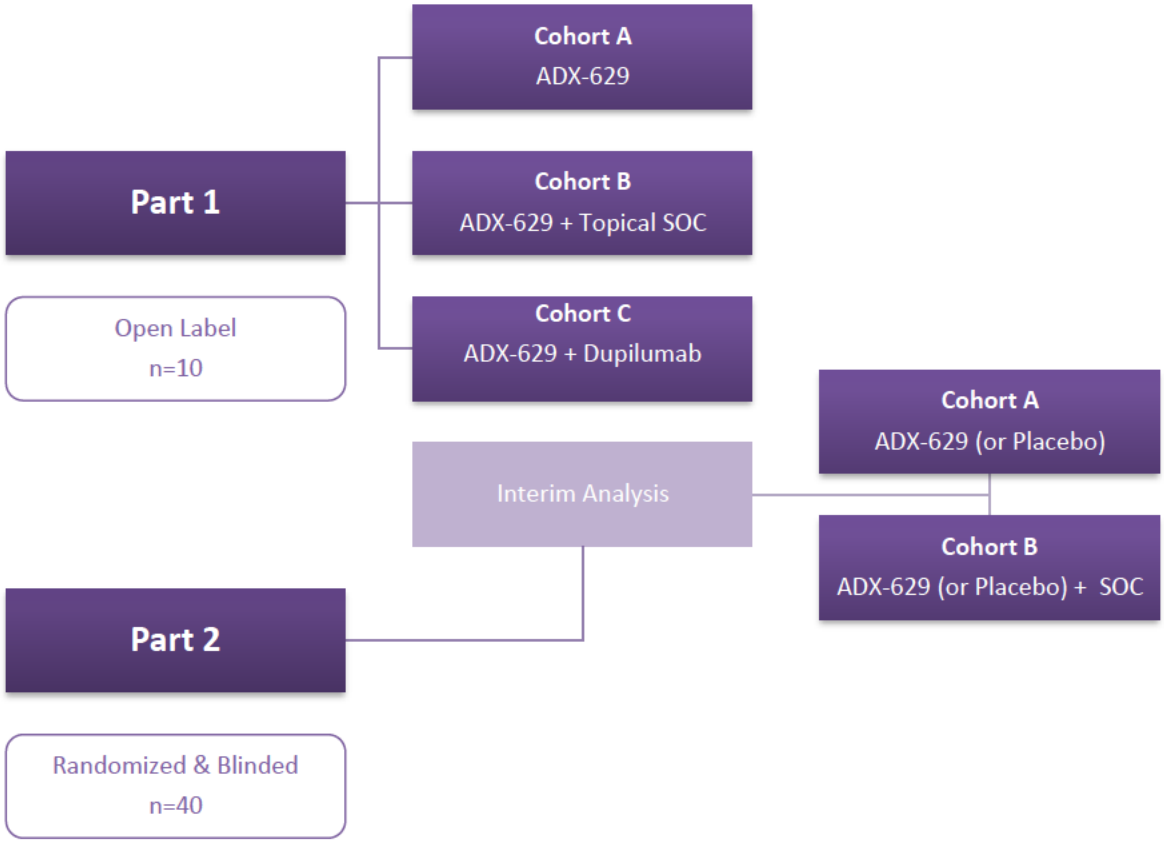
3. Study Design and Procedures

3.1 General Study Design

ADX-629-ATD-001 is a Phase 2, multicenter, 2-part clinical trial is designed to evaluate the safety and efficacy of ADX-629 alone and in combination with standard-of-care in subjects ≥ 18 years of age with atopic dermatitis. The trial will enroll approximately 50 adults with mild, moderate, and severe atopic dermatitis, as defined by the inclusion and exclusion criteria. Trial drug will be administered orally, every 12 hours, to eligible subjects for 90 days. Subjects will be enrolled in cohorts based on standard-of-care treatment (SOC) for AD at baseline. Subjects not receiving SOC treatment are assigned to Cohort A and will receive trial drug only (i.e., monotherapy). Subjects receiving SOC AD therapy (i.e., topical therapy or dupilumab) will be assigned to another cohort and will receive trial drug and SOC. The trial will not provide SOC treatment and therefore, must be obtained independently by the subject.

The trial is divided into 2 parts; the first part of the trial (Part 1) is open-label, and the second part (Part 2) is randomized, double-blind, and placebo controlled. In Part 1, approximately 10 subjects will receive open-label ADX-629 twice daily for 90 days alone or in combination with SOC treatment for AD. In Part 2, approximately 40 subjects will be randomized to receive either ADX-629 or matching placebo twice daily for 90 days. The final protocol for Part 2 will be determined following analysis of Part 1.

Figure 1 - Schematic of Trial Design:



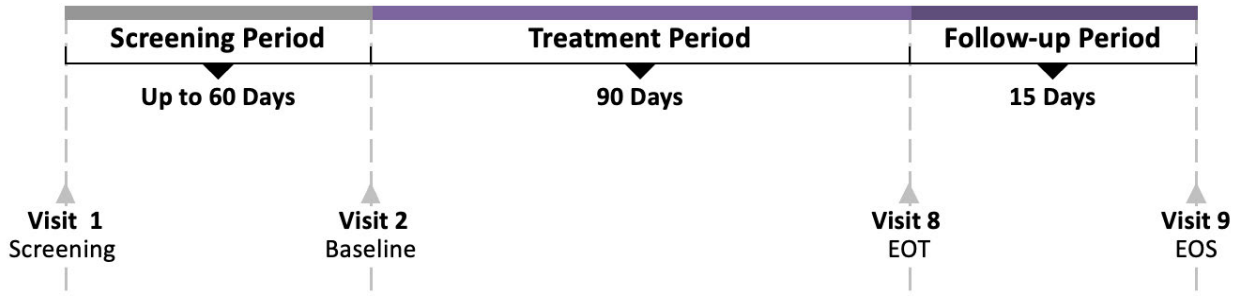
a) Part 1 will be analyzed prior to Part 2.

b) The trial design in Part 2 may be adapted based on the data from Part 1.

The trial duration for each subject is approximately 5 months and involves 9 trial visits. The trial is divided into 3 periods: Screening, Treatment, and Follow-up. The screening period ranges from 3 days to 60 days to and allow for adequate washout of prohibited concomitant medications. Prior to any trial procedure/assessment, written informed consent will be obtained. Eligibility will be confirmed during screening and prior to dosing at Visit 2 (Day 1). Trial-related assessments and procedures will be performed at the timepoints indicated in the Schedule of Assessments. The use of emollients must be stable in the 5 days prior to Visit 2. Eligible subjects will receive the first dose of trial drug at Visit 2 (Day 1) and complete trial visits every 15 days during the 90-day treatment period. Visits can be performed on-site, remotely (i.e., phone call, telehealth visit) or at home. After the treatment period, subjects will undergo a follow-up period and complete an end of trial visit approximately 15 days from the last dose of trial drug. Unscheduled visits or assessments may be performed if clinically warranted, in the opinion by the Investigator. Subjects who require rescue medication for an AD flare-up during the treatment period will be asked to discontinue trial drug and complete remaining scheduled trial visits.

The trial periods are illustrated in Figure 2.

Figure 2 - Schematic of Trial Periods:



Part 1

Part 1 of the trial will include at least 10 subjects with mild, moderate, or severe AD whose disease is not adequately controlled with current standard-of-care treatment. The purpose of Part 1 is to evaluate the safety of ADX-629 and confirm the target patient population and background therapy selection prior to expansion into Part 2. All subjects in Part 1 will receive open-label ADX-629 for 90 days either alone or in combination with SOC treatment. Subjects will be enrolled in either Cohort A, Cohort B, or Cohort C based on their SOC treatment at baseline. Subjects that are not receiving standard-of-care therapy will be assigned to Cohort A, subjects on a stable topical therapy will be assigned to Cohort B, and subjects on a stable dose of dupilumab will be assigned to Cohort C. Subjects in Cohort B must be able to discontinue topical therapy within 14 days of taking trial drug or by Visit 3 (Day 15) or will be discontinued from trial drug. Subjects in Cohorts C must be willing and able to continue background therapy throughout the duration of the clinical trial. The cohorts for Part 1 are described in Figure 3.

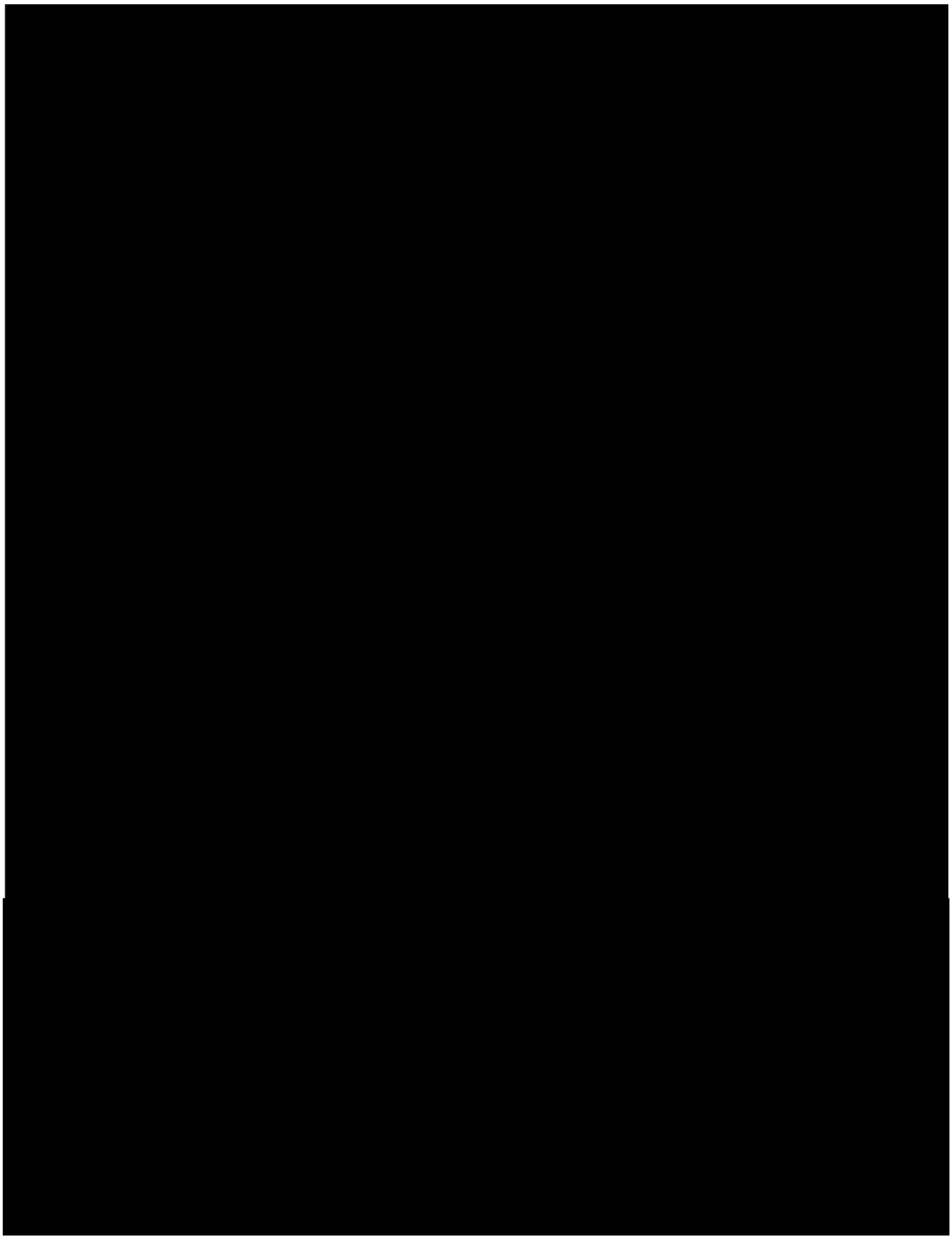
Part 2

Part 2 of the trial will be a randomized, double-blind, and placebo controlled and will include at least 40 subjects with AD. Subjects will be assigned to cohorts based on their standard-of-care therapy at baseline. Subjects will be randomized on Day 1 in a 1:1 or 2:1 ratio to receive ADX-629 (250 mg) or matching placebo for 90 days. Investigators, subjects, and the trial team will be blinded to treatment allocation. The purpose of Part 2 is to compare ADX-629 to placebo and standard-of-care treatment(s). The trial design will be adapted after the review of the safety and efficacy data from Part 1 and before any subjects are randomized into Part 2. Adaptations or modifications may include increasing the sample size, adjusting the number of cohorts or allocation of subjects in each cohort, and revising eligibility criteria and endpoints.

Figure 3 - Description of Cohorts for Part 1

Cohort	SOC Treatment	Requirements
Cohort A	**None**	• No topical therapies in the 14 days prior to Day 1 • No oral systemic therapies in the 45 days prior to Day 1 • No injectable systemic therapies in the 90 days prior to Day 1
Cohort B	**Topical therapy**	• Stable dose and consistent use of topical therapy required for at least 30 days prior to Day 1 and through Day 15 of the trial. • No oral systemic therapies in the 45 days prior to Day 1 • No injectable systemic therapies in the 90 days prior to Day 1
Cohort C	**Dupilumab**	• Stable dose and consistent use of dupilumab required for at least 6 months prior to Day 1 and throughout the trial. • No topical therapies in the 14 days prior to Day 1 • No oral systemic therapies in the 45 days prior to Day 1

3.2 Schedule of Visits and Assessments



[redacted]

3.3 Method of Assigning Subjects to Treatment Groups

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be enrolled into the trial. Subjects will be assigned to Part 1 or Part 2 based on the timing of their participation.

Part 1: Part 1 will be open to enrollment first. Subjects will be assigned to Cohort A, Cohort B, or Cohort C based on their prior and concomitant atopic dermatitis medications. All subjects will receive ADX-629 open-label for 90 days.

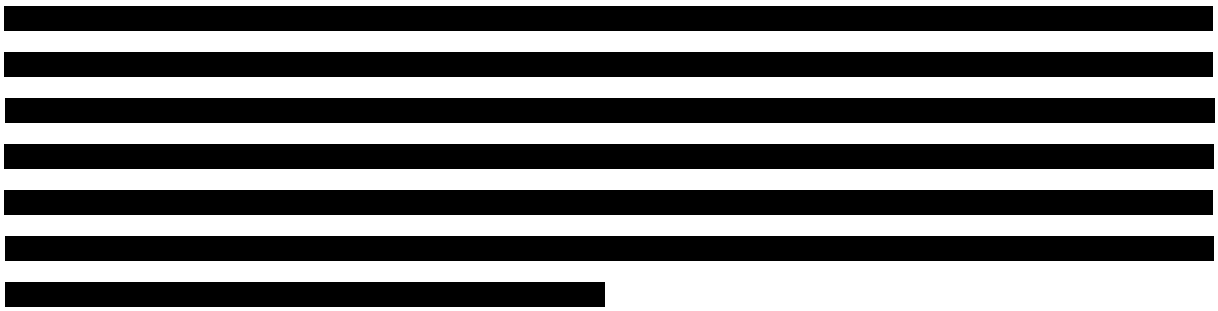
Part 2: Subjects will be randomized in Part 2 once all the subjects in Part 1 complete the treatment period in Part 1 and adaptations/modifications for Part 2 have been implemented. Subjects will be assigned to a cohort based on their prior and concomitant AD medications Cohorts may be added or dropped in Part 2, based on the data from Part 1. In Part 2, eligible subjects will undergo randomization at Visit 2 (Day 1), after eligibility has been confirmed. Subjects will be randomized in a 1:1 or 2:1 ratio to receive ADX-629 or placebo, either alone or in combination with SOC treatment. The treatment assignments will be allocated via IRT. Treatment assignment will be blinded to Investigator, subjects, and study team. The randomization plan will be followed. Blinded kit dispensation to eligible subjects will be managed by investigative site staff.

3.4 Masking and Unmasking

Part 1 of the trial is open-label and not blinded. Part 2 of the trial is double-blinded. The trial blind in Part 2 will not be broken until the clinical trial is complete and the database has been locked. Unblinding of a subject's treatment assignment is only permitted in emergency situations where the identification of treatment group is required for further management of the subject's condition by the Investigator. In case of emergency in which neither the Principal Investigator nor the sub-Investigator are available, the Medical Monitor may, as a last resort, perform the unblinding.

In any case of unblinding, the date, time, and reason for breaking the blind will be recorded, and the Sponsor and Medical Monitor will be notified. This information will be stored in the subject's source files with as few of the investigative site staff unblinded as is clinically reasonable.

4. Sample Size and Power Considerations



5. Data Preparation

Data will be collected on electronic case report forms (eCRFs) that are specifically designed for this trial. The Investigator or person designated by the Investigator will record subject data as accurately as possible in the eCRFs.

The Investigator must provide an electronic signature to attest to the accuracy and completeness of all the data. If any changes are made to an eCRF after a form has been locked and electronically signed, the Investigator will be required to perform an additional electronic signature authorizing agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change is always required.

Detailed information on data management will be provided in a data management plan (DMP) that will be written specifically for this trial. All plans and deviations will be documented in the DMP, unless a trial-specific plan, guideline, or specification is created.

The trial database will be defined according to the corresponding eCRFs and the trial protocol. Standard design templates will be used, and trial-specific items will be created as required. Data validation or data cleaning procedures are designed to assure validity and accuracy of clinical data, and will consist of reviewing data entered, as well as computerized edit checks and queries for identifying data values that are out of range, protocol violations, incomplete or inconsistent. The Data Management Plan (DMP) will specify the checks that are to be performed on subject data to raise data discrepancies or queries and will define the electronic edit checks and data validation queries to be created for the trial.

Queries will be raised for all errors discovered in the clinical data, when information is missing, or needs further clarification.

All data entry, verification, medical encoding, and data validation activities will be finalized before the database is locked. Quality control activities will be completed to acceptable error rates. All unnecessary user privileges to the trial will be removed, except for the Data Manager who will perform the database lock.

In exceptional circumstances, when critical reasons are justified, there may be a need to perform updates to the database after it has been locked. A database that is locked and released for analysis will only be unlocked if an error is identified that will significantly affect the statistical outcome of the analysis of the efficacy parameters or change the safety profile of the trial.

6. Analysis Populations

Analysis populations include the intent-to-treat (ITT) population, the per-protocol (PP) population, and the Safety population. The statistical analysis of safety data will be performed on the Safety population. The analysis of baseline and exploratory efficacy data will be performed on the ITT population, and may be performed on the PP population as sensitivity analyses if it differs substantially from the ITT population.

6.1 Intent-to-Treat

The ITT population includes all subjects who were met eligibility criteria and were enrolled into the trial. Subjects in the ITT population will be analyzed as randomized.

6.2 Per Protocol

The PP population includes subjects in the Safety population who do not have significant protocol deviations and who complete the trial. Protocol deviations will be assessed prior to database lock. Subjects in the PP population will be analyzed as treated.

6.3 Safety

The Safety population includes all subjects in the ITT population who have received at least one dose of the investigational product. Subjects in the Safety population will be analyzed as treated.

7. General Statistical Considerations

7.1 Unit of Analysis

All safety analyses will be based upon the safety population. Subjects will be analyzed by background therapy and treatment group. Frequency distributions and individual listings of all adverse events will be generated. Treatment-emergent adverse events (TEAE) will be summarized by treatment group and by system organ class and preferred term, in accordance with the latest MedDRA coding dictionary. A TEAE is defined as an adverse event that emerges during the treatment period (having been absent pre-treatment) or worsens relative to the pre-treatment period. Safety variables will be summarized descriptively by treatment and background therapy. The number of subjects reporting each AE preferred term will be tabulated for all TEAEs and separately for those considered as at least possibly related to trial treatment by the Investigator.

The ITT Population will be the primary analysis population for efficacy. Subjects will be analyzed by planned treatment, disease severity at baseline, and background therapy. The PP set will be used for a sensitivity analysis of the efficacy data. Efficacy data will be summarized by treatment group, AD severity at baseline, and background treatment. The analysis for Part 2 will be performed once all subjects complete the end-of-study visit or discontinue prematurely. The double-blind analysis for Part 2 will include the analysis of the primary efficacy endpoint and all other efficacy endpoints.

7.2 Missing or Inconclusive Data Handling

All analyses will be performed on the ITT population without imputation for missing data.

7.3 Definition of Baseline

Baseline measures are defined as the last non-missing measure prior to the initiation of study treatment. Change from baseline will be calculated as follow-up visit minus baseline value.

7.4 Data Analysis Conventions

All data analysis will be performed by Summit Analytical after the trial is completed and the database has been locked. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in RTF (Rich Text Format) for tables and PDF (Portable Document Format) for tables, listings, and figures using landscape orientation. All data will be listed by subject, treatment, and visit (as applicable) based on all enrolled subjects unless otherwise specified.

All summaries will be presented by treatment group, and visit, where appropriate, unless otherwise specified. Summaries will be provided for demographics, baseline medical history, concurrent therapies, and subject disposition. For the purpose of summarization, medical history, concurrent therapies, and adverse events will be coded to Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization (WHO) Drug dictionaries, as appropriate.

7.5 Adjustments for Multiplicity

[redacted]

8. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized, completed the study, and discontinued. Subjects who are not discontinued will be considered completers. Disposition will be summarized by treatment group and for all subjects.

The number of subjects in each of the analysis populations (ITT, PP, and Safety) will be displayed by treatment and percentages will be calculated using randomized subjects as the denominator.

The number and percentage of subjects prematurely discontinued and the reasons for discontinuation will be summarized by treatment group for all randomized subjects. The reasons for discontinuation that will be summarized include: (AE, protocol violation, administrative reasons (e.g., inability to continue, lost to follow up), Sponsor termination of the trial, subject choice, and other. A subject listing will be provided that includes the date of and reason for premature study discontinuation.

The number and percentage of subjects with major protocol deviations will be summarized by treatment group for all randomized subjects. The protocol deviations that will be summarized include: Informed Consent, Inclusion / Exclusion and Randomization, Test Article / Study Drug Instillation and Assignment at Site, Improper Protocol Procedures at Site, Site's Failure to Report SAE / AE, Visit Out of Window, Subject's Non-compliance with Test Article, Subject's Use of Prohibited Concomitant Medication, Subject's Failure to Follow Instructions, and Other. A subject listing will be provided that includes the date and description of each deviation.

In addition, subject listings will be provided that include treatment, whether inclusion and exclusion criteria were met, and inclusion in the ITT, Safety, and PP populations.

9. Demographic and Pretreatment Variables

9.1 Demographic Variables

The demographic variables collected include age, sex, race, ethnicity and iris color. Demographic variables will be summarized, overall and by treatment group, for the ITT and Safety populations, separately.

Age (years) will be summarized using continuous descriptive statistics. Age will also be categorized as follows: <65 years and ≥65 years. Age will be reported in years and calculated using the following formula:

Age = (informed consent date – date of birth) / 365.25 truncated as an integer

The number and percentage of subjects will be presented for age category, sex, race, ethnicity and iris color.

A subject listing that includes all demographic variables for the ITT population will be provided.

10. Medical History and Concomitant Medications

10.1 Medical History

Medical history will be coded using MedDRA Version 25.0 or later.

Medical history will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by System Organ Class (SOC) and Preferred Term (PT) using the ITT population. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once.

10.2 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary March 2023 or later and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical (ATC) 4 classification) and preferred name. ATC classifications are applied based on the route and indication by which the drug was taken. If no route or indication is reported/available, the first ATC in alphabetic order will be applied. Additional coding guidelines are specified in the Data Management Plan (DMP). Terms that remain uncoded after the coding guidelines have been followed will be forwarded to the Medical Monitor along with a list of potential coding links available in the dictionary. The Medical Monitor will either select one of the terms from the potential coding links or specify an alternate term that is available in the dictionary.

Concomitant medications will be summarized using the ITT population. Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than 1 medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she

reports 1 or more medications. Percentages will be based on the number of subjects in each treatment group. Listings of concomitant medications will be generated.

11. Dosing Compliance and Treatment Exposure

11.1 Dosing Compliance

If the subject is less than 80% or more than 120% compliant with dosing based on the expected number of used tablets, then the subject will be deemed non-compliant and a deviation should be recorded.

Dosing compliance (% compliance) will be assessed by calculating the number of doses taken and comparing that to the number of doses expected. The number of doses taken will be calculated from the number of used vials on the drug accountability eCRF.

A categorical dosing compliance variable will also be derived as non-compliant (<80% or >120%) or compliant (≥80% and ≤125%).

Dosing compliance (%) will be summarized with continuous descriptive statistics for each treatment group using the Safety population. The compliance category defined above will be summarized with discrete summary statistics. Under-compliance (<80%) and over-compliance (>125%) will also be separately summarized.

A subject listing of dosing compliance will also be produced.

11.2 Treatment Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

Extent of Exposure (days) = Date of completion/discontinuation – date of Visit 1 (Day 1)

Extent of treatment exposure for subjects who were lost to follow-up will be calculated in days using the following:

Extent of Exposure (days) = Date of last recorded visit – date of Visit 1 (Day 1) + 1

Extent of treatment exposure (days) for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group, using the Safety population. A subject listing of treatment exposure will also be produced.

12. Efficacy Analyses

12.1 Primary Analyses

Incidence and severity of treatment-emergent adverse events and serious adverse events will be analyzed and will be based upon the Safety population. Subjects will be analyzed by background therapy and treatment group. Frequency distributions and individual listings of all serious adverse events will be generated. Treatment-emergent adverse events (TEAE) will be summarized by treatment group and by

system organ class and preferred term, in accordance with the latest MedDRA coding dictionary. A TEAE is defined as an adverse event that emerges during the treatment period (having been absent pre-treatment) or worsens relative to the pre-treatment period. Safety variables will be summarized descriptively by treatment and background therapy. The number of subjects reporting each AE preferred term will be tabulated for all TEAEs and separately for those considered as at least possibly related to trial treatment by the Investigator.

12.2 Key Secondary, Secondary, and Exploratory Analyses

Quantitative measures collected at each visit will be summarized descriptively (n, mean, SD, median, min and max). Generally, continuous secondary endpoints and the exploratory endpoint for will be analyzed using mixed model for repeated measures (MMRM) with change from baseline as the dependent variable, baseline as a covariate, and time point as a factor. Results at each time point and over all time points will be assessed relative to baseline using MMRM LS mean results versus 0 (no change from baseline). Responder secondary endpoints and the exploratory endpoint will be assessed using binomial generalized estimating equation (GEE) analysis with time point as a factor. Results at each time point and over all time points will be assessed relative to 0 (no response) using GEE LS mean results. Other statistical methods for continuous and dichotomous endpoints may be utilized as appropriate. All statistical testing will be at the 5% level of significance (2-sided) and all point estimates for the comparison between treatment groups. Two-sided 95% confidence intervals will also be provided. All measures will also be presented in subject listings.

The following key secondary endpoint will be tested:

- Proportion of subjects with an IGA score of 0 or 1 at Day 90 will be analyzed using the ITT Population.

The following secondary endpoints will be tested:

- Proportion of subjects with an IGA score of 0 or 1 and ³2-grade improvement from Day 1
- Proportion of subjects achieving a ≥50%, 75% and 90% improvement in the EASI
- Proportion of subjects achieving ≥4 points improvement in the Peak Pruritus NRS
- Time to AD flare-up (days), as defined by use of rescue medication
- Proportion of subjects with a 4-point or more improvement in POEM total score at Day 90
- Percent change in HDL-C, LDL-C, and triglycerides from Baseline
- Change from Baseline in IGA Score, EASI Score, HAM-D score, and BAI Score

12.3 Investigator Global Assessment

The IGA is a five-point scale that provides a global clinical assessment of AD severity ranging from 0 to 4, where 0 indicates clear and 4 indicates severe AD. A decrease in score relates to an improvement in signs and symptoms. The clinical evaluator of atopic dermatitis will perform an assessment of the overall appearance of the lesions at the timepoints indicated in the schedule of assessments. The IGA score is

determined using descriptors that best describe the affected area. It is not necessary that all characteristics under the morphological description be present. The evaluator that completes the IGA at baseline must complete all subsequent IGA for the same subject, to the extent that is possible. The IGA score will be documented in subject's source and recorded in eCRF.

12.4 Eczema Area and Severity Index and Affected Body Surface Area

The Eczema Area and Severity Index quantifies the severity of a subject's atopic dermatitis based on both severity of lesion clinical signs and the percent of BSA affected. The EASI score is a composite score, and scores the degree of erythema, edema/papulation, excoriation, and lichenification for 4 separate body regions on a 4-point scale (0 to 3). The evaluator that completes the EASI at baseline must complete all subsequent IGA for the same subject, to the extent that is possible. The EASI and BSA assessment will be completed at the timepoints indicated in the schedule of assessments.

The number of handprints, or unit of measurement using the size of the subject's hand with closed fingers, of skin afflicted with atopic dermatitis in a body region can be used to determine the extent (%) to which a body region is involved with atopic dermatitis. 1% BSA is equal to the palm plus 5 digits, with fingers tucked together and thumb tucked to the side (handprint) and the thumb is equal to 0.1% BSA. The BSA ranges from 0 to 100%, with higher values representing greater severity of atopic dermatitis. The scalp, palms, and soles may be included in the BSA assessment.

12.5 Peak Pruritus Numerical Rating Scale

The Peak Pruritus NRS is an assessment tool that subjects used to report the intensity of their pruritus (itch) during a 24-hour period. Subjects will be asked to rate their itch daily, on a horizontal scale from 0 to 10, at the worst moment in the previous 24-hour period.

12.6 AD Flare

An atopic dermatitis flare is defined as worsening of disease by extent or severity, for which requires escalation or intensification of treatment, in the opinion of the Investigator. Flares may induce or exacerbate skin inflammation and pruritus. Flares may be triggered by several factors including exposure to allergens, stress, hormonal changes, irritating clothing, or fabric, change in weather (hot or cold), or change in medications. Start and stop dates, as well as possible triggers for flares will be documented in source and captured in eCRF.

12.7 Scoring Atopic Dermatitis

The SCORAD is a validated, clinical scoring index for atopic dermatitis, which provides a total score based on the area affected or extent of disease (0-100), severity/intensity (0-18), and subjective symptoms based on pruritus and sleep loss (0-20). A total score of under 25 represents mild AD, score between 25 and 50 represents moderate AD, and a score over 50 represents severe AD. The SCORAD will be completed at the timepoints indicated in the schedule of assessments

12.8 Patient-Reported Outcomes

Subjects will complete the self-administered patient-reported outcome assessments and questionnaires as indicated in the schedule of assessments. Subjects should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Subjects who are functionally unable to read the instruments may have site personnel read the questionnaire to them. The subject should complete the questionnaires at the timepoints indicated in the schedule of assessments and before site personnel perform any clinical assessments to avoid biasing the subject's response.

12.9 Patient-Oriented Eczema Measure

The POEM is a 7-item PRO measure used to assess the impact of AD over the past week.

12.10 Hamilton Depression Rating Scale

The HAM-D is a widely used clinician-administered depression assessment scale. The questionnaire contains items relating to symptoms of depression experienced in the past week (Williams JB 1988). The questionnaire is completed by the Investigator, after an unstructured interview with the subject to determine their symptoms. A total score is calculated by summing the individual scores from each question. The HAM-D rating scale will be completed at the timepoints indicated in the schedule of assessments.

12.11 Beck Anxiety Inventory Questionnaire

The Beck Anxiety Inventory questionnaire is a 21 item self-reported scale measuring anxiety (Beck et al., 1988). The total score is calculated by finding the sum of the 21 items. A score of 0 – 21 equates to low anxiety, a score of 22 – 35 equates to moderate anxiety, and a score of 36 and above equates to potentially concerning levels of anxiety.

13. Safety Analyses

All safety analyses will be conducted using the Safety population.

13.1 Adverse Events

Adverse Event: an adverse event is any untoward medical occurrence or worsening of a pre-existing medical condition in a trial subject. Adverse events include unfavorable, or unintended signs or symptoms and worsening of pre-existing diseases that may or may not be related to the investigational treatment administered. Adverse events may be caused by something other than the investigational product, and therefore, do not necessarily have to have a causal relationship to IP.

Abnormal laboratory values or vital signs abnormalities are considered to be AEs, only if they are medically relevant or clinically significant. In the case of chronic disease, if the disease is known and present when the subject enters the trial, only worsening of the disease (i.e., increased frequency or intensity) will be considered as an AE. All AEs will be coded using MedDRA Version 25.0 or later.

Serious Adverse Event: a serious adverse event is an adverse event that meets one of the following criteria:

- Results in death
- Life-threatening, (i.e., immediate risk of death)
- Requires in-patient hospitalization, or prolongation of existing hospitalization
- Results in residual or significant disability or incapacity
- A congenital anomaly/birth defect
- An important medical event, requiring intensive treatment (i.e., bronchospasms, blood dyscrasias, convulsions, development of cancer, or drug abuse).

The following are not considered to be SAEs: elective procedures that require admission to the hospital, in-patient procedures planned prior to signing the inform consent form (e.g., angioplasty), or emergency room visits for less than 24 hours that are an event that is not medically important or life-threatening.

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported by the subject. The assessment of severity is made irrespective of relationship to trial procedures or seriousness of the event and should be evaluated according to the following scale:

- **Grade 1 (Mild)** - asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2 (Moderate)** - minimal, local, or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily living (ADL)
- **Grade 3 (Severe)** - medically significant but not immediately life-threatening; hospitalization indicated; disabling; limiting self-care ADL
- **Grade 4 (Life-threatening)** - serious consequences; urgent intervention indicated
- **Grade 5 (Death)** - AE resulting in death

Assessment of causality is based on the following considerations: associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, or absence of alternative explanations.

The Investigator will assess the causal relationship to the trial treatment according to the following classifications:

- **Definite:** A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically using

a satisfactory re-challenge (the drug is readministered to determine if the same reaction occurs) procedure if necessary.

- **Probable:** A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible.
- **Possible:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to the drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Unlikely**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations.
- **Not related**: Any event that does not meet the above criteria; there is sufficient information that etiology of the event is in no relation to the trial treatment.

An overall summary will be presented that includes the number of AEs, TEAEs, and serious AEs (SAE) The summary will also include the number and percentage of subjects withdrawn due to an AE, the number and percentage of subjects with an AE resulting in death, and the number and percentage of subjects who experienced at least one AE, TEAE, and SAE.

14. Interim Analyses

An interim analysis may be performed after Part 1. Modifications to the trial design or adjustments to the sample size in Part 2 or termination of enrollment of subjects in a treatment arm may be made upon review of the data.

15. Changes from Protocol-Stated Analyses

There are no changes from the protocol-stated analyses.

16. Revision History

Documentation of revision to the SAP will commence after approval of the Final version 1.0.

17. Tables and Listings

Summary tables and listings will be generated. The ITT population will be used to analyze the efficacy endpoints in Part 1 and the Safety population will be used to analyze the safety endpoints in Part 1. Part 2 will use the ITT, Per-protocol, and Safety populations.