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STATISTICAL ANALYSIS PLAN
Escient Pharmaceuticals, Inc.
EP-262-202

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STATISTICAL ANALYSIS PLAN APPROVAL

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ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AD	Atopic dermatitis
AE	Adverse event
ANCOVA	Analysis of Covariance
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ATC	Anatomical Therapeutic Chemical
AST	Aspartate aminotransferase
BLQ	Below the limit of quantification
BMI	Body mass index
BSA	Body surface area
CCL	Chemokine ligands
CONSORT	Consolidated Standards of Reporting Trials
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
DE	Differentially expressed
DILI	Drug-induced liver injury
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGF	Epidermal growth factor
FAS	Full Analysis Set
HDM	House dust mite
HEENT	Head, eyes, ears, nose, throat
ICF	Informed consent form
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukins
INR	International normalized ratio
IPD	Important Protocol Deviation
IWRS	Interactive Web Response System
[redacted]	[redacted]
Log_2	Log base 2
LS	Least-square

Abbreviation	Definition
LSMD	Least-square mean difference
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
[redacted]	[redacted]
Q1	1st quartile (25th percentile)
Q3	3rd quartile (75th percentile)
QoL	Quality of life
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Fridericia's formula
[redacted]	[redacted]
rlog	Regularized log transformation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
S. aureus	*Staphylococcus aureus*
TEAE	Treatment-emergent adverse event
TNF-α	Tumor necrosis factor-alpha
[redacted]	[redacted]
UGT1A1	Uridine 5' diphospho-glucuronosyltransferase 1A1
ULN	Upper limit of normal
[redacted]	[redacted]
vst	Variance stabilizing transformation
WHO	World Health Organization

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Escient Pharmaceuticals, Inc. Protocol EP-262-202 (Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of EP262 in Subjects with Atopic Dermatitis). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials (E9)* (1998) and *Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (E9[R1], Rev 1)* (2021).

This SAP will be finalized prior to data analysis and before treatment unblinding and database lock to provide comprehensive details of the tables and listings to be presented in the Clinical Study Report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables and listings need not be documented in the CSR.

2. STUDY OBJECTIVES

2.1 Primary Study Objective

The primary objective of this study is to evaluate the safety and tolerability of EP262 compared to placebo in subjects with atopic dermatitis (AD).

2.2 Secondary Study Objective

The secondary objective of this study is to evaluate the pharmacodynamic (PD) effects of EP262 compared to placebo in subjects with AD on skin biopsy-derived biomarkers.

2.3 Exploratory Objectives

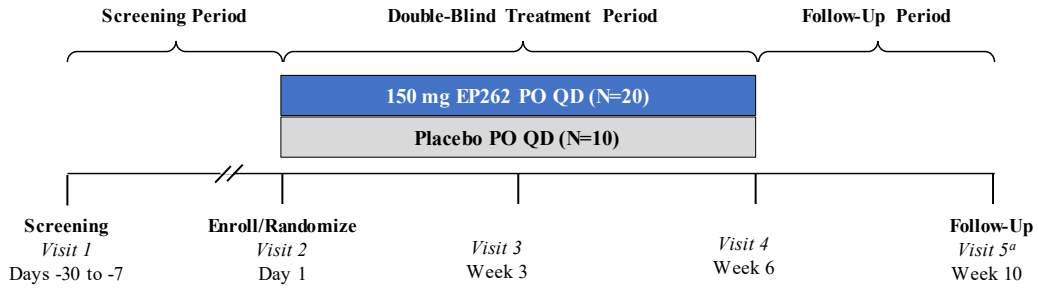
3. INVESTIGATIONAL PLAN

3.1 Overall Study Design

Study EP-262-202 is a Phase 2a, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and PD of EP262 over 6 weeks in subjects with AD.

The study includes a Screening Period of at least a week and up to 30 days to assess subject eligibility that includes collection of daily [redacted] ([redacted]) scores; a 6-week Double-Blind Treatment Period; and a 4-week Follow-Up Period after administration of the last dose of study drug for a total study duration of up to approximately 14 weeks for each subject. Approximately 30 subjects will be randomized in a 2:1 ratio to receive either a 150 mg dose of EP262 or placebo orally (PO), once daily (QD) during the 6-week Double-Blind Treatment Period (Figure 1).

Figure 1 EP-262-202 Study Design



PO = oral; QD = once daily.
[a] Any subject who completes the Double-Blind Treatment Period or discontinues study drug (EP262 or placebo) early will have a Follow-Up Visit approximately 4 weeks (±3 days) after the last dose of study drug.

3.2 Schedule of Assessments

For the complete schedule of assessments, refer to Appendix A of the clinical study protocol.

3.3 Treatment

3.3.1 Treatment Administered

Capsules containing 75 mg of EP262 or placebo will be supplied in bottles in a manner to ensure the study blind. Each subject will take 2 capsules per dose, with subjects randomized to EP262 receiving a total of 150 mg per day.

Each study drug dose is to be administered PO as intact capsules (swallowed whole, not split, opened, or chewed) and taken with approximately 240 mL (8 fluid ounces) of water on an empty stomach. Subjects will be instructed to take the study drug at approximately the same time of the day after a fast of at least 4 hours. Subjects should refrain from eating for at least 2 hours postdose. On the days of clinic visits, the time of study drug administration may differ depending on the scheduled visit time. The first

dose of study drug will be administered at the clinical site on Visit 2 (Day 1) after all baseline study procedures are completed.

3.3.2 Method of Assigning Subjects to Treatment Groups

Approximately 30 subjects with AD will be randomized in a 2:1 ratio to receive either a 150 mg dose of EP262 or placebo PO, QD for 6 weeks during the Double-Blind Treatment Period beginning at Visit 2 (Day 1). Randomization will be conducted centrally via an Interactive Web Response System (IWRS). The master randomization list will be kept secured until the study blind is broken at the end of study.

Subjects who withdraw for any reason without completing all screening evaluations successfully will be considered "screening failures". A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

3.3.3 Blinding Procedures

The Sponsor, Medical Monitor, Contract Research Organization (CRO) staff, Investigators, site staff, and subjects will be blinded to subject's assigned treatment until the database is locked except for CRO or vendor staff involved in the analysis of pharmacokinetic samples. Procedures for emergency unblinding and unblinding for regulatory reporting are described below.

If an emergency unblinding during the Double-Blind Treatment Period is required, the subject's treatment assignment may be unblinded through IWRS by the Investigator. If a treatment assignment is unblinded, the subject will be discontinued from randomized treatment.

Blinding codes should only be broken in emergency situations for reasons of subject safety and when knowledge of the treatment assignment will impact the clinical management of the subject. Every reasonable attempt should be made to complete the post-treatment evaluation procedures prior to unblinding as knowledge of the treatment arm could influence subject assessment. In all emergency cases, the reasons and rationale for unblinding will be documented in writing and maintained in the study file.

Access to randomization codes and corresponding treatment assignment will be made available through the IWRS system to the appropriate individual(s) responsible for unblinding suspected unexpected serious adverse reactions for reporting to the Regulatory Authorities.

3.3.4 Background Therapy Emollient Use

Subjects are to use a protocol-permitted, non-urea-containing emollient on lesional and nonlesional skin daily for at least 1 week before Day 1 and agree to continue using that same emollient daily at the same frequency (ideally once or twice daily) throughout the study. Subjects will record emollient use in a daily diary throughout the study. Every

effort should be made to keep the same emollient throughout the study for the same body region.

Subjects will delay emollient use on the days of study visits until after study procedures are completed.

3.3.5 Rescue Medications

New concomitant medications and procedures for treatment of AD are prohibited during the study. If a patient requires treatment with a new medication or procedure due to intolerable AD symptoms, study drug should be discontinued. Whenever possible, subjects should remain in the study and complete the remaining study visits and assessments even when study drug has been discontinued.

3.4 Pharmacodynamic and Safety Variables

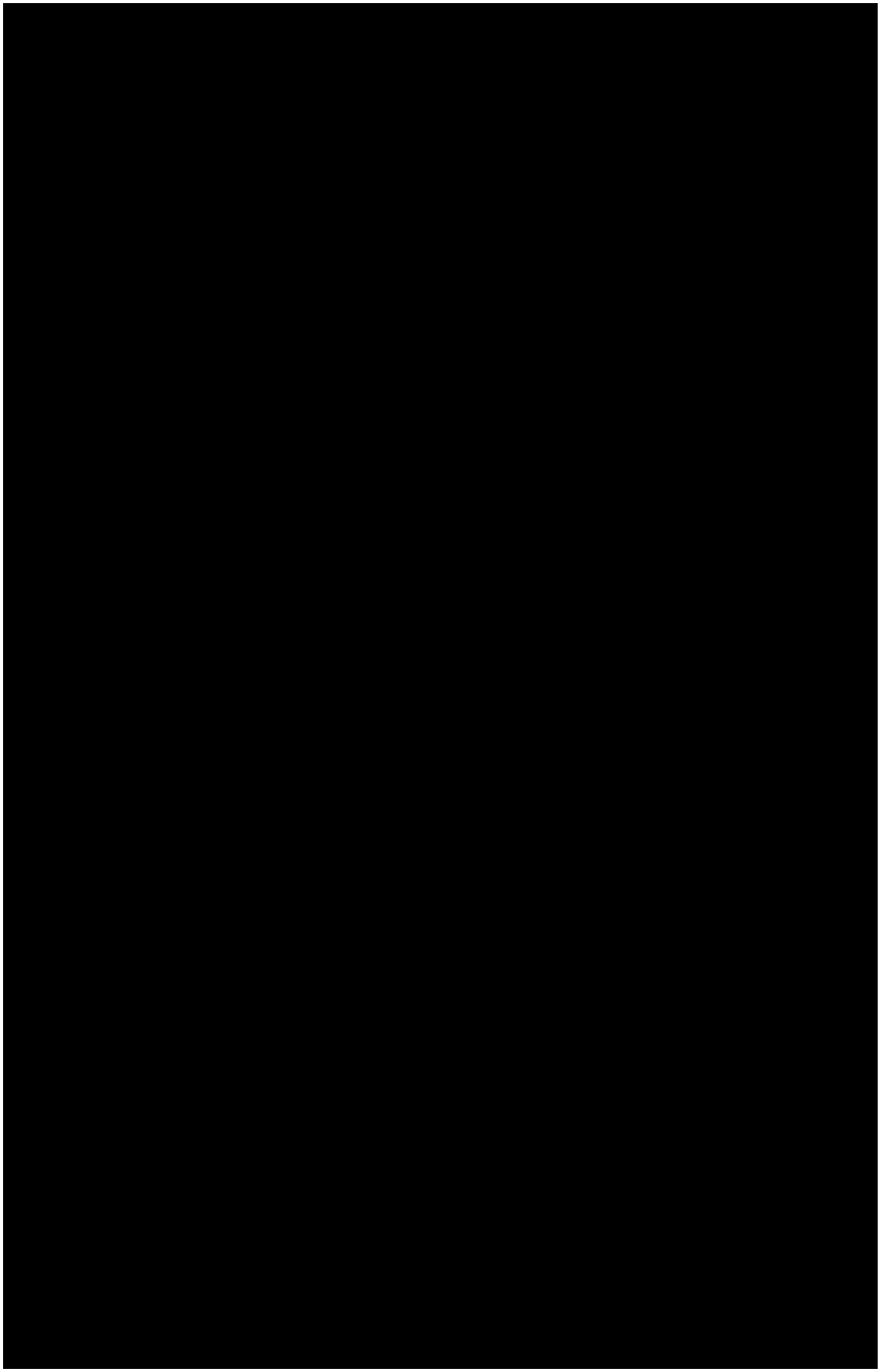
3.4.1 Pharmacokinetic Variables

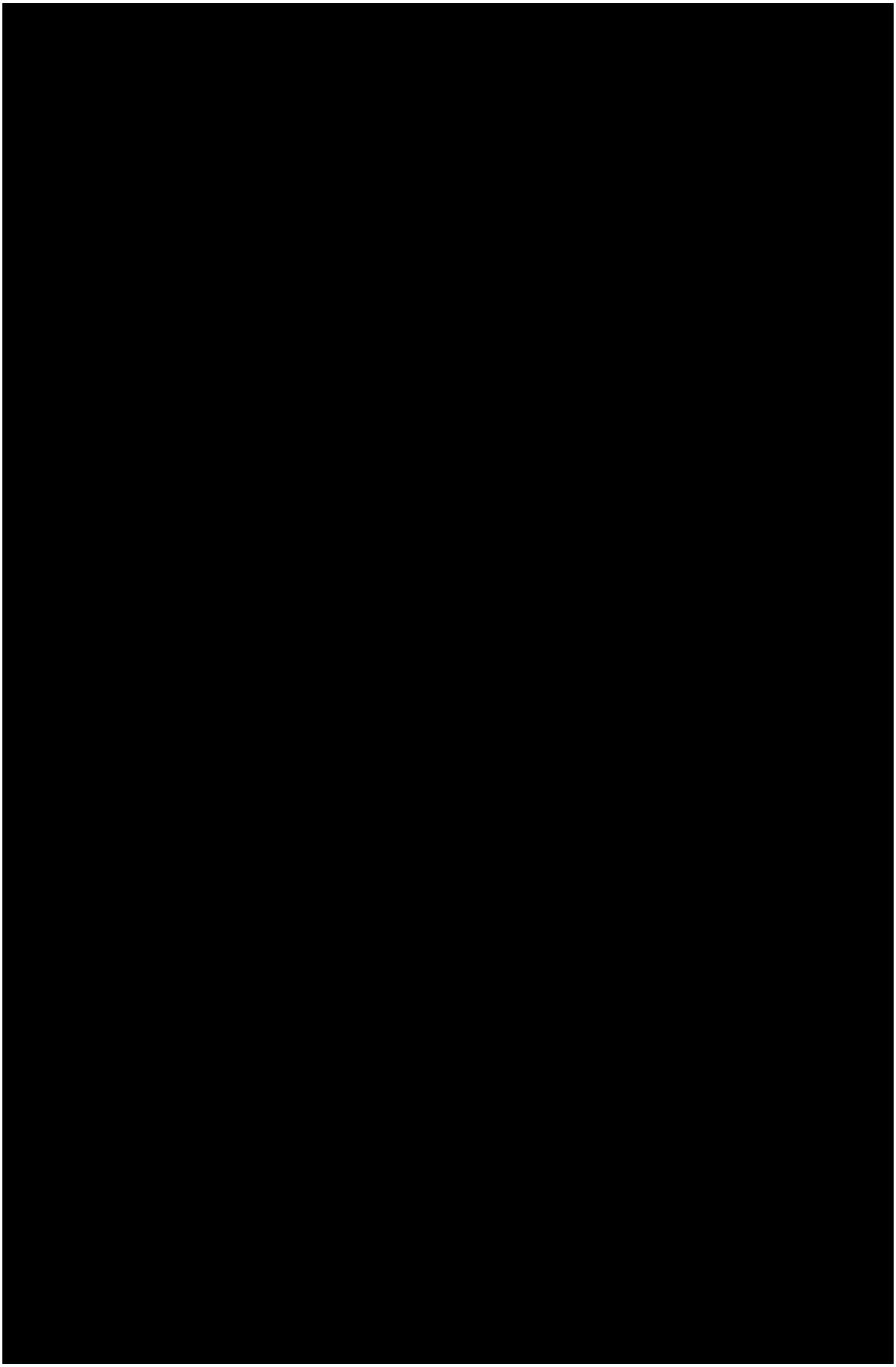
Blood sampling will be collected predose (as applicable) at Visit 2 (Day 1), and each visit thereafter to analyze trough EP262 concentrations. The EP262 metabolite profile may also be analyzed from these trough samples.

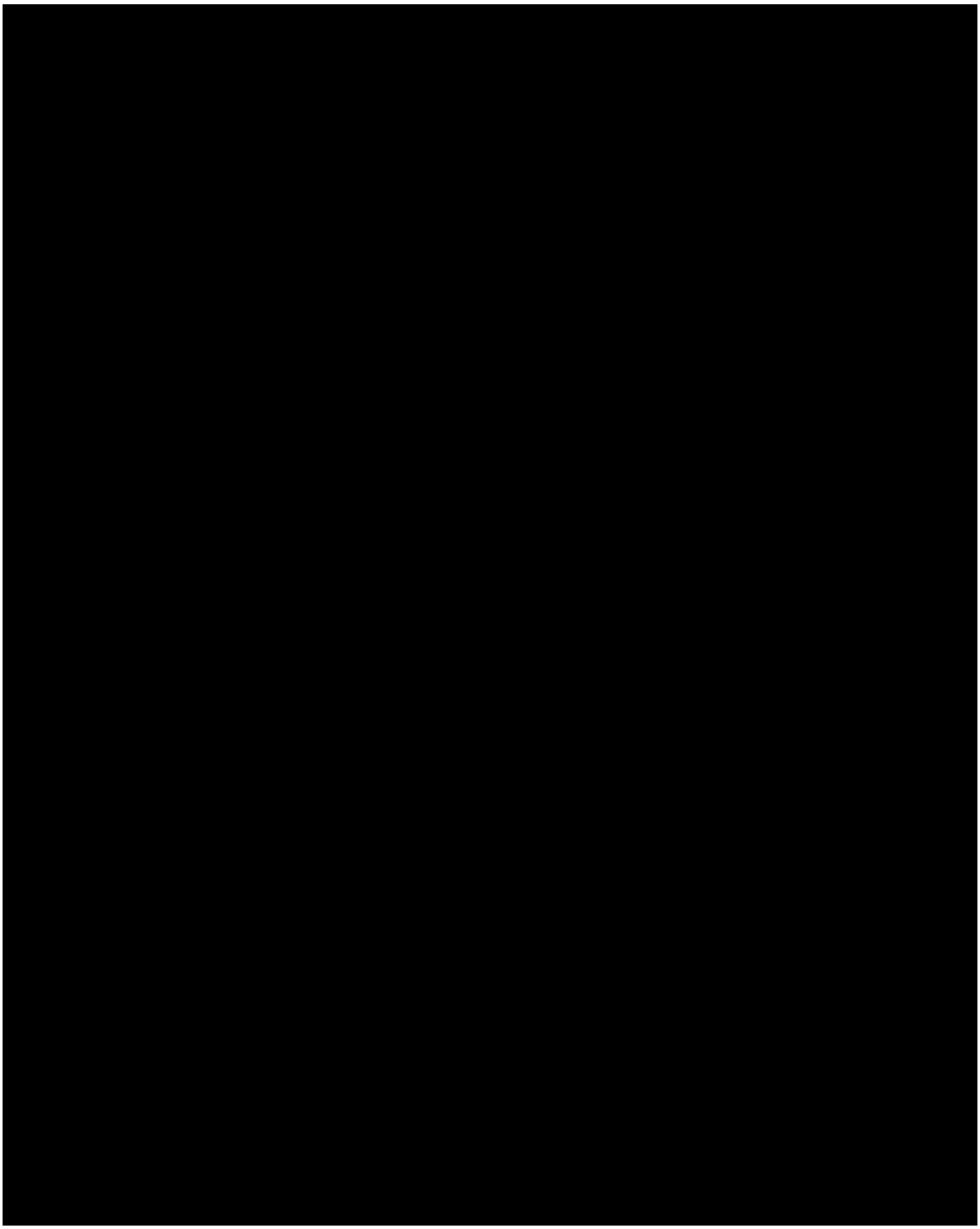
3.4.2 Pharmacodynamic Variables

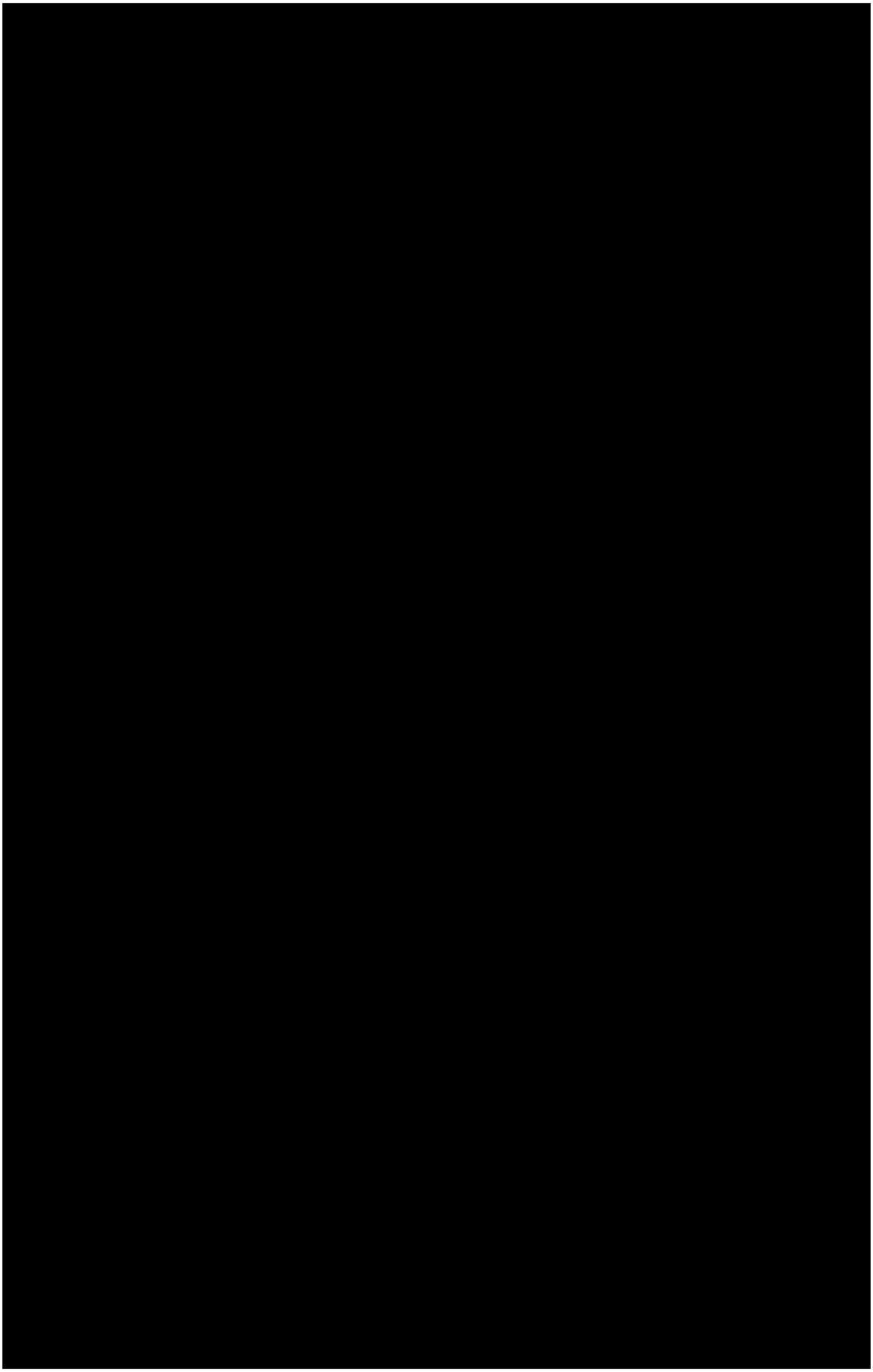
Pharmacodynamic assessments [redacted] be taken of the area of worst lesional involvement at Visit 2 (Day 1) and of the same area at Visit 3 (Week 3), Visit 4 (Week 6), and Visit 5 (Follow-Up). Photographs will also be taken of areas selected for skin swabs, skin tape strips application, and biopsies before these procedures are conducted.

[redacted]









3.4.3 Baseline Characterization

A blood sample will be collected at Visit 2 (Day 1) for measurement of house dust mite (HDM)-specific IgE.

Blood samples will also be taken at Visit 2 (Day 1) for genotyping to evaluate uridine 5' diphospho-glucuronosyltransferase 1A1 (UGT1A1) and filaggrin polymorphisms to enable pharmacogenomic analyses.

3.4.4 Safety Variables

Safety evaluations, including adverse events (AEs), concomitant medications, medical history, vital signs, physical examinations, standard 12-lead electrocardiograms (ECGs), and laboratory evaluations of safety will be performed as indicated in the Schedule of Assessments (Appendix A) of the clinical study protocol.

3.4.4.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product.

Medical conditions present at baseline that worsen in severity or frequency after exposure to study drug are considered treatment-emergent adverse events (TEAEs). A TEAE is any condition that was not present prior to treatment with the study drug but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated). Planned hospital admissions or surgical procedures for an

illness or a disease that existed before administration of study drug, and for which the condition has not worsened since starting study drug, are not to be considered TEAEs/treatment-emergent serious AEs. Events with emergency room visits that are less than 24 hours will also not be considered SAEs unless they meet one of the criteria listed in Section 11.2.1 of the clinical study protocol.

Abnormal laboratory tests, 12-lead ECG assessments, or vital sign results may constitute an AE if they meet one of the criteria listed in Section 11.1.4.1 of the clinical study protocol. However, whenever possible, the underlying diagnosis should be listed in lieu of associated abnormal results.

Subjects will be assessed for potential drug-induced liver injury (DILI) during the study, although there was no evidence of hepatotoxicity in previous studies related to EP262. Monitoring, interruption, and stopping rules based on multiples of the upper limit of normal (ULN) of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin values are described in section 11.10.3 of the clinical study protocol.

AEs are graded for severity (i.e., intensity) using Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (HHS 2017). A severity category of mild, moderate, severe, life-threatening, or death, as defined in Appendix B of the clinical study protocol, will be entered on the AE Electronic Case Report Form (eCRF).

Additional considerations are made for TEAEs falling under certain system organ classes. The study drug must be discontinued for the following TEAEs and CTCAE grades:

- CTCAE Grade 2 or higher in the Cardiac Disorders system organ class
- CTCAE Grade 2 or higher in terms of Bone marrow hypocellular, lymphocyte count decreased, lymphocyte count increased, or myelodysplastic syndrome
- CTCAE Grade 3 or higher in other system organ classes

3.4.4.2 Laboratory Parameters

Samples for the following laboratory tests should be collected after an overnight fast (at least 8 hours):

- Chemistry: sodium, albumin, alkaline phosphatase (ALP), bicarbonate, calcium, corrected calcium, chloride, bilirubin (total, indirect, and direct), AST, ALT, blood urea nitrogen, urea, creatinine, glucose, magnesium, phosphorus, potassium, creatine phosphokinase, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lactate dehydrogenase, gamma-glutamyl transferase, and total protein
- Hematology: hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, white blood cell count (total and differential), red blood cell count, platelet count, and platelet volume

- Urinalysis: leukocyte esterase, nitrites, pH, protein, specific gravity, glucose, occult blood, ketones, bilirubin, and urobilinogen; microscopic analysis is to be performed only if protein, leukocyte esterase, blood or nitrite is positive

- Coagulation: activated partial thromboplastin time, international normalized ratio (INR), and prothrombin time

- Pregnancy testing: required for all females; serum test at Screening (Visit 1) and urine test for all other visits where pregnancy testing is required

The urine pregnancy test for female subjects will be conducted locally; all other planned laboratory evaluations of safety will be conducted at a central laboratory. Details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

3.4.4.3 Other Laboratory Evaluations

Samples for the following laboratory tests will be collected:

- Serology: HIV I/II, HBV (hepatitis B surface antigen), HCV

These planned laboratory evaluations will be conducted at a central laboratory. See the Laboratory Manual for additional details.

3.4.4.4 Medical History

The Investigator or designee will collect and review the subject's medical history, including AD disease history, to evaluate the subject's eligibility for study participation. The new onset of signs, symptoms, or other findings that occur from before signing of the informed consent form (ICF) will be captured as medical history.

3.4.4.5 Vital Signs

Vital signs, including sitting systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate, will be measured pre-dose (as applicable) after at least 5 minutes of rest. Vital signs are to be performed pre-dose if the dose is administered at the site.

3.4.4.6 Body Weight and Height

Body weight should be measured with no shoes and heavy clothing (outdoor clothing such as coats) on and using a calibrated scale throughout the study. Height should be measured using a stadiometer with no shoes.

3.4.4.7 Physical Examinations

Physical examinations will include but are not limited to an assessment of general appearance, skin, HEENT (head, eyes, ears, nose, throat), musculoskeletal, thyroid/endocrine, cardiovascular, chest/lung, neurologic, abdomen, and extremities/general body systems.

Abbreviated, symptom-directed physical examinations to assess clinically significant changes from Screening or any new signs or symptoms will be conducted at Visit 3 (Week 3), Visit 5 (Week 10), and the Early Treatment Termination Visit, and may be conducted at other visits as determined by the Investigator based on subject complaint.

Clinically significant abnormalities from before signing of the ICF will be recorded as medical history, and clinically significant changes after signing the ICF will be recorded as AEs.

3.4.4.8 12-Lead Electrocardiograms

Twelve-lead ECGs are to be performed pre-dose (as applicable) with subjects in a supine position after at least 5 minutes of rest. An ECG is to be performed pre-dose if the dose is administered at the site.

3.5 Data Quality Assurance

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.

4. STATISTICAL METHODS

4.1 General Methodology

Data will be analyzed by Emanate biostatistics personnel. Statistical analyses will be reported with tables and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the Electronic Common Technical Document Specification (Apr 2003).

4.1.1 Reporting Conventions

Tables will be summarized by treatment group. All tables, exclusive of PD and pharmacokinetic (PK) analyses, will also include a column for all subjects combined. In general, all data collected and any derived data will be presented in subject data listings, for all enrolled subjects. Listings will be ordered by subject number, treatment

group, and assessment or event date. The treatment group presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of subjects with available data (n), mean, SD, SE, median, first (Q1) and third (Q3) quartiles, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the eCRF or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data.

No formal statistical analysis will be performed to compare treatment groups. This study is exploratory in nature; descriptive statistics will be tabulated by treatment group and reviewed to evaluate all study endpoints. Any p-values presented are to be considered nominal in their evaluation and interpretation. P-values will be reported for statistical tests, rounded to four decimal places. P-values less than 0.0001 will be displayed as "<0.0001"; p-values greater than 0.9999 will be displayed as ">0.9999".

4.1.2 Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit label as reported on the eCRF.

Whenever possible, subjects should remain in the study and complete the remaining study visits and assessments even when study drug has been discontinued. Subjects who discontinue study drug for any reason and continue with the study visits as planned through Visit 4 (Week 6) (participating only in PD and safety, but not PK measures) will participate in the Follow-Up Visit if the last dose of study drug was administered less than 4 weeks before Visit 4 (Week 6) to ensure that at least 4 weeks of follow-up data are collected for all randomized subjects. Subjects that discontinue treatments early and complete the remaining study visits will be summarized according to their planned treatment group, unless otherwise noted.

If a subject discontinues study drug and chooses not to complete all of the remaining study visits, the subject should have the Early Treatment Termination visit conducted as soon as possible after the last dose of study drug, ideally within 2 days after the last dose of study drug, and a Follow-Up Visit approximately 4 weeks (±3 days) after the last dose of study drug if at least 4 weeks of follow-up data have not already been collected. The Early Treatment Termination visit will be mapped and summarized with the next treatment scheduled nominal visit, according to the schedule of events, based on the last visit completed per protocol if the Early Treatment Termination visit falls within the study day visit window defined for that nominal visit.

Data collected at unscheduled visits will not be included in by-visit summaries, but will be considered when endpoint derivations potentially include multiple visits (e.g., determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in subject listings.

4.1.3 Data Handling Rules

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (e.g., "< 1.0") will be summarized with the sign suppressed in summary tables, using the numeric value reported. Data will display on subject listings to include the sign.

4.1.4 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on subject data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose of study drug, if the assessment/event date is prior to the date of first dose; and

- The assessment/event date minus the date of first dose of study drug, plus one, if the assessment/event date is on or after the date of first dose.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:

    - Later date – earlier date + 1, if the earlier date is on or after the reference date of interest (e.g., date of first dose of study drug); or

    - Later date – earlier date, if the earlier date is prior to the reference date of interest.

- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12).

- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25.

- **Change from Baseline:** Change from baseline will be calculated as the post baseline value minus the baseline value.

- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

- **Geometric CV**: calculated as 100*sqrt[exp(σ2)-1], where σ2 is the variance of the log-transformed data.

- **Log2 Fold Change**: calculated as B - A, where: B is the value of interest and A is the value of reference, where B and A are log scale base 2 transformed.

4.2 Analysis Sets

The analysis sets are defined as follows:

- Full Analysis Set: All subjects who are randomized and take at least 1 dose of randomized study drug will be included in the Full Analysis Set (FAS). Subjects in the FAS will be analyzed according to randomized treatment assignment. All PD analyses will be based on the FAS.

- Per Protocol Set: The Per Protocol (PP) Set is a subset of the FAS containing subjects who meet study eligibility requirements and had no protocol deviations that might impact the assessment of PD measurements. Subjects will be analyzed according to randomized treatment assignment. The PP Set will be used for sensitivity analyses relating to PD. Protocol deviations that qualify for exclusion from the PP Set include:

    - Deviations of inclusion/exclusion criteria

    - Non-permitted concomitant medications or procedures that may meaningfully impact PD outcomes

    - Meaningful dosing and/or randomization error(s)

    - Any other important protocol deviation deemed by the Sponsor to warrant exclusion from the PP set

  Any protocol deviations that govern exclusion from the PP Set will be determined prior to database lock.

- Safety Analysis Set: All subjects who are randomized and take at least 1 dose of randomized study drug will be included in the Safety Analysis Set. Safety analyses will be based upon treatment actually received.

- PK Set: All subjects who receive at least 1 dose of EP262 and provide adequate blood samples for bioanalysis will be included in the PK Set.

Data summaries to be presented on both the Safety Analysis Set and the FAS will only be produced on both analysis sets if there is a difference in the population groups.

4.3 Study Subjects

4.3.1 Disposition of Subjects

Subject disposition will be summarized for all randomized subjects by treatment group and overall subjects combined. Summaries will include the number and percentage of subjects in each analysis set, completing the study, and discontinuing the study early by the primary reason for discontinuation. Subject disposition will also be summarized separately for each study site for all randomized subjects.

The number and percentage of screen failures will be presented based on the total number of subjects screened. The reason for screen failure will also be summarized for screen failures. Screen failures will also be presented in a subject-level listing.

4.3.2 Protocol Deviations

Important Protocol Deviations (IPDs) will be summarized by treatment group and overall subjects combined for the FAS. Important Protocol Deviations are identified by the Sponsor and are defined in the ICH guideline *Structure and Content of Clinical Study Reports – Questions and Answers (E3[R1], 2013)* as a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

All IPDs will be determined and appropriately categorized prior to database lock and prior to breaking the blind of the treatment group assignments. The number and percentage of subjects with any IPDs as well as the number and percentage of subjects with IPDs within each category will be presented. A listing of important protocol deviations will be provided.

4.4 Statistical Evaluation

4.4.1 Datasets Analyzed

All PD summaries will be based on the FAS; select summaries will also be produced on the PP Set. A data listing of subjects excluded from the FAS or PP Set, to include the reason for exclusion, will be presented.

4.4.2 Demographic and Other Baseline Characteristics

Demographic variables including age, sex, ethnicity and race will be summarized by treatment group and overall subjects combined for the Safety Analysis Set, FAS, PP Set, and PK Set.

Age will be summarized using descriptive statistics. Sex, ethnicity, and race will be summarized with the number and percentage of subjects in each parameter category.

Medical history conditions will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 26.0). Frequency counts and percentages to summarize subjects reporting medical history by

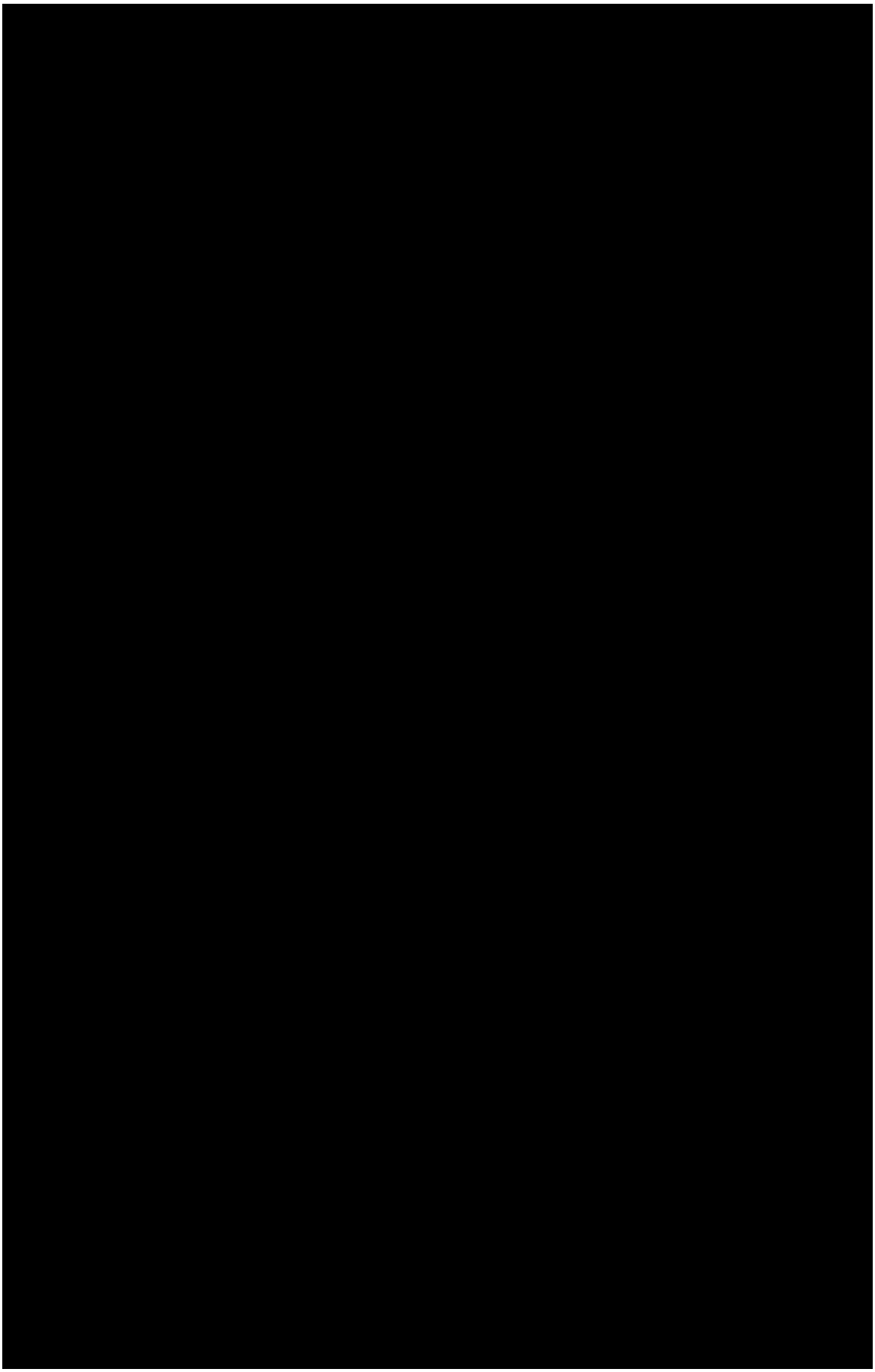
system organ class and preferred term will be presented for the FAS and summarized by treatment group and overall subjects combined.

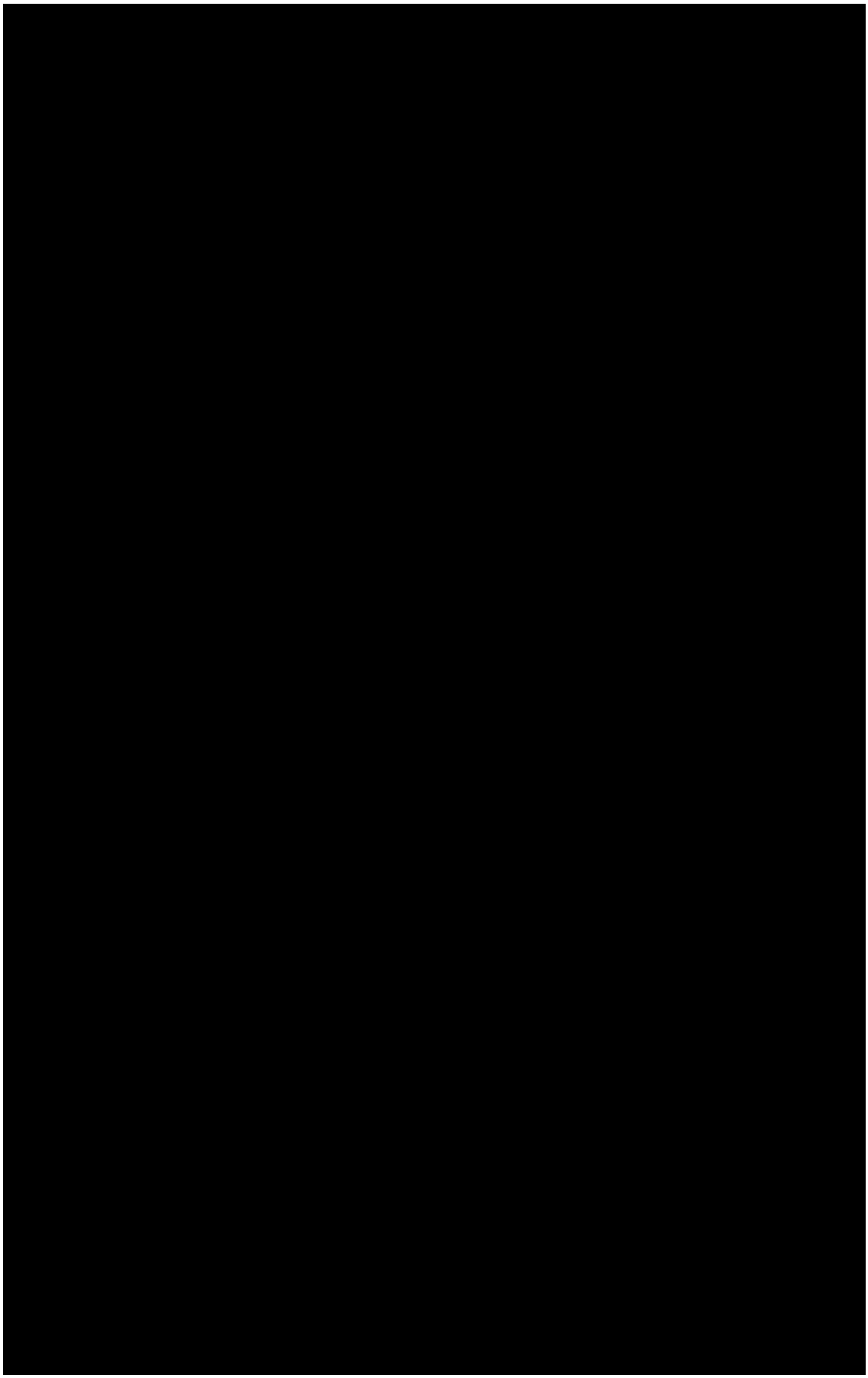
Baseline disease characteristics to be summarized include baseline total IgE (kU/L), time since AD diagnosis (as reported on the Disease History eCRF), presence of *S. aureus*, history of asthma, allergic rhinitis, HDM allergy, whether or not the subject has had phototherapy for AD, previously taken other AD medications, or has taken any emollients after diagnosis. The number and percentage of subjects with a baseline total IgE greater than 100 kU/L will also be summarized. Time since AD diagnosis (in years) is calculated as the informed consent date – the date of diagnosis divided by 365.25. Subjects with partial dates reported for the date of diagnosis will have time (years) calculated utilizing the available date information reported. Time since AD diagnosis will be summarized using descriptive statistics. Baseline characteristics will be summarized for the Safety Analysis Set, FAS, PP Set, and PK Set by treatment group and overall subjects combined.

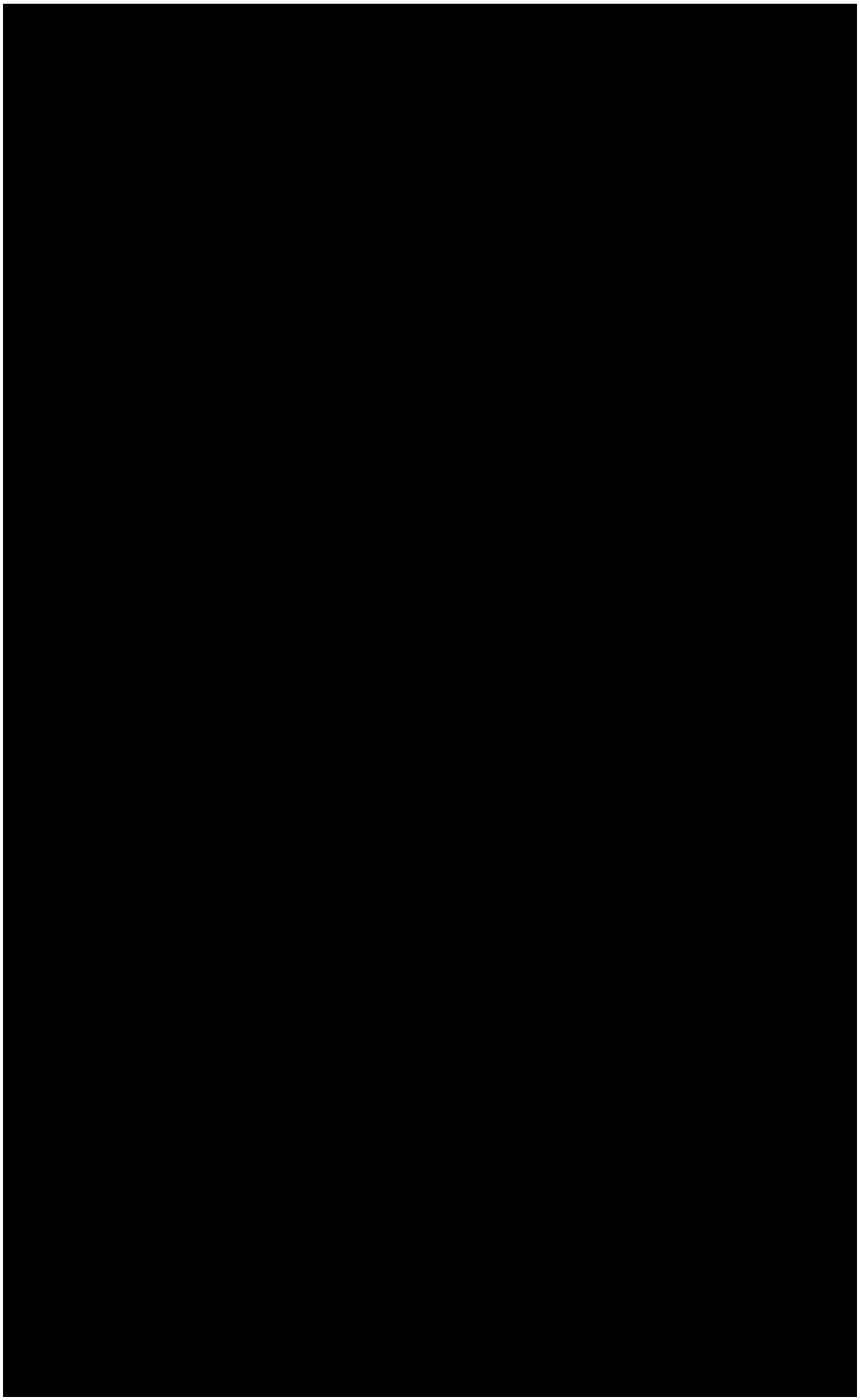
Prior reported AD therapies will be coded using the World Health Organization (WHO) Drug Global B3, version March 1, 2023. Therapies entered on the Prior AD eCRF will be mapped to Anatomical Therapeutic Chemical (ATC) drug class (level 2) and preferred name. The number and percentage of subjects receiving any therapy will be summarized by treatment group and overall subjects combined in the FAS, as will the number and percentage receiving any therapy by ATC drug class and preferred name. Subjects reporting use of more than one therapy at each level of summarization (any medication received, ATC class, and preferred name) will be counted only once.

Baseline characterization data including UGT1A1, filaggrin polymorphisms, and total HDM – specific IgE will be presented in a listing.

4.4.3 Pharmacodynamic Analysis Methods







[redacted]

4.4.4 Statistical/Analytical Issues

4.4.4.1 Adjustments for Covariates

The ANCOVA model to compare treatment groups for the skin biopsy-derived biomarkers secondary endpoint of skin histology will include a covariate adjustment for the baseline value. All statistical results presented are to be considered nominal in their evaluation and interpretation.

4.4.4.2 Handling of Dropouts or Missing Data

No imputations will be performed on missing data; all analyses will be descriptive in nature and based on observed data only. Any responder analysis will be based on the number of subjects reporting data at the visit of interest.

4.4.4.3 Interim Analyses and Data Monitoring

No interim analysis will take place for the study.

4.4.4.4 Multicenter Studies

This is a multicenter study to be conducted within North America. Pharmacodynamic data collected from all study sites will be pooled for data analysis. The effect of study site on the analysis results may be explored post-hoc, as needed.

4.4.4.5 Multiple Comparisons/Multiplicity

For analysis of gene expression, the Bonferroni correction will be used to control the alpha at 5%. For analysis of other parameters, there will be no adjustments for multiple comparisons in the analysis for this study. Results are descriptive in nature and there will be no formal comparisons made among treatment groups. All statistical results presented are to be considered nominal in their evaluation and interpretation.

4.4.4.6 Use of an "Efficacy Subset" of Subjects

The primary analysis will be performed on the FAS; the PP Set will be utilized as a sensitivity analysis. The PP Set will exclude subjects with IPDs.

4.4.4.7 Active-Control Studies Intended to Show Equivalence

This study does not include an active-control product and is not intended to demonstrate equivalence between any two drug products.

Additional subgroup analyses may be performed post-hoc, as appropriate.

4.4.5 Plasma Concentrations

Raw plasma concentration values will be summarized for the PK Set by treatment group and sampling time point using descriptive statistics, to include the geometric mean and CV (%). For summaries of plasma concentrations, below the limit of quantification (BLQ) values will be set to missing. The number and percentage of subjects with BLQ values will be summarized by time point and treatment group.

4.4.6 Pharmacokinetic Analysis

Pharmacokinetic analysis is based on the analysis of plasma concentrations of EP262 as described in Section 4.4.5.

4.5 Safety Evaluation

Safety analysis will be carried out for the Safety Analysis Set, to include all subjects who receive at least one dose of study drug. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis, as described in Section 4.1.2. For safety analysis presented by study visit, the baseline value will be defined as the last value reported prior to first dose of study drug.

4.5.1 Extent of Exposure

Extent of exposure to study treatment will be summarized for the Safety Analysis Set by treatment group and overall subjects combined. The duration of exposure will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study drug, plus one. Total dose received (mg) will be determined as the summation of all entries of "Dispensed Amount (Capsules)" reported on the "Drug Accountability – Dispensed" eCRF minus the summation of all entries of "Amount Returned (Capsules)" reported on the "Drug Accountability – Returned" eCRF. Any capsules reported as lost will be further subtracted from this total. Subjects that are missing their return records are assumed to have taken all dispensed capsules for the missing bottle. The number of capsules taken is then multiplied by 75 to obtain the total dose received (mg). Duration of exposure and total dose received (mg) will be summarized using descriptive statistics.

4.5.2 Measurements of Treatment Compliance

4.5.2.1 Study Treatment Compliance

Compliance to the study treatment regimen will be based on the drug accountability records. Compliance will be determined as the percentage of expected capsules that a subject should have taken based on their dosing days on study relative to the drug accountability reporting of their actual number of capsules taken. The following definitions are applied:

- Expected Number of Dosing Days: the last dose date reported on the End of Treatment eCRF minus the onsite first study administration that takes place at Visit 2 (Day 1) + 1.

- Expected Number of Capsules to be Taken: Expected Number of Dosing Days multiplied by two (standard dosing includes two capsules per day).

- Actual Number of Capsules Taken: The summation of all entries of "Dispensed Amount (Capsules)" reported on the "Drug Accountability – Dispensed" eCRF minus the summation of all entries of "Amount Returned (Capsules)" reported on the "Drug Accountability – Returned" eCRF. Any capsules reported as lost will be further subtracted from this total. Subjects that are missing their return records are assumed to have taken all dispensed capsules for the missing bottle.

Treatment compliance (%) is defined as the Actual Number of Capsules Taken divided by the Expected Number of Capsules to be Taken, multiplied by 100.

Dosing compliance will be summarized using descriptive statistics, by treatment group and overall subjects combined, for the Safety Analysis Set. The number and percentage of subjects who are < 80% compliant and ≥ 80% compliant within each treatment group and overall subjects combined will be summarized.

4.5.2.2 Emollient Use

Subject exposure to on-study background therapy emollient-use will be summarized by treatment group and overall subjects combined for the Safety Analysis Set. The number and percentage of subject's reporting use of a non-study permitted emollient at any time on study will be summarized based on self-reporting of emollient use by the daily diary. Summarization of concomitant emollient based on the medication reported will also be provided as described in Section 4.5.6.4.

4.5.3 Adverse Events

A TEAE is defined as those AEs with onset after the first dose of study drug or existing events that worsened after the first dose during the study. Treatment-emergent AEs will be summarized by treatment group and overall subjects combined. Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using MedDRA, version 26.0.

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and treatment-emergent SAEs and subject incidence of TEAEs meeting various criteria;
- Subject incidence of TEAEs by MedDRA system organ class and preferred term;
- Subject incidence of the most frequently-occurring TEAEs (i.e., TEAEs occurring in ≥ 10% of the Safety Analysis Set) by MedDRA preferred term;
- Subject incidence of TEAEs by CTCAE grade, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to study drug, MedDRA system organ class, and preferred term;
- Subject incidence of the most frequently-occurring TEAEs related to study drug (i.e., related TEAEs occurring in ≥ 10% of the Safety Analysis Set) by MedDRA preferred term;
- Subject incidence of CTCAE grade 3 or higher TEAEs related to study drug by MedDRA system organ class and preferred term; and
- Subject incidence of SAEs by MedDRA system organ class and preferred term.

At each level of summarization (e.g., any AE, system organ class, and preferred term), subjects experiencing more than one TEAE will be counted only once. In the summary of TEAEs by CTCAE grade, subjects will be counted once at the highest grade reported at each level of summarization; in the summary of TEAEs by relationship, subjects will be counted once at the closest relationship to study drug. Related events include those reported as "Related" to study treatment; events considered not related are those reported as "Not Related" to study treatment.

Adverse event data will be presented in data listings by subject, treatment group, and event. Serious AEs and AEs leading to discontinuation of the study drug will be presented in separate data listings.

4.5.4 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, including the post treatment follow-up period, will be listed by subject, to include any corresponding details associated with death. Serious AEs and other significant AEs, including those that led to discontinuation or interruption of the study drug, will be provided in separate subject data listings.

4.5.5 Clinical Laboratory Evaluation

All descriptive summaries of laboratory results will be based on data analyzed by the central laboratory and presented in conventional units. All data will be included in by-subject data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by subject, laboratory test, and unit. In addition, normal ranges provided by the central laboratory will be presented in a separate listing.

Clinical laboratory measurements, including serum chemistry, hematology, and coagulation will be summarized by treatment group and overall subjects combined. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the clinical study protocol.

Where applicable, laboratory results will be classified as "low," "normal," or "high" with respect to the parameter-specific reference ranges (i.e., below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Three-by-three contingency tables will be presented for each laboratory parameter to summarize the shift from the baseline category to the worst post-baseline measurement, defined as the value numerically farthest outside of the normal range across all post-baseline visits through the end of the study. Summary results will include the count and percentage of subjects within each shift category and treatment group and overall subjects combined.

The clinical study protocol includes guidance associated with the monitoring and interruption of study drug for suspected DILI. Subjects with the following post-baseline ALT or AST values will be assessed for the following DILI criteria:

- ALT or AST >8× ULN
- ALT or AST >5× ULN for more than 2 weeks: subjects must have confirmed elevated values by subsequent repeat testing that shows at least two weeks of elevated values.
- ALT or AST >3× ULN AND total bilirubin >2× ULN OR INR >1.5
- ALT or AST >3× ULN with the appearance of new onset fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Subjects qualifying in any of the above treatment-emergent DILI criteria will be presented in a data listing.

4.5.6 Vital Signs, Physical Findings, and Other Observations Related to Safety

4.5.6.1 Vital Signs

Vital sign parameter measurements will be summarized by treatment group and overall subjects combined. Descriptive statistics will be presented for results and change from baseline at each visit where parameters were scheduled to be collected.

Height, body weight and body mass index (BMI) will be summarized by treatment group and overall subjects combined. Body mass index will be calculated as weight (kg) / (height at screening [cm] / 100)^2. Height at screening, body weight, and BMI will be summarized using descriptive statistics for observed measurements and changes from baseline (body weight only) at each visit where parameters were scheduled to be collected.

4.5.6.2 12-Lead Electrocardiogram

Twelve-Lead ECG interval parameters will be summarized by treatment group and overall subjects combined. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected.

Twelve-lead ECG will be classified by the investigator as "normal," "abnormal, not clinically significant," or "abnormal, clinically significant." Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline value. Summary results will include the count and percentage of subjects within each shift category and treatment group and overall subjects combined.

Prolonged QTc (using corrected QT interval using Fridericia's formula [QTcF] and QTc interval using Bazett's formula [QTcB]) intervals will be summarized as QTc measurements (msec) that are >450, >480, and >500 at each visit where ECG is routinely collected per the clinical study protocol. Change from baseline categories will also be summarized for measurements that represent a change >30 or >60 relative to the baseline value. Summary results will include the percentage of subjects within each category and treatment group and for all subjects combined.

4.5.6.3 Physical Examination

Any clinically significant findings from the physical examination assessment will be reported on the Medical History form (prior to first dose) or Adverse Events form (post first dose). A separate subject listing of physical examination results will not be provided.

4.5.6.4 Prior and Concomitant Medications

Medications captured in the Prior AD Therapy and Prior and Concomitant Medications will be coded using the WHO Drug Global B3, version March 1, 2023. Medications entered on the eCRF will be mapped to ATC drug class (level 2) and preferred name.

The study phase of each medication will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication administered prior to the date of the first dose of study drug. A concomitant medication is defined as any medication administered on or after the date of the first dose of study drug. A medication may be defined as both prior and concomitant. If it cannot be determined whether a medication was received prior to the start of study drug dosing due to partial or missing medication start and/or end dates, it will be considered a prior medication. Likewise, if it cannot be determined whether a medication was received after the start of study drug dosing, it will be considered concomitant.

Prior AD therapy and concomitant medications will be summarized separately. Summarization of Prior AD Therapy is described in Section 4.4.2. The number and percentage of subjects receiving any medication will be summarized by treatment group and overall subjects combined, as will the number and percentage receiving any medication by ATC drug class and preferred name. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and preferred name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will preferred names within each ATC class. The study phase during which each medication was received (e.g., prior, concomitant, or both) will be presented on the listing of prior and concomitant medications. Prior AD Therapy will be included on a separate listing.

A summary of the number and percentage of subjects reporting any concomitant emollient use will also be provided; emollient use is considered any reporting of a concomitant medications within the ATC drug level 2 of "EMOLLIENTS AND PROTECTIVES." A corresponding listing of concomitant emollient use, to include the medication preferred name, will also be provided.

Subjects who require the use of a rescue medication for their atopic dermatitis within the double-blind treatment period will be presented in a separate listing.

4.5.6.5 Non-drug Therapies and Surgical Procedures

The use of any non-drug therapies or surgical procedures will be presented in a subject data listing. Subjects who require the use of a rescue procedure for their atopic dermatitis within the double-blind treatment period will also be presented in a separate listing.

4.6 Determination of Sample Size

No formal sample size calculation has been made. The sample size has been selected to provide adequate information on the safety, tolerability, PK, and PD of EP262 over 6 weeks.

4.7 Changes in the Conduct of the Study or Planned Analyses

Section 15.11 of the clinical study protocol defines the following planned interim analysis:

Given the hypothesis-generating nature of this study, an interim analysis may be conducted. The interim analysis would evaluate the effects of EP262 on select PD endpoints and safety.

The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the study files prior to conduct of the interim analysis. The SAP will be amended if emerging data from the completed interim analysis leads to substantial change in the study protocol that has significant impact on the statistical analyses.

No interim analysis will be conducted for the study.

Section 15.7 of the clinical study protocol defines the following planned PD analysis:

PD analyses will compare placebo and EP262 descriptively. No formal statistical testing will be performed. For select PD endpoints, the 90% confidence interval and/or nominal p-values will be presented.

When confidence intervals are presented for PD endpoints, the SAP includes a 95% confidence interval across all parameters.

5. REFERENCE LIST

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