Official Title: Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP262 in Subjects with Chronic Spontaneous Urticaria

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STATISTICAL ANALYSIS PLAN

Escient Pharmaceuticals, Inc., an Incyte company

EP-262-201

Protocol Title:	Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP262 in Subjects with Chronic Spontaneous Urticaria
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STATISTICAL ANALYSIS PLAN APPROVAL

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Emanate Biostats, Inc.

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ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AAS	Angioedema Activity Score
[redacted]	[redacted]
AE	Adverse event
[redacted]	[redacted]
AIC	Akaike's information criterion
ANCOVA	Analysis of Covariance
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AR(1)	First-Order Autoregressive
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the limit of quantification
BMI	Body mass index
CCL	Chemokine ligand
CI	Confidence interval
CRO	Contract Research Organization
CS	Compound symmetry
CSR	Clinical Study Report
CSU	Chronic spontaneous urticaria
CTCAE	Common Terminology Criteria for Adverse Events
CU-Q_2oL	Chronic Urticaria Quality of Life questionnaire
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full Analysis Set
FcεRI	high affinity IgE receptor
GM-CSF	Granulocyte macrophage colony-stimulating factor
H1AH	H1 antihistamine
HEENT	Head, eyes, ears, nose, throat
HRQoL	Health-related quality of life
HSS	Hive Severity Score
[redacted]	[redacted]
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation
IgE	Immunoglobulin E
IgG	Immunoglobulin G

Abbreviation	Definition
IL	Interleukin
INR	International normalized ratio
IPD	Important Protocol Deviation
ISS	Itch Severity Score
[redacted]	[redacted]
IWRS	Interactive Web Response System
LLOQ	Lower limit of quantification
LS	Least-square
LSMD	Least-square mean difference
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MMRM	Mixed-effects model for repeated measures
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Oral
PP	Per Protocol
Q1	1st quartile (25th percentile)
Q3	3rd quartile (75th percentile)
QTc	Corrected QT
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Fridericia's formula
RAE	Recurrent angioedema
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
TEAE	Treatment-emergent adverse event
TNF-α	Tumor necrosis factor-alpha
TPO	Thyroid peroxidase
UAS	Urticaria Activity Score
[redacted]	[redacted]
UCT	Urticaria Control Test
[redacted]	[redacted]
UGT1A1	uridine 5'-diphospho-glucuronosyltransferase 1A1
ULN	Upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide comprehensive and detailed descriptions of the statistical methods and presentation of data collected for Escient Pharmaceuticals, Inc., an Incyte company Protocol EP-262-201 (Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP262 in Subjects with Chronic Spontaneous Urticaria). 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 efficacy of EP262 compared to placebo in subjects with chronic spontaneous urticaria (CSU).

2.2 Secondary Study Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of EP262 compared to placebo in subjects with CSU
- To evaluate the efficacy of EP262 compared to placebo in subjects with CSU as assessed by the following:
    - Pruritus severity
    - Hive severity

2.3 Exploratory Objectives

[redacted]

[redacted]

3. INVESTIGATIONAL PLAN

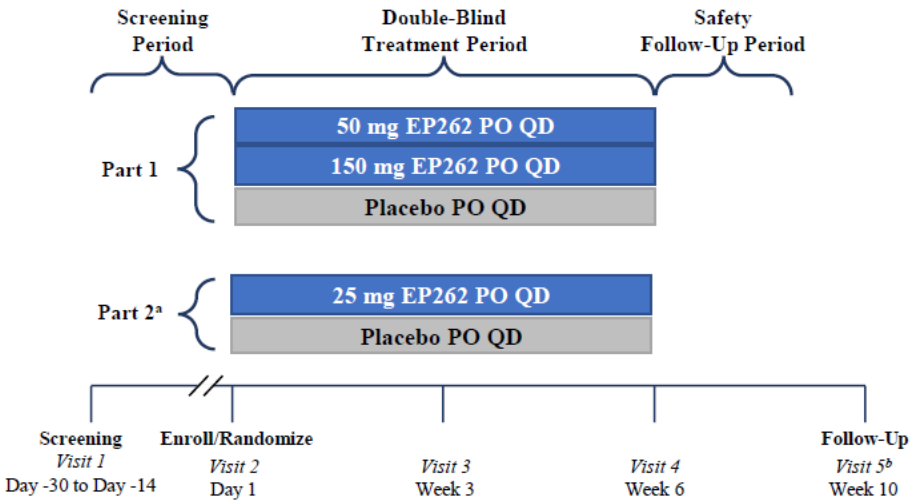
3.1 Overall Study Design

Study EP-262-201 is a Phase 2 randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of EP262 over 6 weeks in subjects with CSU. The study will be conducted in 2 parts: Part 1 will assess 50 mg and 150 mg doses of EP262 and Part 2 will assess a 25 mg dose of EP262 to further characterize the therapeutic dose range. [redacted]

Each part includes a Screening Period of at least 2 weeks and up to 30 days to assess subject eligibility that includes collection of the daily Urticaria Activity Score (UAS) score; a 6-week Double-Blind Treatment Period; and a 4-week Safety Follow-Up Period after administration of the last dose of study drug (EP262 or placebo) for a total study duration of up to approximately 14 weeks for each subject (Figure 1).

In Part 1, approximately 114 subjects will be randomized in a 1:1:1 ratio to receive a 150 mg dose of EP262, 50 mg dose of EP262, or placebo through oral (PO) administration, once daily (QD) during the 6-week Double-Blind Treatment Period. In Part 2 of the study, approximately 40 subjects will be randomized in a 3:1 ratio to receive either a 25 mg dose of EP262 or placebo PO, QD, during the 6-week Double-Blind Treatment Period. Enrollment of subjects with prior omalizumab use will be limited to 15 subjects in Part 1 and 5 subjects in Part 2. Approximately 154 subjects with CSU will be randomized into this study.

Figure 1 EP-262-201 Study Design



PO = oral; QD = once daily.

[a] Part 2 will begin after the last subject is randomized into Part 1.

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

3.1.1 Screening Period

The Screening Period will consist of 1 study visit (Visit 1). During this period, subjects will undergo assessments to determine study eligibility per inclusion and exclusion criteria and must remain on their prescreening background therapy. Visit 1 (Day -30 to Day -14 [inclusive]) may be conducted over more than 1 day but must be completed between Day -30 and Day -14 (inclusive).

3.1.2 Double-Blind Treatment Period

The Double-Blind Treatment Period will consist of 3 study visits (Visits 2, 3, and 4 [Day 1, Week 3, and Week 6]). During this period, all subjects who meet eligibility requirements will be enrolled into the study and will be randomized on Visit 2 (Day 1) to receive double-blind, QD, PO doses of EP262 or placebo for 6 weeks. In Part 1, subjects will be randomized in a 1:1:1 ratio to receive a 150 mg dose of EP262, 50 mg dose of EP262, or placebo PO, QD. In Part 2, subjects will be randomized in a 3:1 ratio to receive either a 25 mg dose of EP262 or placebo PO, QD. Randomization will be conducted centrally via an Interactive Web Response System (IWRS) and stratified based on prior use of omalizumab (yes/no). QD PO dosing of study drug should occur after at least a 4 hour fast and administered at approximately the same time of day. Subjects should refrain from eating for at least 2 hours postdose. The time and date of all dose administrations will be recorded in a daily diary. 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. Visit 2 (Day 1) will not have a visit window; all other visits in the Double-Blind Treatment Period will have a visit window of ±3 days. Subjects who discontinue from treatment early 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. Throughout the treatment period, subjects must remain on their prescreening background therapy, although rescue medication may be taken as needed.

3.1.3 Safety Follow-Up Period

Any subject who completes the Double-Blind Treatment Period or discontinues study drug (EP262 or placebo) early will have a Safety 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 Treatments

3.3.1 Treatments Administered

In Part 1, capsules containing 25 mg of EP262, 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.

[redacted]

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.

3.3.1.1 Background Therapy

All subjects must be on daily stable doses of H1 antihistamine (H1AH) that is consistent with standard of care for CSU starting at least 3 consecutive days immediately prior to the Screening Visit and willing to remain on stable doses through the Safety Follow-Up Visit.

3.3.1.2 Rescue Medications

In addition to their daily background therapy, for the duration of the study (Screening, Double-Blind Treatment, and Safety Follow-Up Period), if symptoms worsen, all subjects will be able to use a second generation H1AH that is different from background therapy as rescue medication as needed. The choice of H1AH and dosage will be determined by the Investigator; however, discussion with the subject prior to initiation of any rescue medication is encouraged. Once a rescue medication has been selected,

switching to a different rescue medication during the study is not permitted. Use of rescue medication must be documented.

3.3.1.3 Permitted Medications

Allowed second generation H1AH include bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and rupatadine. Additional H1AH not listed above may be permitted at the discretion of the Medical Monitor.

3.3.2 Method of Assigning Subjects to Treatment Groups

Beginning at Visit 2 (Day 1), subjects will be randomized in a 1:1:1 ratio to receive a 50 mg dose of EP262, 150 mg dose of EP262, or placebo PO, QD for Part 1 or a 3:1 ratio to receive either a 25 mg dose of EP262 or placebo for Part 2 for 6 weeks during the Double-Blind Treatment Period. Randomization will be conducted centrally via an IWRS and stratified based on prior use of omalizumab (yes/no). Separate randomization lists will be utilized for each part of the study.

The master randomization lists will be kept secured until the study blind is broken as specified in the study-specific blinding and unblinding plan.

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 (PK) samples or safety reporting to regulatory agencies. Procedures for emergency unblinding and unblinding for regulatory reporting are described in Section 9.3.2.1 and Section 9.3.2.2 of the clinical study protocol, respectively.

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.

3.4 Efficacy and Safety Variables

3.4.1 Efficacy Variables

3.4.1.1 Primary Efficacy Variable

The primary efficacy endpoint is change from baseline to Visit 4 (Week 6) in the sum of the daily UAS over a 7-day period (UAS7).

The UAS is a CSU-specific, 24-hour self-evaluation, patient-reported outcome measure (Zuberbier 2022). It is based on the assessment of key CSU symptoms: intensity of itch and number of wheals. The UAS scale for both itch (Itch Severity Score; ISS) and wheal assessment (Hive Severity Score; HSS) are recorded as a score from 0 to 3 (Total = 0 to 6), with 0 representing no itch/hives to 3 representing intense itch/hives (i.e., Itch – interferes with normal daily activity or sleep; Hives – More than 50 wheals). Daily UAS scores are summed over 7 consecutive days to derive the UAS7. The UAS7 scores range from 0 to 42, with higher scores indicating greater disease severity. Well-controlled urticaria (minimal disease activity) is defined as a UAS7 score ≤6. The minimally important difference (MID) for UAS7 is considered a reduction in baseline of ≥10 (Mathias 2012).

Subjects will be instructed to complete the UAS daily, in the morning before dosing (as applicable), and at approximately the same time of day, beginning at the Screening Visit to the Safety Follow-Up Visit. The questionnaire will be completed during the Screening Visit. For all other days that coincide with a study visit (for Visit 2 and beyond), the UAS is to be completed in the morning before the study visit.

The UAS scores from Day -7 through Day -1 will be summed to determine subject eligibility for continued participation regarding disease activity. An example of the UAS is included in Appendix C of the clinical study protocol.

For UAS, a weekly score will be computed as the sum of the daily UAS over the 7 days prior to or on the timepoint of interest. The UAS7 will be derived for the following analysis visits: Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, and Week 6 of the Double-Blind Treatment Period. Analysis visits will also be derived for Week 7, Week 8, Week 9 and Week 10 of the Safety Follow-Up Period. The following visit window considerations will be applied:

- The UAS scores from Day -6 through Day 1 will be summed to serve as the baseline UAS7 score.
- The 7 daily UAS scores prior to the nominal Visit 4 (Week 6) date (including the nominal Week 6 visit date UAS score) will be summed for the primary endpoint analyses. For the remaining visits within the Double-Blind Treatment Period, each preceding analysis visit will be the 7 prior days.
- Within the Safety Follow-Up period, analysis of Week 7 will be the first 7 days after the nominal Visit 4 (Week 6) date. Subsequent analysis visits will be counted using the next 7 days.

For subjects who early terminate during the Double-Blind Treatment Period, the subject's first day of dosing (i.e., study day 1) will be the anchor date for weekly analysis visit derivations. Week 1 will be study days 2 through 8 and subsequent weekly analysis visits will be the next 7 days, deriving all applicable analysis visits until study termination.

The following additional general considerations will be applied in deriving the weekly UAS scores:

- No UAS daily score is to be utilized in more than one analysis visit derivation.
- Data from at least 4 of the 7 days for each week are required to be considered an acceptable profile.
- If a subject has at least 4 completed daily scores on the UAS (both domains) over the 7 days prior to the timepoint of interest, the UAS7 will be defined as the average daily scores, multiplied by 7. The daily UAS is considered missing if either the ISS or HSS is missing. If a subject has fewer than 4 completed daily scores on the UAS over the 7 days prior to the timepoint of interest, then the UAS7 will be considered missing for that analysis timepoint.
- For weeks where less than 7 calendar days are available for a given week due to visit anchoring rules, at least 57% of the daily scores for the available calendar days must be reported, maintaining the same rate of reported scores as seen for a full week (i.e., 4 out of 7 days). If 6 calendar days are available for a given week, 4 non-missing daily scores are required. If 4 or 5 calendar days are available for a given week, 3 non-missing daily scores are required. If less than 4 calendar days are available for a given week, the weekly score will be considered missing.

3.4.1.2 Secondary Efficacy Variables

All efficacy assessments will be performed as indicated in the Schedule of Assessments (Appendix A) of the clinical study protocol. Secondary efficacy endpoints include the following:

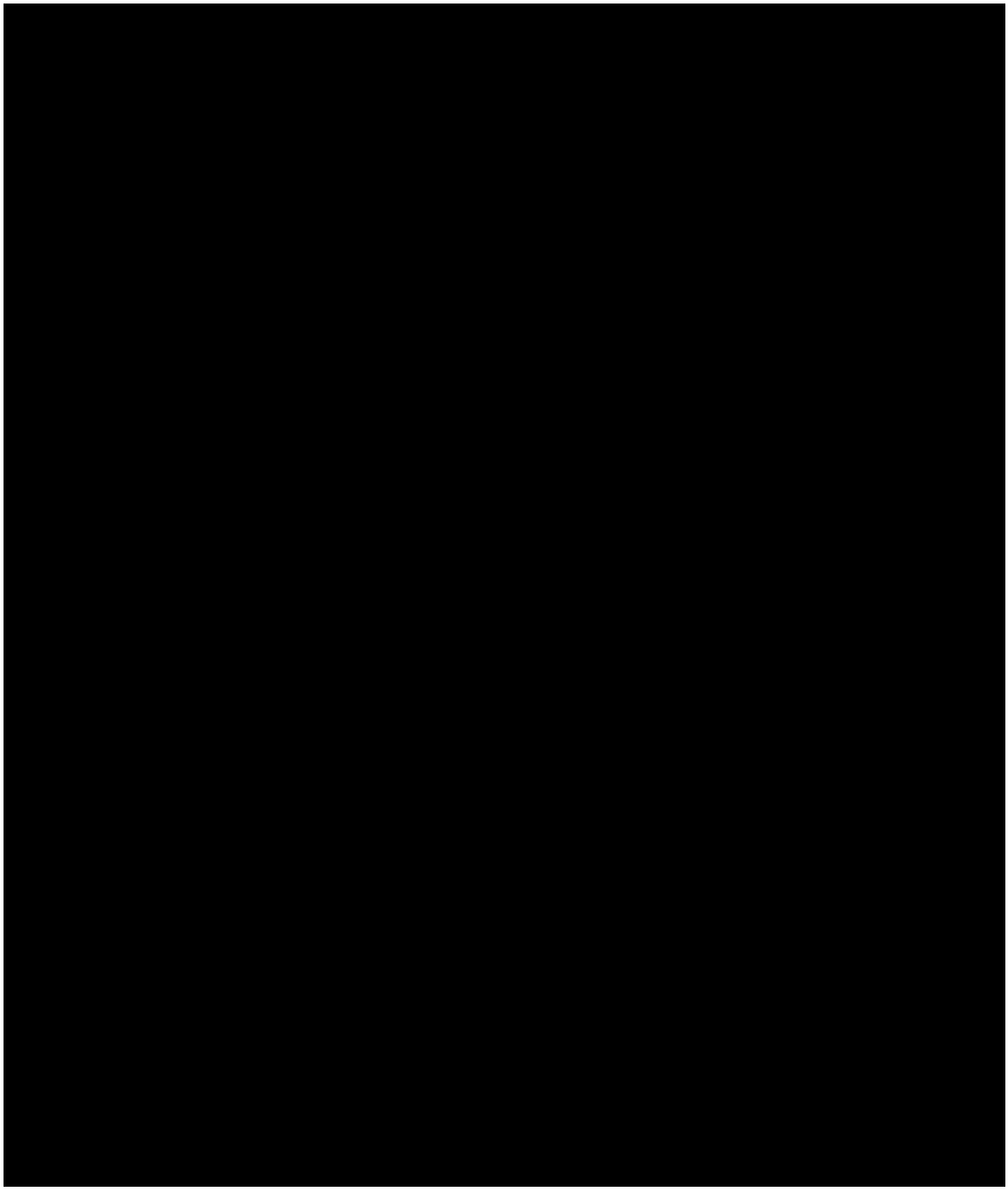
- Change from baseline to Visit 4 (Week 6) in the sum of the daily ISS over a 7-day period (ISS7)
- Change from baseline to Visit 4 (Week 6) in the sum of the daily HSS over a 7-day period (HSS7)

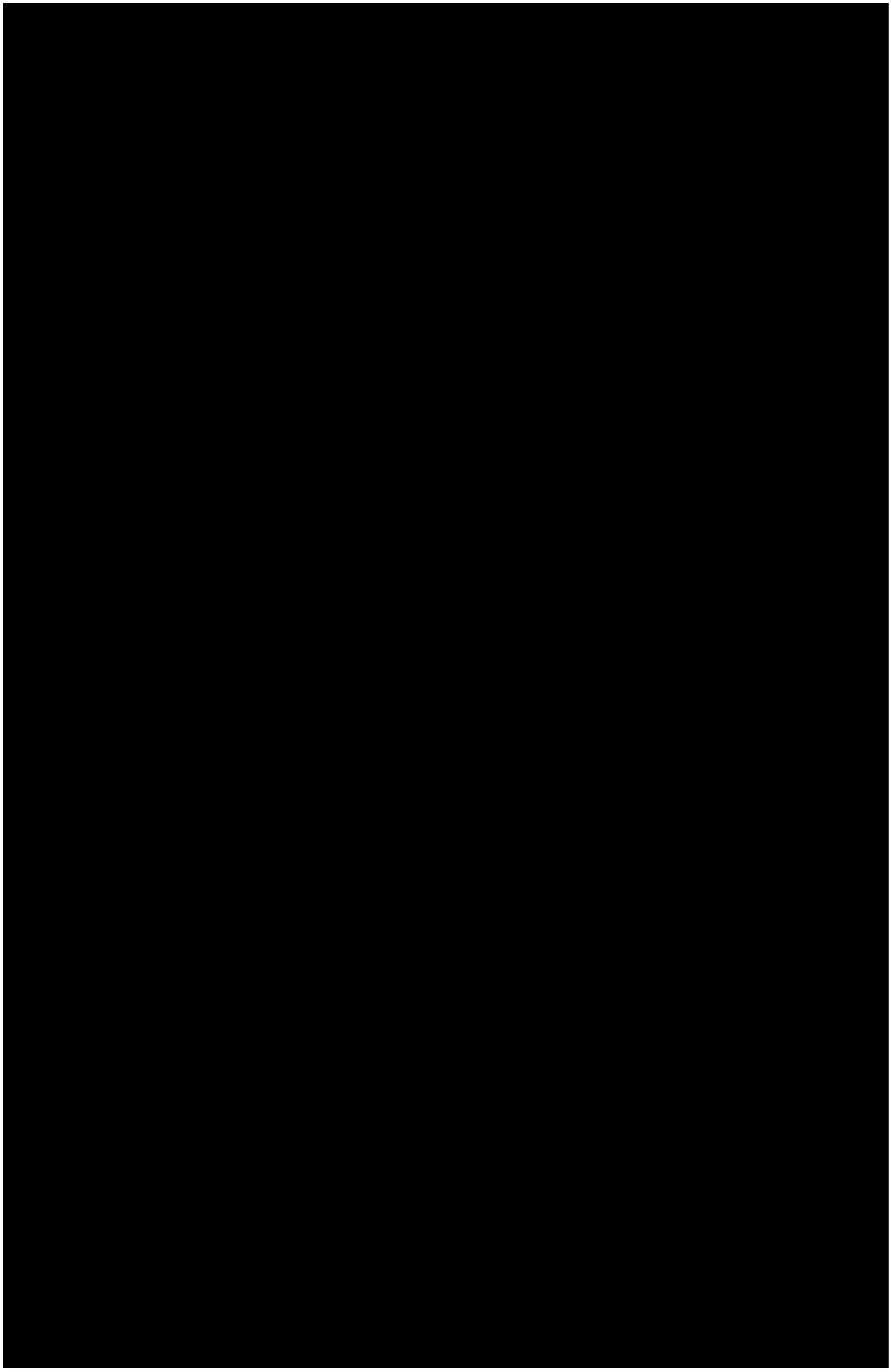
Description of the UAS is provided in Section 3.4.1.1. The ISS7 is the sum of the daily ISS over a seven-day period; similarly, the HSS7 is the sum of the daily HSS scores over a seven-day period. The ISS7 and HSS7 scores range from 0 to 21, where 0 is no itching/no wheals and 21 is the worst possible score. The MID for ISS7 and HSS7 is considered a reduction in baseline of ≥5 for each (Mathias 2012).

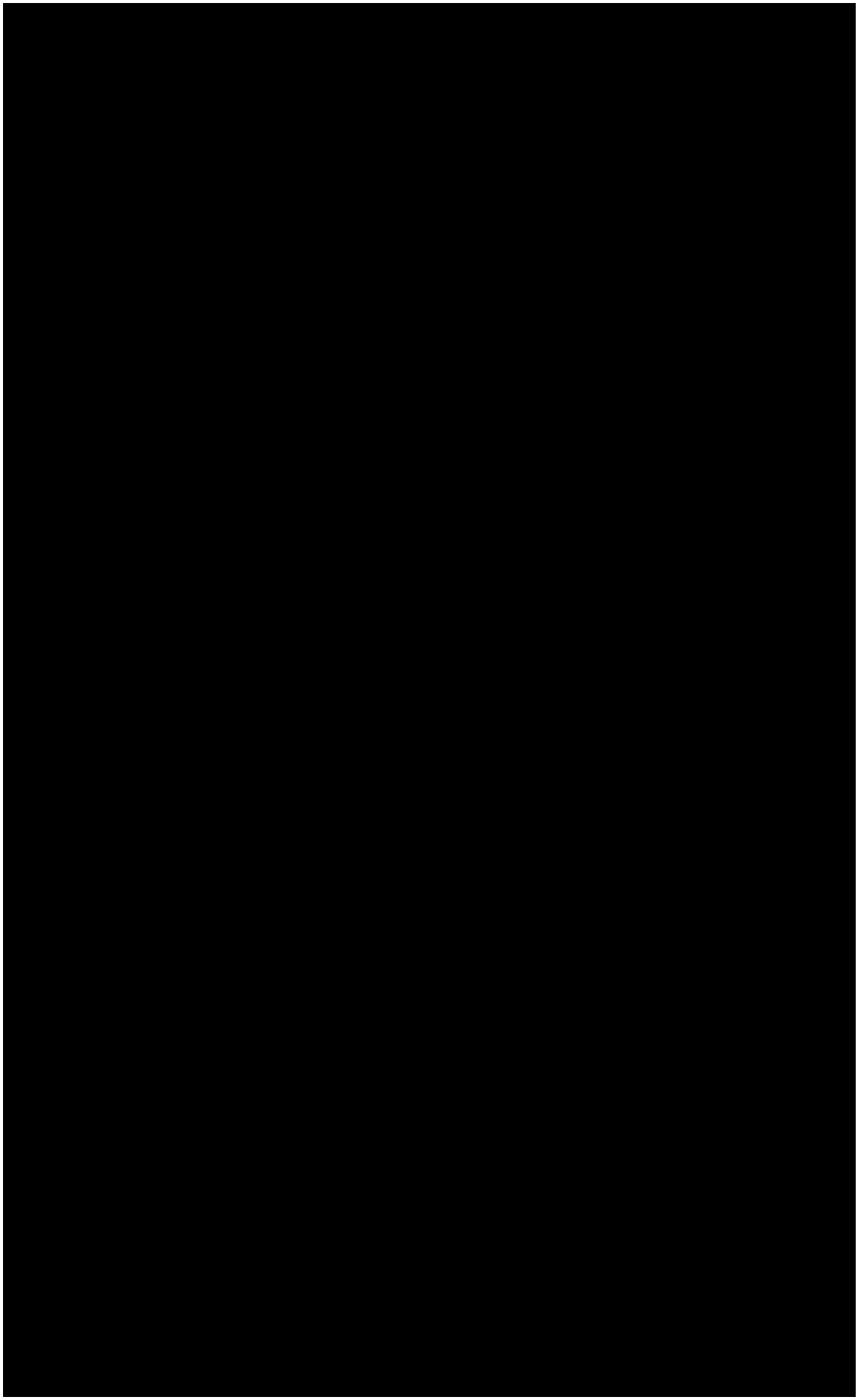
The same general windowing rules used to determine analysis visits for the UAS7 described in Section 3.4.1.1 will be applied to the ISS7 and HSS7 endpoints. The ISS7 can be derived if the minimum required number of ISS scores are reported within each

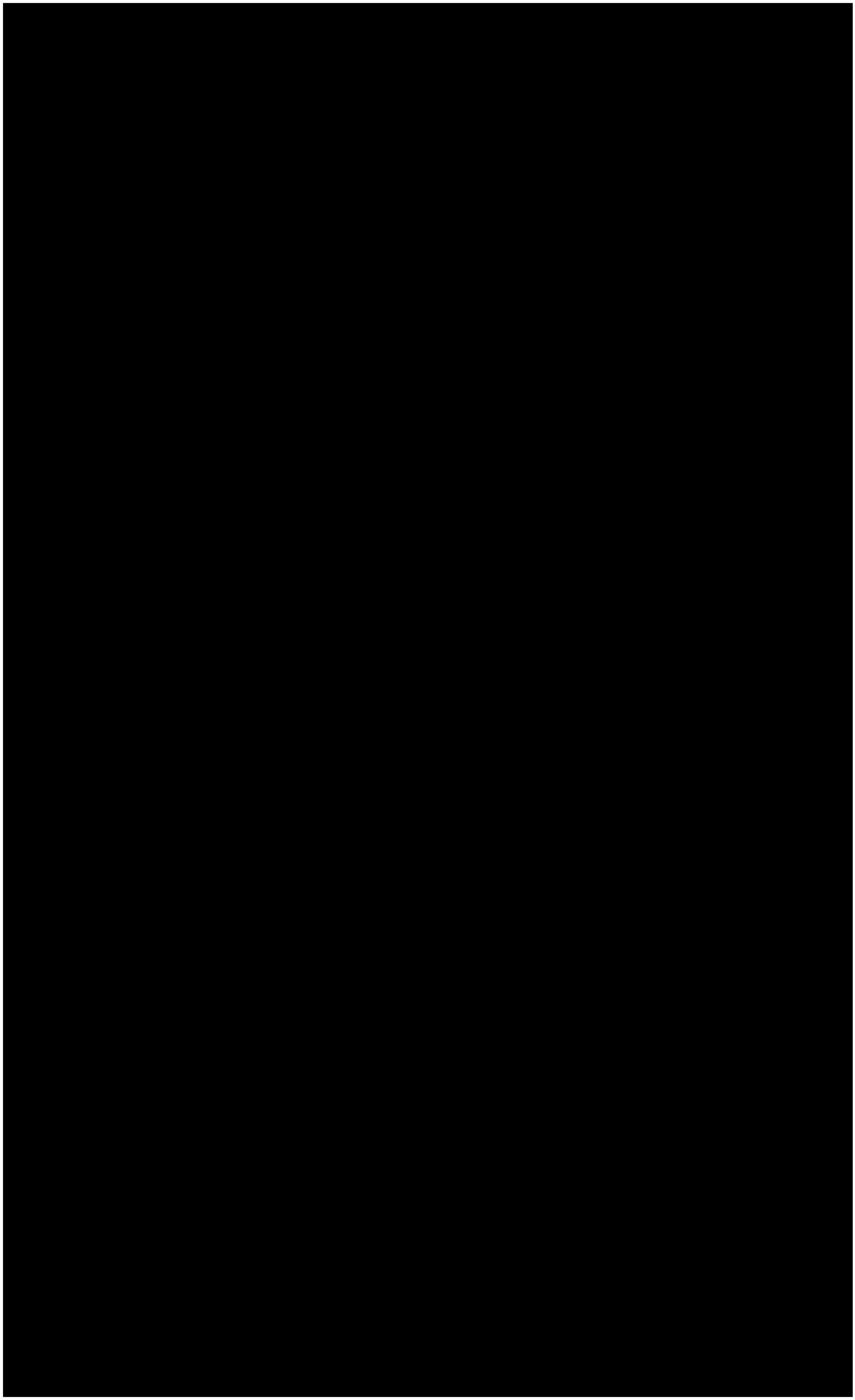
analysis visit. Similarly, the HSS7 can be derived in the minimum required number of HSS scores are reported within each analysis visit.

3.4.1.3 Exploratory Efficacy Variables









3.4.2 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.

3.4.2.1 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 AEs (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 adverse events (SAEs). 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 12.2.1 of the clinical study protocol.

Clinically significant 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 12.1.4.1 of the clinical study protocol. However, whenever possible, the underlying diagnosis should be listed in lieu of associated abnormal results. Abnormalities deemed not clinically significant by the Investigator should not be reported as AEs.

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, must be entered on the AE electronic case report form (eCRF).

Subjects will be assessed for potential drug-induced liver injury (DILI) during the study. Test results from local laboratories and the associated normal ranges are to be captured in the database. 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 or international normalized ratio (INR) values are described in section 12.10.3 of the clinical study protocol.

3.4.2.2 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, 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.

3.4.2.3 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.

3.4.2.4 Vital Signs

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

3.4.2.5 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.

3.4.2.6 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.

Symptom directed physical examinations to assess clinically significant changes from Screening or any new signs or symptoms may be conducted at other visits as determined by the Investigator based on subject complaint.

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

3.4.2.7 Standard 12-Lead Electrocardiograms

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

3.4.3 Pharmacokinetic Variables

Blood sampling will be collected predose (as applicable) at Visits 2, 3, 4, and 5 (Day 1, Week 3, Week 6, and Safety Follow-Up Visit) to analyze trough EP262 concentrations. The EP262 metabolite profile may also be analyzed from these trough samples.

3.4.4 Pharmacodynamic Variables

3.4.5 Baseline Characterization

4. STATISTICAL METHODS

4.1 General Methodology

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.

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 within each study part, as well as by pooled placebo across both study parts (if applicable). All tables, exclusive of efficacy, PD and PK analyses, will also include a column for all subjects combined as well as a treatment column for all EP262 doses pooled together across Part 1 and Part 2 (if available). 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 study part, site, 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, standard deviation (SD), standard error (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., confidence intervals [CIs]) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data.

Statistical significance testing will be two-sided and performed using α=0.10. P-values will be reported for all 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". Tests of interaction terms, if applicable, will be two-sided and performed using α=0.10.

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.

Subjects who discontinue from treatment early 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. The Early Treatment Termination visit will be summarized based on the nominal visit label in by-visit summaries.

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 efficacy and safety, but not PK measures) will participate in the Safety 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 who early terminate will be summarized in any nominal visits in which data is reported.

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.

Analysis of efficacy by-visit assessments that include assignment of analysis visit labels ([redacted]) will apply the visit windowing described in Section 3.4.1.1 and Section 3.4.1.3, respectively.

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.

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 efficacy and PD analyses will be based on the FAS.
- 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 Full Analysis Set 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 within each study part, pooled treatment groups, and over all subjects combined. Summaries will include the number and percentage of subjects in each analysis set, completing treatment, completing the study, and discontinuing the treatment or study

early by the primary reason for discontinuation. Subject disposition will also be summarized separately for each study site.

The number and percentage of screen failures based on the total number of subjects screened will be summarized. Additionally, the screen failure reason will be summarized based on the total number of screen failure subjects.

4.3.2 Protocol Deviations

Important Protocol Deviations (IPD) will be summarized by treatment group within each study part, pooled treatment groups, and over all subjects combined for the Full Analysis Set. 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. Important protocol deviations will be included in a listing.

4.4 Efficacy Evaluation

4.4.1 Datasets Analyzed

All efficacy summaries will be based on the Full Analysis Set. A data listing of subjects excluded from the Full Analysis 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 within each study part, pooled treatment group, and over all subjects combined for the Safety Analysis Set, Full Analysis Set, and PK Set (to include applicable EP262 treatment groups only).

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.

Baseline characteristics include medical history, height, weight, and body mass index (BMI), and disease characteristics. Body mass index will be calculated as: weight (kg) / [height (cm) / 100]^2. Height, weight, and BMI at baseline will be summarized using descriptive statistics.

Baseline disease characteristics include time since CSU diagnosis (as reported on the Disease History eCRF), history of angioedema, baseline [redacted] score, baseline [redacted] score and disease severity category, baseline [redacted] baseline total [redacted] (kU/L), prior use of omalizumab, prior CSU therapy, and best response to prior CSU therapy. Presence

of baseline angioedema will be determined by a subject's response to the medical history question "presence of angioedema."

Time since CSU 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 will be calculated using the available date information relative to informed consent. If only year is present, time is calculated relative to the informed consent year. If year and month are present, time is calculated relative to informed consent year and month. Time since CSU diagnosis will be summarized using descriptive statistics.

The remaining variables will be summarized by the number and percentage of subjects within each category. Best response to prior CSU therapy will be based on all reported individual prior CSU therapies to determine the overall best response reported, where a Complete Response would be the best possible response and No Response is the worst possible response. Unknown responses will take the lowest priority in the evaluation.

[redacted]

Baseline characteristics will be summarized by treatment group within each study part, pooled treatment groups, and over all subjects combined for the Safety Analysis Set, Full Analysis Set, and PK Set (to include applicable EP262 treatment groups only).

Prior CSU therapies will be coded using the World Health Organization (WHO) Drug Global B3, version March 1, 2023. Medications entered on the eCRF will be mapped to Anatomical Therapeutic Chemical (ATC) drug class (level 2) and preferred name. The number and percentage of subjects receiving any prior CSU therapy will be summarized by treatment group, 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.

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.

A summary of background therapy medications (as described in Section 3.3.1.1) will be provided. Background therapies include CSU therapies reported on the Prior CSU Therapy eCRF with an ongoing end date or an end date that continues through first dose of study drug). The number and percentage of subjects reporting a background H1AH will be determined as any medication reported in the ATC level 2 of "ANTIHISTAMINES FOR SYSTEMIC USE."

The number and percentage of subjects receiving any background therapy will be summarized by treatment group, as will the number and percentage receiving any H1AH background medication by preferred name. In addition, a summary of any "other" background therapy medications will also be provided and summarized by preferred name. The summary of "other" background therapy medications will include

any CSU therapies ongoing at the initiation of study treatment that are not captured in the ATC level 2 of "ANTIHISTAMINES FOR SYSTEMIC USE." A listing of qualifying background therapy medications will be provided.

4.4.3 Primary Efficacy Endpoint Analysis Methods

The core attributes of the estimand for the analysis of the primary endpoint are as follows:

- **Population:** The primary endpoint will be analyzed among all subjects in the Full Analysis Set. The population is further defined via the inclusion and exclusion criteria as part of the protocol. A key aspect of eligibility is that subjects must have moderate-to-severe disease activity in CSU at baseline, defined as a UAS7 of at least 16.

- **Treatment Conditions:** Participants are randomized in a 1:1:1 ratio to receive 50 mg of EP262, 150 mg of EP262, or placebo in Part 1 and randomized in a 3:1 ratio to receive 25 mg of EP262 or placebo in Part 2, to receive once daily drug administration during a 6-week Double-Blind Treatment Period. The primary analysis will compare each active EP262 group to Placebo at Week 6.

- **Endpoint:** The primary efficacy endpoint is the change from baseline in UAS7 at Visit 4 (Week 6).

- **Summary Measure:** The difference in model-adjusted means between each EP262 treatment group and Placebo in the change from baseline weekly UAS7 value.

- **Handling of Intercurrent Events (ICEs):** Potential ICEs that a subject may experience on study include:

    - Premature discontinuation from study drug as described in Section 8.6.1 of the clinical study protocol.

    - Use of prohibited and/or rescue medication as described in Section 8.2 (Subject Exclusion Criteria) of the clinical study protocol and Section 3.3.1.2 of the SAP, respectively.

  Subjects who experience an ICE prior to Week 6 will have data collection handled by the treatment policy strategy, consistent with the intent-to-treat principle.

Placebo subjects in Part 1 and Part 2 (if available) will be pooled for the treatment comparison analysis. The null hypothesis to be tested is that there is no difference in the mean change from baseline between EP262 (each dose level) and Placebo:

$$H_0: \mu_A = \mu_P;$$

Where μ_A and μ_P represent the mean change from baseline values for EP262 and Placebo, respectively. The alternate hypothesis to be tested is that the treatment group means differ:

$$H_1: \mu_A \neq \mu_P;$$

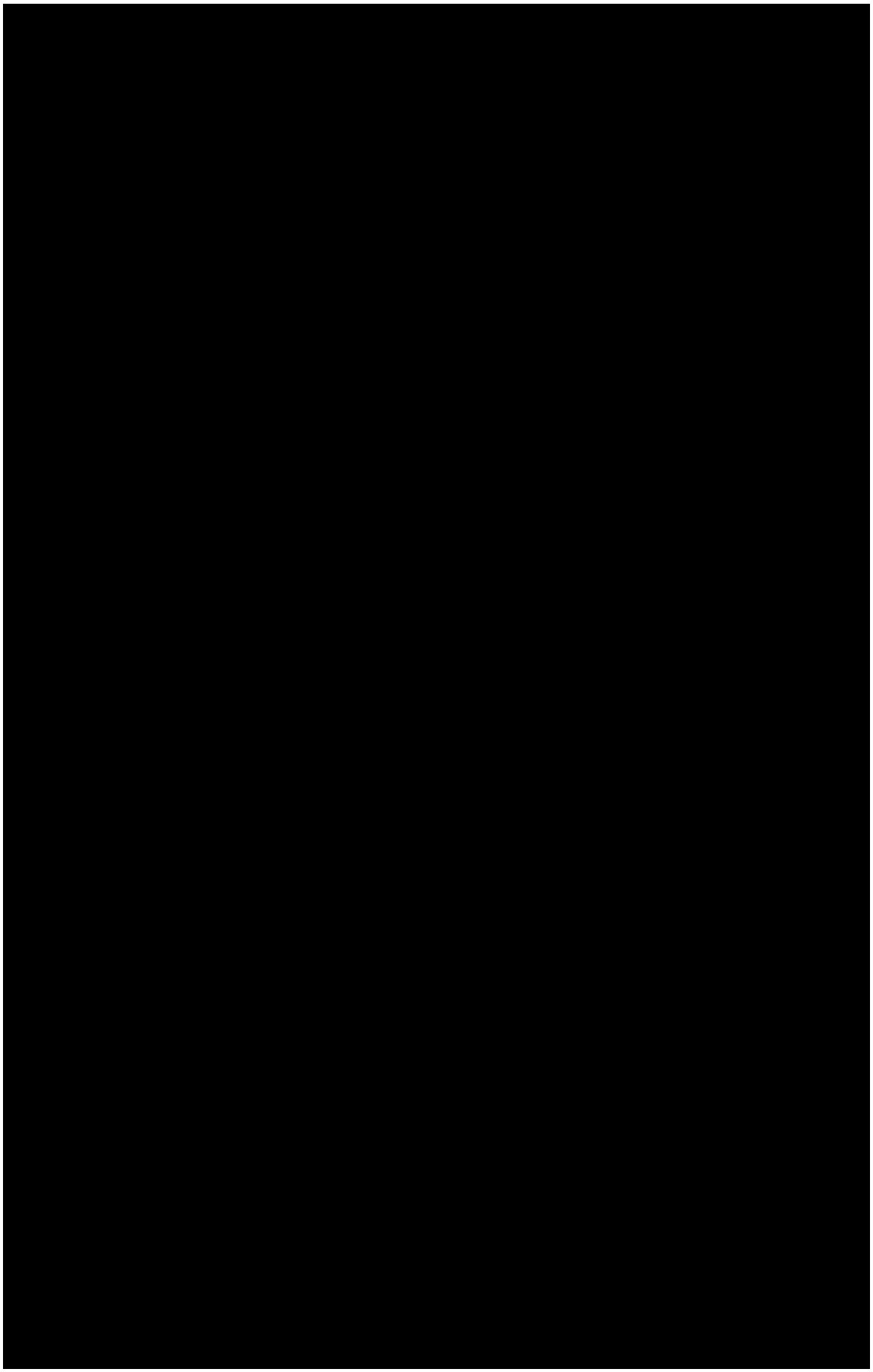
Treatment groups will be compared at Week 6 using a mixed-effects model for repeated measures (MMRM). The model will include fixed effects for treatment group, week (visit), treatment group by week interaction, the stratification factor of prior omalizumab use (randomization strata), and the UAS7 baseline value as a covariate. The model will include data at all post-baseline visits scheduled for collection in the Double-Blind Treatment Period and the comparison will be made using the treatment group by week interaction term for the Week 6 assessment. The unstructured covariance matrix will be used; in the event the computational algorithm fails to converge, the following structures will be executed: heterogeneous Toeplitz, Toeplitz, heterogeneous First-Order Autoregressive [AR(1)], AR(1), heterogeneous compound symmetry (CS), and CS. The covariance structure converging to the best fit, as determined by Akaike's information criterion (AIC), will be used. The Kenward and Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects. The model uses a likelihood-based estimation method that assumes data to be missing at random to account for subjects who discontinue the study prior to Week 6.

Statistical testing will be performed as a 2-sided test with a statistical significance level of 0.10 (alpha = 0.10). Estimates of least-square (LS) means, standard error, and 90% CIs will be presented by treatment group. In addition, the LS mean difference (LSMD) of each comparison between EP262 and placebo, the standard error of the difference, and 90% CI of the difference will be presented. Each pairwise comparison between EP262 and placebo will be conducted at a 10% level, with no adjustment for multiplicity.

4.4.4 Secondary Endpoint Analysis Methods

The secondary endpoints of change from baseline to Visit 4 (Week 6) in ISS7 and HSS7 will be summarized with descriptive statistics. Descriptive statistics will be presented for observed values and changes from baseline at each analysis visit where parameters are to be derived.

4.4.5 Exploratory Endpoint Analysis Methods



4.4.6 Statistical/Analytical Issues

4.4.6.1 Adjustments for Covariates

The MMRM to compare treatment groups for the primary endpoint will include a covariate adjustment for the baseline UAS7 value.

4.4.6.2 Handling of Dropouts or Missing Data

For assessment of responder endpoints, subjects with missing data at the time point of interest will not be analyzed; only observed values will be used.

Derivations of the weekly UAS7, ISS7, [redacted] scores will consider the minimum daily score requirement and management of missing scores as defined in Section 3.4.1.1.

The [redacted] data collection does not allow for individual questions to be skipped within a questionnaire response; therefore, the management of missing scores relative to the derivation of each total score and the dimension scores is not required.

For the primary endpoint, treatment groups will be compared for observed and change from baseline in weekly UAS7 score using a MMRM. The model will include fixed treatment group by week interaction, the stratification factor of prior omalizumab use (randomization strata), and the UAS7 baseline value as a covariate. The Kenward and Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects. All other endpoints are summarized descriptively and are based on observed data.

4.4.6.3 Interim Analyses and Final Analysis

The sponsor will perform an interim analysis after all subjects have completed Part 1. Part 1 subject data will be locked and Part 1 treatment assignments will be unblinded to the study team to allow for statistical analysis of the primary endpoint, specific to the Part 1 interim analysis and treatment groups. The whole result package (all SAP-defined analysis, specific to Part 1) will be delivered. Hypothesis testing will be based on the active arms in Part 1 versus the part 1 placebo group.

The final analysis will be conducted after all subjects have completed Part 1 and Part 2, if applicable. The two study parts will be pooled, and statistical analysis including hypothesis testing will be performed between each active arm versus the pooled placebo groups from Part 1 and Part 2 (if applicable) for the primary endpoint. The whole result package (all SAP-defined analysis incorporating both Part 1 and Part 2 subjects) will be delivered.

4.4.6.4 Multicenter Studies

This is a global, multicenter study with approximately 64 sites planned, dependent on the completion of both. Efficacy data collected from all study sites will be pooled for data analysis. The effect of study site on the efficacy analysis results may be explored post-hoc, as needed.

4.4.6.5 Multiple Comparisons/Multiplicity

No adjustment for multiplicity will be performed to control overall family-wise type I error due to the hypothesis generating nature of this study. Each pairwise comparison between EP262 and placebo will be conducted at a 10% level.

4.4.6.6 Use of an "Efficacy Subset" of Subjects

The primary efficacy analysis will be performed on the Full Analysis Set. No additional efficacy subsets or sensitivity groups will be applied to the primary endpoint.

4.4.6.7 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.

4.4.6.8 Examination of Subgroups

Given the small sample size, no formal subgroup analyses are planned for this study.

4.4.7 Plasma Concentrations

Raw plasma concentration values will be summarized for the PK Set by EP262 dose level and sampling time point using descriptive statistics, to include the geometric mean and CV (%). The geometric CV is calculated as $100*\text{sqrt}[\exp(\sigma^2)-1]$, where σ^2 is the variance of the log-transformed data. For summaries of plasma concentrations, values below the BLQ will be set to missing. The number and percentage of subjects with BLQ values will be summarized by time point and EP262 dose level.

4.4.8 Pharmacokinetic Analysis

Pharmacokinetic analysis will be based on analysis of the EP262 concentration data as outlined in Section 4.4.7.

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. 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 within each study part, pooled treatment groups, and over all subjects combined.

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. This value is considered to be the Action Number of Capsules Taken per subject. The Actual Number of Capsules Taken is then multiplied by the following within each group to obtain the total dose received (mg):

- Subjects assigned to the EP262 150 mg treatment group in Part 1 have their total amount of capsules multiplied by 75 mg (i.e., each capsule received contains 75 mg of study drug).

- Subjects assigned to the EP262 50 mg treatment group in Part 1 or the 25 mg treatment group in Part 2 have their total amount of capsules taken multiplied by 25 mg (i.e., each capsule received contains 25 mg of study drug).

Duration of exposure and total dose received (mg) will be summarized using descriptive statistics. 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. Duration of exposure and total dose received (mg) will be summarized using descriptive statistics.

4.5.2 Measurements of 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:

    - Part 1: two (standard dosing includes two capsules per day)

    - Part 2: one (standard dosing includes one capsule 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 within each study part, pooled treatment groups, and over all subjects combined for the Safety Analysis Set. The number and percentage of subjects who are < 80% compliant, ≥ 80% compliant to < 120% compliant and ≥ 120% compliant within each treatment group and overall subjects combined will be summarized.

4.5.3 Adverse Events

Treatment-emergent adverse events (TEAEs) are 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 within each study part, pooled treatment groups, and over all 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 serious adverse events (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 severity 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 severe 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 severity grade, subjects will be counted once at the highest severity 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 drug; events considered not related are those reported as "Not Related" to study drug.

Adverse event data will be presented in data listings by study part, subject, treatment group, and event. Serious AEs and AEs leading to interruption or 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 reported details associated with the death. Serious AEs and other significant AEs, including those that led to withdrawal 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. In the event any local laboratory testing is required, the corresponding data will be included in applicable analysis.

Clinical laboratory measurements, including serum chemistry, hematology and coagulation, will be summarized by treatment group within each study part, pooled treatment groups, and over all 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.

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
- 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 (including weight over time) will be summarized by treatment group within each study part, pooled treatment groups, and over all subjects combined. Descriptive statistics will be presented for results and change from baseline 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 within each study part, pooled treatment groups, and over all 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 groups presented.

Prolonged corrected QT (QTc) intervals including the corrected QT interval using Bazett's formula (QTcB) and the corrected QT interval using Fridericia's formula (QTcF) 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 groups presented.

4.5.6.3 Physical Examination

Any clinically significant abnormalities with onset prior to signing of the ICF will be recorded on the Medical History form and recorded on the Adverse Events form if onset is after signing of the ICF. A separate subject listing of physical examination results will not be provided.

4.5.6.4 Prior and Concomitant Medications

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.

Prior and concomitant medications 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.

For concomitant medications summaries, the number and percentage of subjects receiving any medication will be summarized treatment group within each study part, pooled treatment groups, and over all 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.

Subjects may use a second generation H1AH that is different from background therapy as rescue medication if symptoms worsen, as needed. Rescue medications will be reported on the Prior and Concomitant Medications eCRF. While rescue medications may be initiated during the Screening period of study participation (see Section 3.3.1.2), summary of rescue medications for analysis will include those medications initiated on or after the first dose of study drug that were reported with an indication labelling the medication as a "rescue" treatment. The number and percentage of subjects initiating a rescue medication at any time after study treatment initiation as well as those initiating

a rescue medication during the Double-Blind Treatment Period or Safety Follow-Up Period, specifically will be summarized by treatment group within each study part, pooled treatment groups, and over all subjects combined. Additionally, the number and percentage receiving a rescue medication by preferred name will be provided for each study period (Double-Blind Treatment Period versus Safety Follow-Up Period). Any subjects that require the use of a rescue medication will also be presented in a listing.

4.6 Determination of Sample Size

The study will enroll approximately 154 subjects.

In Part 1, approximately 114 subjects will be randomized in a 1:1:1 ratio to receive 50 mg of EP262, 150 mg of EP262, or placebo.

In Part 2, approximately 40 subjects will be randomized in a 3:1 ratio to receive 25 mg of EP262 or placebo.

Overall, approximately 30, 38, 38, and 48 subjects will be randomized to receive 25 mg EP262, 50 mg EP262, 150 mg EP262, and placebo, respectively, across both parts of the study.

For Part 1, a sample size of 34 subjects per treatment group will provide 80% power to detect an 8-point difference in the UAS7 change from baseline at Visit 4 (Week 6), assuming a standard deviation of 13 points, and a 2-sided alpha of 10%.

For Part 2, a sample size of 27 subjects receiving 25 mg of EP262 and 43 subjects receiving placebo pooled from both parts of the study will provide 80% power to detect an 8-point difference in the UAS7 change from baseline at Visit 4 (Week 6) between EP262 25 mg and placebo, with the same assumption of 13-point standard deviation and 2-sided alpha of 10%.

4.7 Changes in the Conduct of the Study or Planned Analyses

Section 16.8.3 of the clinical study protocol defines the following planned primary and sensitivity analysis to address missing data in the primary analysis:

The primary analysis of the primary endpoint of change from baseline in UAS7 will include all observed data (weekly UAS7 scores considered non-missing) with no data imputations, under the assumption of missing at random.

As a sensitivity analysis, the primary endpoint will also be analyzed with multiple imputation procedures. The SAP will provide full detail of the methodologies that will be used.

Section 16.1 of the clinical study protocol defines the Per Protocol Set as: 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 efficacy and/or PD measurements. Subjects will be analyzed according to randomized treatment assignment. The PP Set will be used for sensitivity analyses relating to efficacy and/or PD. The type of protocol deviations governing exclusion from the PP Set will be determined prior to database lock and will be detailed in the SAP.

Section 16.8 states the following additional analysis on efficacy and/or PD endpoints: For select endpoints, percent change from baseline will also be summarized.

The protocol-defined sensitivity and supplemental analyses will not be conducted for this study and percent change from baseline will not be summarized. In addition, a Per Protocol Set will not be determined.

Section 16.8.2 of the clinical study protocol defines the following planned additional efficacy analyses:

Efficacy endpoints that are defined as continuous variables will be analyzed using a similar model as described for the primary efficacy endpoint if they are collected at multiple post-baseline visits; otherwise, they will be analyzed using analysis of covariance (ANCOVA) adjusted for randomization strata and baseline measurements of the response parameter of interest. For continuous endpoints that do not meet the normal distribution assumption, they will be analyzed by stratified Hodgens-Lehmann estimates for the median, with the 90% confidence intervals derived using stratified Van-Elteren test. Other endpoints defined as response proportions will be analyzed using a Cochran-Mantel-Haenszel test stratified by randomization strata. Time-to-event data will be analyzed using a Cox regression model, stratified by randomization strata.

No hypothesis testing will be conducted for secondary and exploratory endpoints; only descriptive analysis results will be provided. Given the limited sample size and the nature of Phase 2 as a proof-of-concept (POC) study, hypothesis testing for secondary endpoints may not be considered appropriate and has been excluded from the SAP.

In addition, supplemental evaluation of normality assumptions and use of the stratified Hodgens-Lehmann and stratified Van-Elteren test (as needed) will not be utilized. Given the sample size of the study, the estimates are assumed to be valid based on Central Limit Theorem, even if select data are not normal.

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