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

NCT Number: NCT06077773

Document Date: EP-262-201 Protocol, Amendment 4.0 (26 July 2024)

1. TITLE PAGE

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

Study Acronym:	CALM-CSU
Protocol Number:	EP-262-201
EU CT Number:	2023-504799-94
IND Number:	161897
Protocol Version Number:	Amendment 4.0
Issue Date:	26 July 2024
Drug Development Phase:	Phase 2
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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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Sponsor Statement

This protocol was subject to critical review and has been approved by the following individuals:

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Signing Reason: I have reviewed this document
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Investigator's Agreement

I have read the protocol for EP-262-201 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL HISTORY

Document	Amendment Type	Date
Amendment 4.0	Global	26 July 2024
Amendment 3.1	Country-specific (Canada)	05 April 2024
Amendment 3.0	Global	05 April 2024
Amendment 2.1 (Obsoleted)	Country-specific (Canada)	11 March 2024
Amendment 2.0	Global	11 March 2024
Amendment 1.1	Country-specific (Canada)	23 January 2024
Amendment 1.0	Global	29 November 2023
Amendment 0.1	Country-specific (Canada)	31 August 2023
Original Protocol	Not applicable	09 May 2023

2. Synopsis

Name of Sponsor/Company: Escient Pharmaceuticals, Inc., an Incyte company (Escient)	
Name of Investigational Product: EP262 oral capsules	
Study Number: EP-262-201	**Phase of Development:** Phase 2
Title of Study: Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP262 in Subjects with Chronic Spontaneous Urticaria	
Study Center(s): Multi-center within North America and Europe	

Objectives	**Endpoints**
Primary Objective	
To evaluate the efficacy of EP262 compared to placebo in subjects with chronic spontaneous urticaria (CSU)	• Change from baseline to Visit 4 (Week 6) in the sum of the daily Urticaria Activity Score (UAS) over a 7-day period (UAS7)
Secondary Objectives	
To evaluate the safety and tolerability of EP262 compared to placebo in subjects with CSU	• Type, frequency, and severity of treatment-emergent adverse events (TEAEs) • Change from baseline in vital signs, electrocardiograms (ECGs), and clinical laboratory parameters
To evaluate the efficacy of EP262 compared to placebo in subjects with CSU as assessed by the following:	
• Pruritus severity	• Change from baseline to Visit 4 (Week 6) in the sum of the daily Itch Severity Score (ISS) over a 7-day period (ISS7)
• Hive severity	• Change from baseline to Visit 4 (Week 6) in the sum of the daily Hive Severity Score (HSS) over a 7-day period (HSS7)

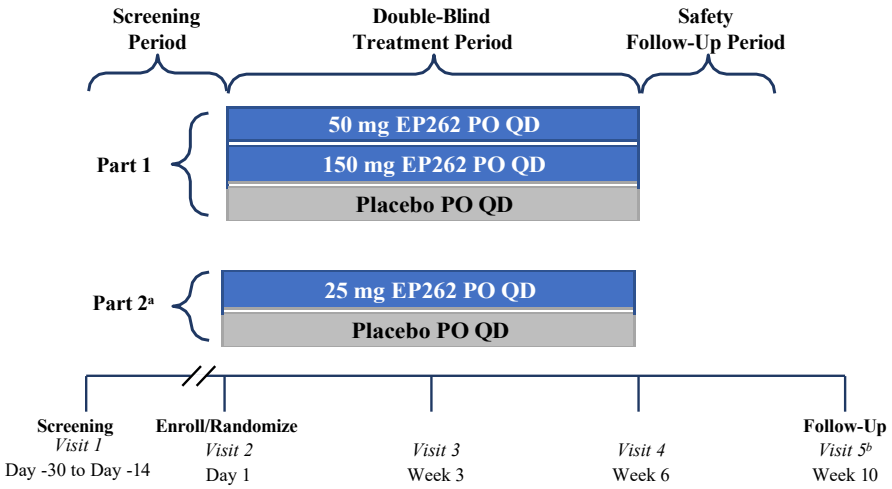
Exploratory Objectives
[redacted]

Methodology:

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. Part 2 will begin after the last subject is randomized into Part 1. Part 1 and Part 2 are identical in terms of their visit structure, procedures conducted, and the populations being studied. The primary difference between the 2 parts is the EP262 dose levels being assessed.

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 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. 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 orally (PO), 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.

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.

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).

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.

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.

Number of Subjects (Planned):

Approximately 154 subjects with CSU will be randomized into this study. Approximately 114 subjects will be randomized in Part 1 and approximately 40 subjects will be randomized in Part 2. **Enrollment of subjects with prior omalizumab use will be limited to 20 subjects (15 subjects in Part 1 and 5 subjects in Part 2).**

Main Criteria for Inclusion and Exclusion:

Subjects who have an exclusionary result during the Screening Period (between Visit 1 and Visit 2) may have that assessment repeated once at the discretion of the Investigator within the screening window and be enrolled if a repeat assessment is within the indicated range as specified below for participating in the study.

Inclusion Criteria

To be eligible for study participation, all subjects must meet all of the following inclusion criteria:

1. Male or female subject, aged 18 to 80 years, inclusive, at the time of consent
2. Diagnosis of CSU (presence of urticaria on most days of the week, for a duration of 6 weeks or longer, at any time before Screening) for ≥6 months
3. Must be on daily stable doses of H1 antihistamine (H1AH) 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
4. Current H1AH treatment up to 4 times the approved dose per local treatment guidelines
5. UAS7 ≥16 during the 7 days prior to randomization (Day 1) (data from at least 4 of the 7 days are required to be considered an acceptable profile)
6. If female, must have a negative serum pregnancy test at Screening, be willing to not donate eggs from Screening until 12 weeks after the last dose of study drug, and:
    a. Is surgically sterile; or
    b. Has been amenorrhoeic for ≥1 year without an alternative medical cause; or

c. If of childbearing potential[1], must agree to use 2 forms of contraception, which includes at least 1 form of highly effective and 1 effective method[2] of contraception from Screening until 12 weeks after the last dose of study drug. The following methods can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered highly effective birth control methods:
   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
   - Progestogen only hormonal contraception associated with inhibition of ovulation
   - Intrauterine device
   - Intrauterine hormone releasing system
   - Bilateral tubal occlusion
   - Vasectomized partner who has received a medical assessment of surgical success
   - Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study drug), the reliability of which needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject

7. If male and is not confirmed surgically sterile, must be willing to not donate sperm and must agree to use a barrier method of contraception (eg, condom with spermicide) during intercourse and at least 1 other acceptable contraceptive measure for his female partner(s) (eg, hormonal contraceptives, intrauterine device, female surgical sterilization, abstinence) from Screening through 12 weeks after the last dose of study drug
8. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study, and understand and provide written consent

Exclusion Criteria

All subjects meeting any of the following criteria will be excluded from this study:

1. Clearly defined underlying etiology for chronic urticarias other than CSU, including diseases with possible symptoms of urticaria or angioedema (eg, urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, mast cell activation syndrome, hereditary or acquired angioedema, lymphoma, leukemia, generalized cancer)
2. Chronic urticaria with clearly defined predominant or sole trigger (chronic inducible urticaria) including urticaria factitia (symptomatic dermographism), cold, heat, solar, pressure, delayed pressure, aquagenic, cholinergic, or contact urticaria
3. Other active skin diseases associated with chronic pruritus that might confound the study evaluations and results (eg, atopic dermatitis [AD], bullous pemphigoid, prurigo nodularis, dermatitis herpetiformis)
4. Use of the following prohibited treatments:
   a. Drugs that are agonists at the mas-related G protein-coupled receptor X2 (MRGPRX2), including icatibant, opioids (eg, codeine, morphine), vancomycin, clomipramine, or

[1] Women of childbearing potential are defined as those who are fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

[2] Effective methods of contraception include barrier methods of contraception (eg, male condom, female condom, cervical cap or diaphragm, and contraceptive sponge).

nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium) within 14 days before Screening

b. Monoclonal antibodies (eg, omalizumab, dupilumab, tezepelumab) within 4 months or 5 half-lives (whichever is longer) before Screening
c. Immunosuppressant drugs, including systemic corticosteroids, hydroxychloroquine, methotrexate, mycophenolate, cyclosporine, or cyclophosphamide within 30 days before Screening
d. Current or anticipated use of corticosteroids, or uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids
e. Drugs that inhibit uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1) [redacted]
f. [redacted]
g. [redacted]

5. Active malignancy or history of malignancy of any organ system (other than localized squamous cell or basal cell carcinoma of the skin that have been excised or resolved), treated or untreated, within the past 5 years from Screening
6. Evidence of clinically significant cardiac, neurologic, psychiatric, pulmonary, renal, hepatic, endocrine (including uncontrolled diabetes mellitus), metabolic, or gastrointestinal disease that, in the Investigator's opinion, would compromise the safety of the subject, interfere with the interpretation of the study results, or otherwise preclude subject participation
7. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect subject safety
8. Any clinically significant abnormalities on screening laboratory tests that, in the opinion of the Investigator, precludes participation in the study. The following abnormalities will specifically be considered exclusionary:
    a. Bilirubin >upper limit of normal (ULN) and/or any known condition that results in abnormal bilirubin elevations or fluctuations (eg, Gilbert's, Dubin-Johnson, Rotor syndrome)
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5× ULN
9. Other co-morbidities that would introduce additional risk factors or interfere with study procedures based on clinically significant physical examination, vital sign, standard 12-lead ECG, chemistry, hematology, urinalysis, or coagulation results at Screening as deemed by the Investigator
10. Positive result for human immunodeficiency virus (HIV) or presence of actively replicating viral hepatitis due to hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at Screening
11. Significant history of abuse of drugs, solvents, or alcohol within the past year
12. Participation in any clinical study with an investigational or approved drug/device within 30 days or 5 half-lives (whichever is longer) before Screening or is planning to participate in another clinical study while enrolled in this study
13. History of known or suspected hypersensitivity to any component of study drug
14. Female who is pregnant, nursing, or intends to become pregnant during the study
15. Had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study

16. Is directly affiliated with the study at the clinical site or is an immediate family member (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at the clinical site
17. Is employed by Incyte Corporation or its wholly owned subsidiary, Escient, (that is an employee, temporary contract worker, or designee responsible for the conduct of the study) or is an immediate family member of an employee of Incyte Corporation or Escient
18. Subject is, in the opinion of the Investigator, not suitable to participate in the study
19. Subject is performing mandatory military service, deprived of liberty and/or due to a judicial decision, cannot take part in clinical studies, or is in a residential care institution

Study Drug Materials and Management:

Study Drug

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.

In Part 2, capsules containing 25 mg of EP262 or placebo will be supplied in bottles in a manner to ensure the study blind. Each subject will take 1 capsule per dose.

Study Drug Packaging and Labeling

Study drug will be packaged into bottles labeled with a unique number and supplied to clinical sites in a blinded manner.

Study Drug Storage

The study drug capsules should be stored at controlled room temperature, 15°C to 25°C (59°F to 77°F), with excursions up to 30°C (86°F).

Study Drug Administration

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.

Study Drug Dispensing and Accountability

Subjects will record self-administration of study drug daily in a dosing diary that will be reviewed at each clinical site visit during the Double-Blind Treatment Period by site staff.

Subjects should be instructed to retain the study drug, including the study drug bottle, even if empty, and to return it and any remaining study drug to the clinical site at their next visit. The site staff should perform study drug accountability and, if applicable, follow-up with the subject to retrieve any remaining study drug that has not been returned.

Key Study Procedures and Efficacy, Safety, Pharmacokinetic, Pharmacodynamic, and Baseline Characterization Assessments:

At specific visits outlined in the Schedule of Assessments (Appendix A), subjects will undergo efficacy, safety, pharmacokinetic (PK), PD, and baseline characterization assessments.

Key Study Procedures

Fasting Requirements

Subjects should fast for at least 8 hours before study visits that require a blood sample for assessment of clinical chemistry. Water is acceptable in the morning of clinic visits to ensure the subject is hydrated for laboratory sample collection. Subjects should fast at least 4 hours before administration of each dose of study drug and refrain from eating for at least 2 hours postdose. Each dose of study drug is to be taken with approximately 240 mL (8 fluid ounces) of water on an empty stomach.

Discontinuation of Study Drug

For subjects who terminate treatment with study drug early, regardless of the reason, every effort will be made to complete the early treatment termination evaluations as soon as possible after the last dose of study drug, ideally within 2 days after the last dose of study drug.

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.

If a subject discontinues study drug and chooses not to complete all 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 Safety 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. If a subject fails to attend the Safety Follow-Up Visit and has not withdrawn consent, all reasonable efforts will be made to contact the subject to ensure that he/she is in satisfactory health. All contacts and contact attempts must be documented in the subject's medical record.

Rescue Medications

In addition to their daily background therapy, for the duration of the study (Screening, Double-Blind Treatment, and Safety Follow-Up Periods), 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.

Efficacy Assessments

The primary efficacy evaluation is based on the UAS, a patient-reported assessment of disease activity. Secondary efficacy evaluations include assessments of itching (ISS) and hives (HSS), both of which comprise the UAS. Exploratory efficacy evaluations include [redacted]. All efficacy assessments will be performed as indicated in the Schedule of Assessments (Appendix A).

Examples of the patient-reported assessments are provided in the appendices but are not to be distributed to subjects for completion. Subjects will be trained on completion of all patient-reported assessments using the study-issued electronic device or application (app).

Urticaria Activity Score 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 and wheal assessment 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 (ie, 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, with higher scores indicating greater disease severity. Well-controlled urticaria is defined as a UAS7 score ≤6. The [redacted]

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. 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 Visit 4 (Week 6) will be summed for primary endpoint analyses. Data from at least 4 of the 7 days for each week are required to be considered an acceptable profile. An example of the UAS7 is included in Appendix C.

[redacted]

[redacted]

Safety Assessments

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

Adverse Event Collection

AEs will be documented from the signing of the Informed Consent Form (ICF) until the end of study participation.

Pharmacokinetic Assessments

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.

Pharmacodynamic Assessments

[redacted]

Baseline Characterization
[redacted]

Statistical Methods:

The primary efficacy endpoint is the change from baseline in UAS7 at Visit 4 (Week 6), defined as the sum of the daily UAS over the 7 days prior to the timepoint of interest. 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 of the available daily scores, multiplied by 7. 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 timepoint.

Efficacy analyses will compare placebo and each EP262 dose separately. Subjects who receive placebo in Parts 1 and 2 will be pooled for analysis. Additional analysis comparing placebo and all EP262 doses combined may be performed as appropriate. Statistical testing will be performed as 2-sided test with statistical significance level of 0.10, with no adjustment for multiplicity.

The primary endpoint will be analyzed using a mixed effects model for repeated measures based on the data from each week up to Week 6. The model will include treatment, week, and treatment by week interaction as fixed effects. Additional model covariates will include baseline UAS7 score and randomization strata. The treatment effect will be the contrast between EP262 and placebo least-squares (LS) means.

The primary analysis of the primary endpoint of change from baseline in UAS7 will include all observed data (weekly UAS7 considered non-missing) with no data imputations, under the assumption of missing at random. Sensitivity analysis using an alternative model and/or data imputation method will be performed.

Additional statistical analysis details will be specified in the Statistical Analysis Plan (SAP).

Sample Size Considerations:

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 EP262, 150 mg 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%.

With an estimated early withdrawal rate of approximately 10%, the planned enrollment of 38 subjects per treatment group (50 mg EP262, 150 mg EP262, and placebo) in Part 1 and 40 subjects (30 subjects in 25 mg EP262 and 10 subjects in placebo) in Part 2 will ensure adequate sample size to complete the 6-week treatment period.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

1. TITLE PAGE 1
2. SYNOPSIS 5
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 17
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 22
5. INTRODUCTION 25
5.1. Role of the MRGPRX2 Receptor in the Pathogenesis of Chronic Spontaneous Urticaria 25
5.2. EP262 and Study Rationale 25
5.3. EP262 Dose Rationale 26
5.4. Summary of Benefits and Risks 28
5.4.1. Benefit Summary 28
5.4.2. Risk Summary 28
5.4.3. Mitigation Strategy 29
5.4.4. Overall Benefit:Risk Conclusion 29
6. TRIAL OBJECTIVES AND PURPOSE 29
7. INVESTIGATIONAL PLAN 31
7.1. Overall Study Design 31
7.1.1. Screening Period 32
7.1.2. Double-Blind Treatment Period 32
7.1.3. Safety Follow-Up Period 33
7.2. Start of Study 33
7.3. End of Study 33
7.4. Number of Subjects 33
7.5. Dose Adjustment Criteria 33
7.6. Criteria for Study Termination 34
8. SELECTION AND WITHDRAWAL OF SUBJECTS 34
8.1. Subject Inclusion Criteria 34
8.2. Subject Exclusion Criteria 35
8.3. Study Restrictions 37
8.4. Concomitant Medications 38

8.5. Auxiliary Medicinal Products 38
8.5.1. Background Therapy 38
8.5.2. Rescue Medications 38
8.5.3. Permitted Medications 38
8.6. Removal of Subjects from Therapy or Assessment 39
8.6.1. Discontinuation of Study Drug 39
8.6.2. Discontinuation from the Study 40
9. TREATMENT OF SUBJECTS 40
9.1. Treatment Assignment 40
9.2. Treatment Compliance 40
9.3. Randomization and Blinding 40
9.3.1. Randomization 40
9.3.2. Blinding 41
9.3.2.1. Emergency Unblinding 41
9.3.2.2. Unblinding for Regulatory Reporting 41
9.4. Study Visits 41
9.4.1. Screening Period 42
9.4.1.1. Visit 1 (Day -30 to Day -14 [inclusive]) 42
9.4.2. Double-Blind Treatment Period 43
9.4.2.1. Visit 2 (Day 1) – Enrollment and Randomization 43
9.4.2.2. Visit 3 (Week 3) 43
9.4.2.3. Visit 4 (Week 6) 44
9.4.3. Safety Follow-Up Period 44
9.4.3.1. Visit 5 (Week 10) 44
9.4.4. Early Treatment Termination Visit 45
10. STUDY DRUG MATERIALS AND MANAGEMENT 45
10.1. Study Drug 45
10.2. Study Drug Packaging and Labeling 45
10.3. Study Drug Storage 46
10.4. Study Drug Administration 46
10.4.1. Instructions for Missed Dose(s) 46
10.5. Study Drug Dispensing and Accountability 46
10.6. Study Drug Handling and Disposal 46

10.7. Product Quality Complaints 47
11. EFFICACY ASSESSMENTS 47
[redacted]
12. SAFETY ASSESSMENTS 49
12.1. Adverse Events 49
12.1.1. Definition of an Adverse Event 49
12.1.2. Determining Severity of Adverse Events 50
12.1.3. Determining Causality of Adverse Events 50
12.1.4. Recording Adverse Events 51
12.1.4.1. Special Instructions for Recording Adverse Events in the eCRF 51
12.2. Serious Adverse Events 52
12.2.1. Definition of a Serious Adverse Event 52
12.2.2. Reporting Serious Adverse Events 52
12.2.3. Pregnancy 53
12.3. Medical History 53
12.4. Vital Signs 53
12.5. Body Weight and Height 54
12.6. Physical Examinations 54
12.7. Standard 12-Lead Electrocardiograms 54
12.8. Laboratory Evaluations of Safety 54
12.9. Other Laboratory Evaluations 55
12.10. Subject Safety Guidelines 55
12.10.1. Potential Side Effects 55
12.10.2. Overdose 55
12.10.3. Management of Liver Test Abnormalities 55
13. PHARMACOKINETICS ASSESSMENTS 56
14. PHARMACODYNAMIC ASSESSMENTS 56
15. BASELINE CHARACTERIZATION 57
16. STATISTICS 57

16.1. Analysis Sets 57
16.2. Estimand 58
16.3. Endpoints 58
16.3.1. Primary Efficacy Endpoint 58
16.3.2. Secondary Efficacy Endpoints 58
16.3.3. Exploratory Endpoints 58
16.4. Sample Size Considerations 59
16.5. Subject Disposition 60
16.6. Demographics and Baseline Characteristics 60
16.7. Study Drug Usage and Compliance 60
16.8. Efficacy and Pharmacodynamic Analysis 60
16.8.1. Primary Efficacy Analysis 60
16.8.2. Additional Efficacy and Pharmacodynamic Analyses 61
16.8.3. Primary and Sensitivity Analyses to Address Missing Data in the Primary Analysis 61
16.9. Safety Analysis 61
16.10. Pharmacokinetic Analysis 61
16.11. Subgroup Analyses 62
16.12. Multiple Comparison/Multiplicity 62
16.13. Interim Analysis 62
17. QUALITY CONTROL AND DATA MANAGEMENT 62
17.1. Data Quality Assurance 62
17.2. Data Management 62
17.3. Monitoring 63
17.4. Confidentiality and Auditing 63
17.5. Case Report Forms 63
17.6. Source Documents 64
17.7. Records Retention 64
17.8. Informed Consent 64
17.9. Ethical Conduct of the Study 65
17.10. Institutional Review Board/Independent Ethics Committee 65
18. STUDY MANAGEMENT 65
18.1. Protocol Deviations 65

18.2. Publications 66
18.3. Change in Clinical Site Staff 66
19. LIST OF REFERENCES 67
APPENDIX A. SCHEDULE OF ASSESSMENTS 70
APPENDIX B. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS 74

APPENDIX H. SUMMARY OF CHANGES BY AMENDMENT 81

LIST OF FIGURES

Figure 1: EP-262-201 Study Design 32

LIST OF TABLES

Table 1: Abbreviations and Specialist Terms 22

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AAS	Angioedema Activity Score
[redacted]	[redacted]
AD	atopic dermatitis
AE	adverse event
[redacted]	[redacted]
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
app	application
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemistry
BCRP	breast cancer resistance protein
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRO	Contract Research Organization
CSU	chronic spontaneous urticaria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
CU	chronic urticaria
CU-Q_2oL	Chronic Urticaria Quality of Life questionnaire
ECG	electrocardiogram
eCRF	electronic case report form
EU	European Union
FAS	Full Analysis Set
FcεR1	high affinity IgE receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation

Abbreviation or Specialist Term	Explanation
GM-CSF	granulocyte macrophage colony-stimulating factor
H1AH	H1 antihistamine
HBV	hepatitis B virus
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, throat
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HSS	Hive Severity Score
[redacted]	[redacted]
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
INR	international normalized ratio
IRB	Institutional Review Board
ISS	Itch Severity Score
[redacted]	[redacted]
IWRS	Interactive Web Response System
LS	least-squares
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MRGPR	mas-related G protein-coupled receptor
NOAEL	no-observed-adverse-effect-level
OATP	organic anion transporting polypeptide
P-gp	P-glycoprotein
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PO	oral
PP	Per Protocol

Abbreviation or Specialist Term	Explanation
PQC	product quality complaint
QC	quality control
QD	once daily
RAE	recurrent angioedema
SAE	serious adverse event
SAER	Serious Adverse Event Report
SAP	Statistical Analysis Plan
SOP	standard operating procedure
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
Th2	type 2 T helper cells
T_{max}	time to reach maximum observed concentration
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
US	United States
WHO	World Health Organization

5. INTRODUCTION

5.1. Role of the MRGPRX2 Receptor in the Pathogenesis of Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CSU; also known as chronic idiopathic urticaria) is a condition characterized by the development of systemic itchy red hives (wheals) and/or deep tissue swelling (angioedema) for periods of at least 6 weeks (Zuberbier 2022) with no specific eliciting factor. The hives and angioedema associated with CSU are directly attributable to the degranulation of mast cells, which can be triggered by many different stimuli.

The mas-related G protein-coupled receptor (MRGPR) family is comprised of 8 human Class A rhodopsin-like G-protein coupled receptors (MRGPRX1-X4 and D-G) that can sense noxious stimuli and appear to have a role in innate immunity. MRGPRX2 is predominantly expressed in mast cells and has been shown to induce degranulation upon binding to a wide variety of agonists (Subramanian 2016, Corbiere 2021). MRGPRX2 has been shown to mediate immunoglobulin E (IgE)-independent activation of mast cells, including degranulation and regulation of inflammatory processes. Activation of MRGPRX2 triggers release of proinflammatory mediators and a multicellular signaling cascade that likely plays a key role in multiple human diseases involving clinically relevant mast cell activation, including CSU (Babina 2020, Thapaliya 2021).

There are several lines of evidence to support a role of MRGPRX2 and IgE-independent mast cell activation in the etiology of CSU. First, many patients with CSU remain inadequately controlled even when receiving antihistamine, with or without concomitant anti-IgE treatment. Second, serum from patients with CSU has been reported to degranulate mast cells lacking the high affinity IgE receptor (FcεR1) to a much larger extent than serum from healthy control subjects (Bossi 2011), whereas loss of MRGPRX2 reduces degranulation stimulated by CSU patient serum (Quan 2022). Third, patients with CSU have been reported to have elevated plasma/serum levels of substance P, an agonist of MRGPRX2 (Metz 2014, Zheng 2016), and a greater number of MRGPRX2 positive mast cells in skin biopsies (Fujisawa 2014). Finally, and in keeping with the aforementioned findings, patients with CSU have been reported to show enhanced skin reactivity to intradermally injected MRGPRX2 drug ligands (Shtessel 2021). Overall, these data provide strong support for the potential therapeutic benefit of MRGPRX2 antagonism in the treatment of CSU and warrant further investigation as a novel, IgE-independent, mast cell-specific treatment approach.

5.2. EP262 and Study Rationale

EP262 is a potent small-molecule antagonist of the human MRGPRX2 receptor under development as an orally (PO) administered therapy for CSU.

Preliminary results from Study EP-262-101, a first-in-human randomized, Phase 1 clinical study of single and multiple daily PO doses of EP262 or placebo in 64 healthy subjects, have provided information on the safety, tolerability, and pharmacokinetics (PK) of EP262. Study EP-262-101 also included an initial food effect evaluation. Thirty healthy subjects received a single 50, 150, 400, 800, or 1200 mg dose of EP262. Eighteen subjects received 50, 150, or 300 mg as a multiple dose regimen over 7 days.

All doses evaluated were well tolerated with no dose-limiting adverse events (AEs), early terminations due to AEs, severe AEs, or serious AEs (SAEs) reported. No adverse trends in safety laboratory measures, vital signs, or electrocardiogram (ECG) parameters have been observed. EP262 concentrations increased with increasing single doses in an approximately linear manner and modeling of single dose data predicted multiple dose concentrations. The time to reach the maximum EP262 observed concentration (T_{max}) was achieved on average at approximately 3.2 hours postdose with a half-life ($t_{1/2}$) of approximately 121 hours for the 150 mg dose, driven by an extended terminal elimination phase. EP262 concentrations were approximately 2-fold higher when administered with a high-fat meal than when administered in the fasted state. The absence of safety signals, in conjunction with favorable PK profiles, supports further investigation of EP262 in subjects with CSU in this clinical study.

Study EP-262-201 will evaluate the efficacy, safety, and tolerability of EP262 over 6 weeks of treatment in subjects with CSU. A 6-week treatment duration is deemed adequate based on the anticipated rapid onset of action of EP262 to directly block activation of MRGPRX2 and is consistent with the treatment duration at which efficacy has been demonstrated for other approved and investigational agents.

The primary efficacy measure will be the change from baseline to Week 6 in patient-reported disease activity, as assessed by the Urticaria Activity Score (UAS) over a 7-day period (UAS7), a widely used CSU-specific patient reported outcome measure. Secondary [redacted] efficacy measures for this study include the Itch Severity Score (ISS) over a 7-day period (ISS7) and the Hive Severity Score (HSS) over a 7-day period (HSS7), which are the components of the UAS7; [redacted] tudy EP-262-201 will also assess the safety and tolerability of EP262. Collectively, the results will guide further development of EP262, including the design of subsequent confirmatory studies.

The study will be randomized to ensure random allocation of subjects to treatment arms and to reduce bias. Because efficacy assessments have a high degree of subjectivity, the study will be double-blinded. In addition, a placebo-controlled design will be used to control for confounding factors, such as potential Investigator bias, and to ensure that the statistical procedures can be appropriately applied.

5.3. EP262 Dose Rationale

The 150 mg and 50 mg EP262 dose levels to be evaluated in Part 1 of Study EP-262-201 were selected based on a variety of factors to explore efficacy without adversely impacting safety, including results from nonclinical pharmacology studies, nonclinical toxicology studies, and preliminary results from Study EP-262-101, a Phase 1 first-in-human clinical study in healthy subjects.

In vivo results from a transgenic, human MRGPRX2 knock-in mouse model of acute mast cell degranulation demonstrated complete inhibition of vascular permeability by all MRGPRX2 agonists tested at EP262 plasma concentrations of approximately [redacted] nM. This was further supported by results from nonclinical studies in a chronic disease mouse model of atopic dermatitis (AD) induced by cutaneous co-exposure to house dust mite extracts and

Staphylococcus aureus Enterotoxin Type B. In the transgenic MRGPRX2 mouse model of AD, treatment produced reductions in disease score, transepidermal water loss, and levels of type 2 T helper cells (Th2) cytokines. Based on several studies in this model evaluating different doses, trough EP262 concentrations of at least [redacted] nM were required to yield full attenuation of disease and inflammatory activity. Lower trough concentrations of EP262 did not result in robust disease improvement. Given that MRGPRX2 is activated by numerous agonists and that it is not known which agonist(s) may be the key factors involved in the pathophysiology of chronic urticaria, it is important to select a dose that completely inhibits the multiple agonists tested. Thus, it was assumed that EP262 trough concentrations of [redacted] nM or higher will likely be necessary for maximum clinical efficacy.

Consequently, Part 1 of Study EP-262-201 was designed to assess 2 dose levels:

- A dose level of 150 mg, which maximizes the likelihood of observing an impact on pharmacodynamics (PD)/efficacy while falling within exposures that are anticipated to be safe and well tolerated. During the course of the 6-week treatment period, the 150 mg dose is predicted to result in the following:
  - EP262 trough concentrations that exceed the full pharmacologic activity threshold ([redacted] nM) while remaining within the range of concentrations achieved in the multiple-dose portion of Study EP-262-101
  - EP262 concentrations that are well tolerated with no undue safety signals based on Study EP-262-101 results at doses [redacted] mg
  - EP262 exposure that remains below the exposures associated with the no-observed-adverse-effect-level (NOAEL) in definitive 42-day toxicology studies
- A lower dose level of 50 mg that will target EP262 trough concentrations between [redacted] and [redacted] nM, which may result in partial pharmacologic activity and will enable dose and exposure response analyses to help better characterize the therapeutic dose range

[redacted]

The PK profile of EP262 in subjects with CSU is anticipated to be similar to that in healthy subjects. To further ensure similar circulating concentrations of EP262 between these two populations, subjects with conditions that may alter PK, such as clinically significant hepatic or renal impairment, are excluded from participating in this study. [redacted]

5.4. Summary of Benefits and Risks

5.4.1. Benefit Summary

While it is currently uncertain whether patients with CSU will benefit from treatment in this study, nonclinical in vitro and in vivo data, as well as scientific publications implicating MRGPRX2 as a mediator of mast cell degranulation and associated inflammation (Kapp 1991, Morita 1995, Nakamura 2013, Azimi 2017, Nattkemper 2018, Green 2019, Meixiong 2019, Serhan 2019, Ogasawara 2020, Wang 2020, Youngblood 2020, Corbiere 2021), provide compelling support that EP262 has the potential to be an effective treatment for patients with CSU.

5.4.2. Risk Summary

The doses evaluated in study EP-262-101 were well tolerated with no dose limiting AEs, early terminations due to AEs, severe AEs, or SAEs reported. Additionally, no adverse trends in safety laboratory measures, vital signs, or ECGs were observed.

5.4.3. Mitigation Strategy

For this initial clinical proof-of-concept study, subjects with clinically significant co-morbidities such as hepatic, renal, or cardiovascular disease will be excluded.

[redacted]

Routine safety measures have been incorporated into the protocol, including AE reviews, vital sign and 12-lead ECG assessments, and laboratory evaluations, including monitoring of bilirubin and management of liver test abnormalities (Section 12.10.3).

[redacted]

5.4.4. Overall Benefit:Risk Conclusion

Overall, the clinical and nonclinical experience to date with EP262 suggests minimal risk to subjects participating in Study EP-262-201. Importantly, there is a clear unmet need for novel treatment options for CSU. Current clinical guidelines recommend second-generation H1 antihistamines (H1AH) as first-line treatment, with the option to increase dosing (Bernstein 2014, Zuberbier 2022), and omalizumab, an anti-IgE monoclonal antibody, or cyclosporine as second-line options for patients who do not adequately respond to antihistamines alone. Nonetheless, nearly 60% of patients continue to experience hives despite treatment with antihistamines, and almost 30% of omalizumab-treated patients report uncontrolled disease, particularly those with moderate-to-severe disease or low serum levels of IgE at baseline (Folci 2018, Maurer 2019, Maurer 2020, Fok 2021). If determined to be effective, EP262 may ultimately have the potential to offer a much-needed novel treatment option for patients suffering from CSU.

6. TRIAL OBJECTIVES AND PURPOSE

Objectives	Endpoints
Primary Objective	
To evaluate the efficacy of EP262 compared to placebo in subjects with chronic spontaneous urticaria (CSU)	• Change from baseline to Visit 4 (Week 6) in the sum of the daily UAS over a 7-day period (UAS7)

Secondary Objectives	
To evaluate the safety and tolerability of EP262 compared to placebo in subjects with CSU	• Type, frequency, and severity of treatment-emergent AEs (TEAEs) • Change from baseline in vital signs, ECGs, and clinical laboratory parameters
To evaluate the efficacy of EP262 compared to placebo in subjects with CSU as assessed by the following: • Pruritus severity • Hive severity	• 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)
Exploratory Objectives	
[redacted]	

7. INVESTIGATIONAL PLAN

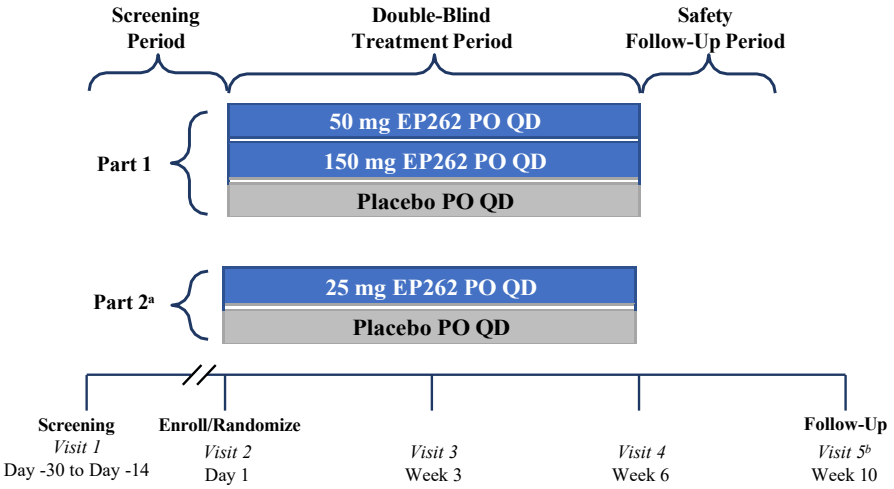
7.1. Overall Study Design

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. Part 2 will begin after the last subject is randomized into Part 1. Part 1 and Part 2 are identical in terms of their visit structure, procedures conducted, and the populations being studied. The primary difference between the 2 parts is the EP262 dose levels being assessed. Designated Sponsor (or designee) personnel will have access to unblinded individual subject treatment assignments as described in Section 9.3.2.

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 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 PO, 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.

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.

7.1.1. 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).

7.1.2. 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.

7.1.3. 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.

7.2. Start of Study

A subject is considered to have started the study when the subject signs his/her first informed consent to participate in the clinical study.

The start of the study is the date of when the first subject signs his/her first informed consent to participate in the clinical study.

7.3. End of Study

A subject is considered to have completed the study if he/she has completed all phases of the study, including the last study visit (ie, the Safety Follow-Up Visit [Visit 5]).

The end of the study is defined as the date of the last study visit of the last subject in the study globally. The end of study may result from the completion of the study according to the protocol or due to early termination by the Sponsor or at the request of a regulatory agency, Institutional Review Board (IRB), or Independent Ethics Committee (IEC) (Section 7.6).

7.4. Number of Subjects

Approximately 154 subjects with CSU will be randomized into this study. Approximately 114 subjects will be randomized in Part 1 and approximately 40 subjects will be randomized in Part 2. **Enrollment of subjects with prior omalizumab use will be limited to 20 subjects (15 subjects in Part 1 and 5 subjects in Part 2).**

7.5. Dose Adjustment Criteria

The dosage for study drug should be maintained constant during the study. However, dosing of study drug may be interrupted or discontinued due to safety findings. Refer to Section 8.6 for guidance on mandatory discontinuation of study drug due to safety findings.

7.6. Criteria for Study Termination

The Sponsor reserves the right to terminate the study at a clinical site at any time for any reason at the sole discretion of the Sponsor. Potential reasons for closure of a clinical site include but are not limited to:

- Good Clinical Practice (GCP) noncompliance
- Poor study data quality

The entire study will be terminated by the Sponsor should new information become available resulting in a clearly negative benefit/risk balance. The entire study may also be terminated by the Sponsor for other reasons or at the request of a regulatory agency, IRB, or IEC. If instructed by the Sponsor or designee, the Investigator must implement the termination of the study in a timeframe to ensure subject safety and well-being. Refer to Section 8.6.2 (Discontinuation from the Study) for instructions for subjects whose participation from the study is discontinued.

The Investigator and/or Sponsor (or designee) must notify the IRB/IEC of discontinuation of a site or the study and the reason for doing so.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects who have an exclusionary result during the Screening Period (between Visit 1 and Visit 2) may have that assessment repeated once at the discretion of the Investigator within the screening window and be enrolled if a repeat assessment is within the indicated range as specified below for participating in the study.

8.1. Subject Inclusion Criteria

To be eligible for study participation, all subjects must meet all of the following inclusion criteria:

1. Male or female subject, aged 18 to 80 years, inclusive, at the time of consent
2. Diagnosis of CSU (presence of urticaria on most days of the week, for a duration of 6 weeks or longer, at any time before Screening) for ≥6 months
3. Must be on daily stable doses of H1AH 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
4. Current H1AH treatment up to 4 times the approved dose per local treatment guidelines
5. UAS7 ≥16 during the 7 days prior to randomization (Day 1) (data from at least 4 of the 7 days are required to be considered an acceptable profile)
6. If female, must have a negative serum pregnancy test at Screening, be willing to not donate eggs from Screening until 12 weeks after the last dose of study drug, and:
    a. Is surgically sterile; or
    b. Has been amenorrhoeic for ≥1 year without an alternative medical cause; or

c. If of childbearing potential[3], must agree to use 2 forms of contraception, which includes at least 1 form of highly effective and 1 effective method[4] of contraception from Screening until 12 weeks after the last dose of study drug. The following methods can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered highly effective birth control methods:
   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
   - Progestogen only hormonal contraception associated with inhibition of ovulation
   - Intrauterine device
   - Intrauterine hormone releasing system
   - Bilateral tubal occlusion
   - Vasectomized partner who has received a medical assessment of surgical success
   - Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study drug), the reliability of which needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject

7. If male and is not confirmed surgically sterile, must be willing to not donate sperm and must agree to use a barrier method of contraception (eg, condom with spermicide) during intercourse and at least 1 other acceptable contraceptive measure for his female partner(s) (eg, hormonal contraceptives, intrauterine device, female surgical sterilization, abstinence) from Screening through 12 weeks after the last dose of study drug
8. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study, and understand and provide written consent

8.2. Subject Exclusion Criteria

All subjects meeting any of the following criteria will be excluded from this study:

1. Clearly defined underlying etiology for chronic urticarias other than CSU, including diseases with possible symptoms of urticaria or angioedema (eg, urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, mast cell activation syndrome, hereditary or acquired angioedema, lymphoma, leukemia, generalized cancer)
2. Chronic urticaria with clearly defined predominant or sole trigger (chronic inducible urticaria) including urticaria factitia (symptomatic dermographism), cold, heat, solar, pressure, delayed pressure, aquagenic, cholinergic, or contact urticaria

[3] Women of childbearing potential are defined as those who are fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
[4] Effective methods of contraception include barrier methods of contraception (eg, male condom, female condom, cervical cap or diaphragm, and contraceptive sponge).

3. Other active skin diseases associated with chronic pruritus that might confound the study evaluations and results (eg, AD, bullous pemphigoid, prurigo nodularis, dermatitis herpetiformis)
4. Use of the following prohibited treatments:
    a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), vancomycin, clomipramine, or nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium) within 14 days before Screening
    b. Monoclonal antibodies (eg, omalizumab, dupilumab, tezepelumab) within 4 months or 5 half-lives (whichever is longer) before Screening
    c. Immunosuppressant drugs, including systemic corticosteroids, hydroxychloroquine, methotrexate, mycophenolate, cyclosporine, or cyclophosphamide within 30 days before Screening
    d. Current or anticipated use of corticosteroids, or uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids
    e. [redacted]
    f.
    g.
5. Active malignancy or history of malignancy of any organ system (other than localized squamous cell or basal cell carcinoma of the skin that have been excised or resolved), treated or untreated, within the past 5 years from Screening
6. Evidence of clinically significant cardiac, neurologic, psychiatric, pulmonary, renal, hepatic, endocrine (including uncontrolled diabetes mellitus), metabolic, or gastrointestinal disease that, in the Investigator's opinion, would compromise the safety of the subject, interfere with the interpretation of the study results, or otherwise preclude subject participation
7. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect subject safety
8. Any clinically significant abnormalities on screening laboratory tests that, in the opinion of the Investigator, precludes participation in the study. The following abnormalities will specifically be considered exclusionary:
    a. Bilirubin >upper limit of normal (ULN) and/or any known condition that results in abnormal bilirubin elevations or fluctuations (eg, Gilbert's, Dubin-Johnson, Rotor syndrome)
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5× ULN
9. Other co-morbidities that would introduce additional risk factors or interfere with study procedures based on clinically significant physical examination, vital sign, standard

12-lead ECG, chemistry, hematology, urinalysis, or coagulation results at Screening as deemed by the Investigator

10. Positive result for human immunodeficiency virus (HIV) or presence of actively replicating viral hepatitis due to hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at Screening
11. Significant history of abuse of drugs, solvents, or alcohol within the past year
12. Participation in any clinical study with an investigational or approved drug/device within 30 days or 5 half-lives (whichever is longer) before Screening or is planning to participate in another clinical study while enrolled in this study
13. History of known or suspected hypersensitivity to any component of study drug
14. Female who is pregnant, nursing, or intends to become pregnant during the study
15. Had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study
16. Is directly affiliated with the study at the clinical site or is an immediate family member (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at the clinical site
17. Is employed by Incyte Corporation or its wholly owned subsidiary, Escient, (that is an employee, temporary contract worker, or designee responsible for the conduct of the study) or is an immediate family member of an employee of Incyte Corporation or Escient
18. Subject is, in the opinion of the Investigator, not suitable to participate in the study
19. Subject is performing mandatory military service, deprived of liberty and/or due to a judicial decision, cannot take part in clinical studies, or is in a residential care institution

8.3. Study Restrictions

Unless stated otherwise, subjects must adhere to the following restrictions from Screening until the end of the study unless subject safety is compromised:

- Do not use any drugs of abuse (cannabinoids [eg, oil, recreation smoking] are not restricted).
- Do not use any investigational drugs/devices.
- Maintain current dose and regimen of all prescribed medication, unless changed in consultation with the Medical Monitor.
- Do not start new medications, including prescription medications and antihistamines (besides protocol-defined rescue therapy), during the Double-Blind Treatment Period unless deemed necessary by a healthcare provider.
- [redacted]

8.4. Concomitant Medications

Subjects are to follow the medication restrictions outlined in the inclusion and exclusion criteria (Section 8.1 and Section 8.2) and subject restrictions (Section 8.3) during the study.

The Investigator should contact the Medical Monitor with any questions about concomitant medication use or timing of administration. In instances where a medication is initiated prior to discussion with the Medical Monitor, the Investigator must notify the Medical Monitor as soon as he/she is aware of the use of the new medication to discuss the subject's concomitant treatment and any impact to participation in the study.

All medications taken within 14 days before Screening and details of concomitant medications from Screening through the end of study participation should be recorded. In addition, all medications taken to treat CSU beginning from the date of diagnosis should also be recorded.

8.5. Auxiliary Medicinal Products

All auxiliary medicinal products to be used in this clinical study are authorized and will be used in accordance with their marketing authorizations.

8.5.1. Background Therapy

All subjects must be on daily stable doses of 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.

8.5.2. Rescue Medications

In addition to their daily background therapy, for the duration of the study (Screening, Double-Blind Treatment, and Safety Follow-Up Periods), 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.

8.5.3. 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.

8.6. Removal of Subjects from Therapy or Assessment

If a subject discontinues study drug and/or is withdrawn from the study, the reason will be recorded on the electronic case report form (eCRF) page and the Sponsor will be notified within 24 to 48 hours.

8.6.1. Discontinuation of Study Drug

Discontinuation of study drug for a subject occurs when the study drug is stopped earlier than the protocol planned treatment duration. Discontinuation of study drug is mandatory in the following instances:

- AEs for which continued exposure to study drug would be detrimental, including AEs that are Common Technical Criteria for Adverse Events (CTCAE) Grade 4 or higher (Section 12.1.2)
- Abnormal liver laboratory results meeting the threshold for discontinuation as listed in Section 12.10.3
- Withdrawal of consent
- Lost to follow-up
- Protocol deviation that results in a significant risk to the subject's safety
- Investigator decision
- Sponsor decision
- Pregnancy during the study (Section 12.2.3)
- Any circumstance that results in a negative benefit:risk balance

For subjects who terminate treatment with study drug early, regardless of the reason, every effort will be made to complete the early treatment termination evaluations as soon as possible after the last dose of study drug, ideally within 2 days after the last dose of study drug.

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.

If a subject discontinues study drug and chooses not to complete all 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 Safety 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. If a subject fails to attend the Safety Follow-Up Visit and has not withdrawn consent, all reasonable efforts will be made to contact the subject to ensure that he/she is in satisfactory health. All contacts and contact attempts must be documented in the subject's medical record.

8.6.2. Discontinuation from the Study

Discontinuation from the study is mandatory for the following reasons:

- Death
- Withdrawal of consent
- Lost to follow-up
- Termination of the study by the Sponsor or at the request of a regulatory agency or an IRB or IEC (Section 7.6)
- Other

A subject may elect to discontinue study participation at any time for any reason without prejudice to their future medical care by the physician or at the institution. If a subject withdraws consent, no further evaluation should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. The Investigator should make a reasonable attempt to document the specific reason why consent was withdrawn.

9. TREATMENT OF SUBJECTS

9.1. Treatment Assignment

In Part 1, approximately 114 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 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.

9.2. Treatment Compliance

The Investigator should assess the subject's compliance with dosing of study drug by counting returned study drug capsules and reviewing the subject's dosing diary as indicated in the Schedule of Assessments (Appendix A).

If the Investigator has concerns about a subject's dosing compliance, the Investigator should discuss this with the subject, assess the reasons for noncompliance and the likelihood that the subject will remain noncompliant, and notify the Sponsor accordingly.

9.3. Randomization and Blinding

9.3.1. Randomization

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.

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 SAEs.

9.3.2. Blinding

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 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, respectively.

9.3.2.1. Emergency Unblinding

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.

9.3.2.2. Unblinding for Regulatory Reporting

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.

9.4. Study Visits

Subjects should fast for at least 8 hours before study visits that require a blood sample for assessment of clinical chemistry. Water is acceptable in the morning of clinic visits to ensure the subject is hydrated for laboratory sample collection. Subjects should fast at least 4 hours before administration of each dose of study drug and refrain from eating for at least 2 hours postdose. Each dose of study drug is to be taken with approximately 240 mL (8 fluid ounces) of water on an empty stomach.

Study procedures are listed for each visit in the following sections and summarized in the Schedule of Assessments (Appendix A). Further details regarding efficacy, safety, PK, PD, and baseline characterization assessments are located in Sections 11, 12, 13, 14, and 15, respectively.

9.4.1. Screening Period

9.4.1.1. Visit 1 (Day -30 to Day -14 [inclusive])

During the Screening Period, subjects will undergo assessments to determine their study eligibility. Subjects will be screened and should meet all inclusion criteria and none of the exclusion criteria to be enrolled in the study. Any questions regarding eligibility may be discussed with the Medical Monitor.

The following assessments may be conducted over more than 1 day but must be completed between Day -30 and Day -14 (inclusive):

- Completion of informed consent before performance of any study procedures or assessments
- Medical history, including CSU disease history
- Height
- Body weight
- Vital signs
- Physical examination
- Standard 12-lead ECG
- Assessment of baseline concomitant medications, including all medications taken to treat CSU beginning from the date of diagnosis, any prior use of omalizumab, and all medications taken within 14 days before Screening
- AE assessment
- Blood and/or urine sample collection for screening and safety laboratory assessments
- Eligibility check
- Electronic device/app training
- [redacted]

Subjects will be instructed to complete the UAS and [redacted] daily, in the morning before dosing (as applicable), and at approximately the same time of day, from the Screening Visit to the Safety Follow-Up Visit and the [redacted] weekly, in the morning before dosing (as applicable), and at approximately the same time of day, from Day 1 to the Safety Follow-Up Visit using the study-issued electronic device or app. The questionnaires will be completed during the Screening Visit. For all other days that coincide with a study visit (for Visit 2 and beyond), the questionnaires are to be completed in the morning before the visit, unless specified otherwise.

Screening results will be reviewed by the Investigator to determine the subject's eligibility. Subjects who have an exclusionary result during the Screening Period (between Visit 1 and Visit 2) may have that assessment repeated once at the discretion of the Investigator within the screening window and be enrolled if a repeat assessment is within the indicated range as specified in Section 8 for participating in the study. Subjects who are confirmed to be eligible

will be asked to return to the site for Visit 2 (Day 1) to be enrolled and randomized into the study.

9.4.2. Double-Blind Treatment Period

9.4.2.1. Visit 2 (Day 1) – Enrollment and Randomization

Subjects who continue to meet study eligibility requirements will be enrolled and randomized during Visit 2 (Day 1).

The following assessments will be performed during Visit 2 (Day 1):

- Complete [redacted]
- Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 2 (Day 1)
- Vital signs
- Standard 12-lead ECG
- Concomitant medication usage assessment
- AE assessment
- Eligibility check
- Blood and/or urine sample collection for PD, safety, PK, and baseline characterization laboratory assessments
- Randomization to study drug treatment assignment via IWRS:
  - Part 1: 50 mg EP262, 150 mg EP262, or placebo in a 1:1:1 ratio
  - Part 2: 25 mg EP262 or placebo in a 3:1 ratio
- Dispense study drug
- Upon completion of the assessments listed above, study drug 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

9.4.2.2. Visit 3 (Week 3)

The following assessments will be performed during Visit 3 (Week 3):

- Complete [redacted]
- Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 3 (Week 3)
- Confirm that the [redacted] was completed weekly from the last visit through Visit 3 (Week 3)
- Collect study drug
- Assess study drug accountability and compliance

- Vital signs
- Concomitant medication usage assessment
- AE assessment
- Blood and/or urine sample collection for PD, safety, and PK laboratory assessments
- Dispense study drug
- Upon completion of the assessments listed above, study drug 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

9.4.2.3. Visit 4 (Week 6)

The following assessments will be performed during Visit 4 (Week 6):

- Complete [redacted]
- Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 4 (Week 6)
- Confirm that the [redacted] was completed weekly from the last visit through Week 5
- Collect study drug
- Assess study drug accountability and compliance
- Body weight
- Vital signs
- Standard 12-lead ECG
- Concomitant medication usage assessment
- AE assessment
- Blood and/or urine sample collection for PD, safety, and PK laboratory assessments

9.4.3. Safety Follow-Up Period

9.4.3.1. Visit 5 (Week 10)

The following assessments will be performed during the Safety Follow-Up Visit, approximately 4 weeks after the last dose of study drug:

- Complete the [redacted]
- Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 5 (Week 10)
- Confirm that the [redacted] was completed weekly from the last visit through Week 9
- Body weight
- Vital signs

- Standard 12-lead ECG
- Concomitant medication usage assessment
- AE assessment
- Blood and/or urine sample collection for PD, safety, and PK laboratory assessments

9.4.4. Early Treatment Termination Visit

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 following assessments will be performed during the Early Treatment Termination Visit:

- Complete [redacted]
- Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of the Early Treatment Termination Visit
- Confirm that the [redacted] was completed weekly from the last visit through the Early Treatment Termination Visit
- Collect study drug
- Assess study drug accountability and compliance
- Body weight
- Vital signs
- Standard 12-lead ECG
- Concomitant medication usage assessment
- AE assessment
- Blood and/or urine sample collection for PD, safety, and PK laboratory assessments

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

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]

10.2. Study Drug Packaging and Labeling

Study drug will be packaged into bottles labeled with a unique number and supplied to clinical sites in a blinded manner.

10.3. Study Drug Storage

The study drug capsules should be stored at controlled room temperature, 15°C to 25°C (59°F to 77°F), with excursions up to 30°C (86°F).

10.4. Study Drug Administration

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.

10.4.1. Instructions for Missed Dose(s)

Subjects should be instructed that if they forget to take a dose, they can take the dose within 8 hours of the normal dosing time; otherwise, they should take their next dose at the regular time on the following day. If the subject vomits the capsules, he/she should be instructed not to take additional capsules on the same day but to take the next dose at the regular time on the following day. Subjects should be instructed to contact the Investigator if they miss 2 or more consecutive doses.

10.5. Study Drug Dispensing and Accountability

Subjects will record self-administration of study drug daily in a dosing diary that will be reviewed at each clinical site visit during the Double-Blind Treatment Period by site staff.

Subjects should be instructed to retain the study drug, including the study drug bottle, even if empty, and to return it and any remaining study drug to the clinical site at their next visit. The site staff should perform study drug accountability and, if applicable, follow-up with the subject to retrieve any remaining study drug that has not been returned.

10.6. Study Drug Handling and Disposal

Study drug will be sent to the clinical site under appropriate storage conditions. Upon receipt of study drug, site staff are to open the shipment, and verify that the amount and identity of the contents match that stated in the enclosed shipping form. The Sponsor (or designee) is to be notified immediately about any irregularities, discrepancies, or damage.

Study drug will be provided for use only in this study and is not to be used for any other purpose. The site staff will maintain a full record of study drug accountability as described in Section 10.5.

Upon completion of the study, used and unused study drug and study drug bottles are to be returned to the Sponsor (or designee) or, if prior Sponsor approval is obtained, disposed of in accordance with applicable site procedures. Site staff must maintain documentation of any missing or unreturned study drug. The final disposition of all study drug received at the site is to be documented.

10.7. Product Quality Complaints

A product quality complaint (PQC) is defined as any suspicion of a product defect or deficiency related to manufacturing, labeling, or packaging (ie, any dissatisfaction relative to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product, including its labeling or package integrity). A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects.

All initial PQCs must be reported to the Sponsor or CRO by clinical-site personnel within 24 hours after being made aware of the potential defect. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from the Sponsor.

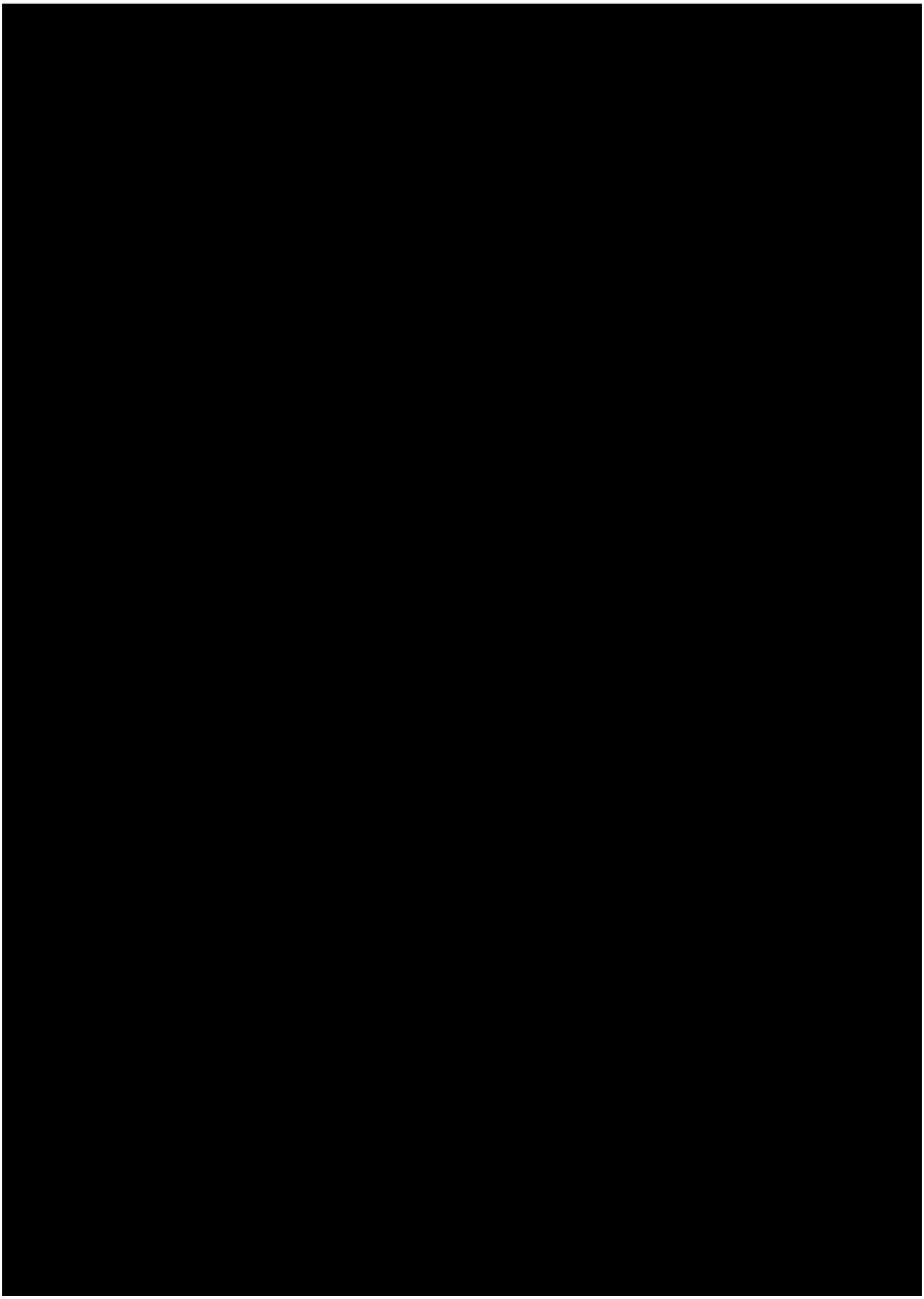
11. EFFICACY ASSESSMENTS

The primary efficacy evaluation is based on the UAS, a patient-reported assessment of disease activity. Secondary efficacy evaluations include assessments of itching (ISS) and hives (HSS), both of which comprise the UAS. Exploratory efficacy evaluations include [redacted] All efficacy assessments will be performed as indicated in the Schedule of Assessments (Appendix A).

Examples of the patient-reported assessments are provided in the appendices but are not to be distributed to subjects for completion. Subjects will be trained on completion of all patient-reported assessments using the study-issued electronic device or application (app).

All subjects who were given a study-issued device, including those who fail Screening, will be required to return it to the site once their participation in the study is complete.

[redacted]



12. SAFETY ASSESSMENTS

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

12.1. Adverse Events

12.1.1. Definition of an Adverse Event

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 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 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.

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. 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.

12.1.2. Determining Severity of Adverse Events

AEs must be graded for severity (ie, intensity) using CTCAE, version 5.0 (HHS 2017). A severity category of mild, moderate, severe, life-threatening, or death, as defined in Appendix B, must be entered on the AE eCRF. The criteria below are to be used for determining the severity of AEs where there is no actual CTCAE term for the specific reported AE found in the CTCAE, version 5.0 guideline (Appendix B). It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious". The assessment of severity is made regardless of the relationship to study drug or of the seriousness of the AE. When reporting AEs, reference should be made to the CTCAE manual for guidance on appropriate grading.

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Grade 3:	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting selfcare activities of daily life (eg, bathing, dressing and undressing, feeding self, using the toilet, taking medications, not bedridden).
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE.

12.1.3. Determining Causality of Adverse Events

Causality refers to the relationship of the event to the study drug (EP262 or placebo). The Investigator will assess the causality of the event according to the following criteria:

- **Not related** – A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug.
- **Related** – A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug, which may or may not reasonably have been produced by a number of other factors including underlying disease, complications, concomitant drugs, or concurrent treatments; and/or that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments; and/or disappears or decreases on cessation or reduction in study drug dose; and/or reappears or worsens when the study drug is administered.

12.1.4. Recording Adverse Events

All AEs must be recorded in the source documents and in the eCRFs provided by the Sponsor from the signing of the Informed Consent Form (ICF) until the end of study participation. AEs will be assessed for likelihood of causal relationship to the study drug (EP262 or placebo) and severity.

The new onset of signs, symptoms, or other findings that occur before signing of the ICF will be captured as medical history (Section 12.3).

12.1.4.1. Special Instructions for Recording Adverse Events in the eCRF

Diagnosis versus Signs and Symptoms

If a diagnosis is known at the time of reporting, this should be recorded in the eCRF rather than the individual signs and symptoms (eg, record only hepatitis rather than elevated transaminases, bilirubin, and jaundice). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an SAE or AE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up and should replace the individual signs and/or symptoms as the event term on the eCRF, unless the signs/symptoms are clinically significant.

Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, clinical sequelae or a cascade of events) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as an SAE or AE on the eCRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if severe vomiting leads to acute renal failure, both events should be recorded on the eCRF.

Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation timepoints. Such events should only be recorded once on the eCRF. If a persistent AE becomes more severe or lessens in severity, it should be recorded as a new AE on the eCRF.

A recurrent AE is one that occurs and resolves between subject evaluation timepoints, and subsequently recurs. Each reoccurrence of an AE should be recorded on the eCRF.

Abnormal Laboratory Values or Vital Signs

Protocol defined laboratory values and vital signs will be reported as AEs if the abnormal laboratory or vital sign result:

- Requires an adjustment in the study drug(s) or discontinuation of treatment;
- Requires additional testing, excluding repeat testing of the lab in question, or surgical intervention;
- Is associated with accompanying signs/symptoms that are not considered part of a preexisting diagnosis or syndrome; or
- Is considered clinically significant by the Investigator

If an abnormal laboratory value or vital sign is the result of an evaluation of clinical signs, symptoms, or suspected diagnosis during the conduct of the study, the signs/symptoms or diagnosis should be reported as an AE (or if appropriate, an SAE) only if clinically significant, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF.

12.2. Serious Adverse Events

12.2.1. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence, that at any dose:

- Results in death;
- Is life-threatening, ie, the subject is, in the opinion of the Investigator, at immediate risk of death from the event as it occurred, (it does not include an event that, had it occurred in a more severe form, might have caused death);
- Requires hospital admission or prolongs hospitalization. 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 SAEs. Emergency room visits that are less than 24 hours will also not be considered SAEs unless any of the other serious criteria is fulfilled;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly/birth defect; or
- Is a medically significant event that, based on appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Note: A distinction should be drawn between SAEs and severe AEs. Severity is a measure of the intensity of an AE, while the criteria for seriousness are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE is not necessarily considered an SAE. For example, a headache that persists for several hours may be considered a severe AE but not an SAE. Conversely, a wound infection that may be considered minor could be an SAE if it prolonged hospitalization.

12.2.2. Reporting Serious Adverse Events

The Investigator and the Sponsor will monitor safety for this study. A Serious Adverse Event Report (SAER) Form is to be completed for each SAE occurring after signing of the ICF until 30 days after the last dose of study drug, regardless of causality.

All SAE reports must be **reported within 24 hours of the Investigator's knowledge of the event** to [redacted]. If requested by the Sponsor, any supporting documentation (eg, medical records) sent to [redacted] with the SAER Form must have subject identifying information (eg, subject names, subject addresses, medical records number) redacted by the site. Follow-up information to all SAEs should be submitted to the Sponsor, or designee, in the same timeframe as initial reports.

All SAEs will be followed until resolution or medical stabilization (in cases where resolution would not be expected).

In accordance with applicable regulations and local laws, the Sponsor or designee will report all serious and unexpected AEs assessed as related to study drug by the Investigator and/or Sponsor, to the regulatory authorities within the required timeframe. The Investigator will be responsible for reporting this safety information to his or her IRB/IEC.

If the Investigator becomes aware of an SAE any time after study completion and determines it is related to the study drug, the SAE must be reported to the Sponsor or designee within 24 hours of the Investigator's knowledge of the SAE.

12.2.3. Pregnancy

Pregnancy in and of itself is not an AE, although pregnancies occurring in subjects or partners of male subjects are considered immediately reportable events. If a pregnancy occurs in a subject, study drug must be discontinued immediately. The pregnancy must be reported to Innovaderm Drug Safety via email at EP-262-201_drugsafety@innovaderm.com within 24 hours of the Investigator's knowledge of the pregnancy using the Pregnancy Reporting Form.

The Investigator will follow the pregnant woman until completion of the pregnancy, and must notify the Sponsor, or designee, of the outcome within 24 hours of the Investigator's knowledge of the pregnancy outcome. The Investigator will provide this information on the Pregnancy Reporting Form. This notification includes pregnancies resulting in live, "normal" births.

If the pregnant subject experiences an SAE during pregnancy, or the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (ie, report the event to the Sponsor via email at [redacted] within 24 hours of the Investigator's knowledge of the event).

All neonatal deaths and congenital anomalies that occur within 30 days of birth (regardless of causality) should be reported as SAEs to the Sponsor or designee. In addition, any infant death or congenital anomaly occurring after study completion that the Investigator suspects is related to the in-utero exposure to the study drug should also be reported to the Sponsor or designee.

12.3. Medical History

The Investigator or designee will collect and review the subject's medical history, including CSU 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 ICF will be captured as medical history.

12.4. 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.

12.5. 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.

12.6. 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 ICF will be recorded as medical history, and clinically significant changes after signing the ICF will be recorded as AEs.

12.7. 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.

12.8. Laboratory Evaluations of Safety

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-glutamyltransferase, 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.

12.9. 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.

12.10. Subject Safety Guidelines

12.10.1. Potential Side Effects

Refer to Section 5.4.2 and the Investigator's Brochure for additional EP262 information regarding potential side effects.

12.10.2. Overdose

No specific information is available on the treatment of overdose of EP262. Additionally, there is no specific antidote to EP262. In a case of overdose, appropriate supportive measures should be employed and the case documented as a protocol deviation (Section 18.1). An overdose does not constitute an AE; however, the subject should be closely monitored for any potential AEs.

The overdose must be reported to Innovaderm Drug Safety via email at [redacted] within 24 hours of the Investigator's knowledge of the overdose using the Overdose Reporting Form.

12.10.3. Management of Liver Test Abnormalities

Subjects with an increase in ALT or AST to >3× ULN OR total bilirubin >2× ULN should be followed by repeat testing within 48 to 72 hours of the initial serum chemistry results, if possible, to monitor for suspected drug-induced liver injury. Test results from local laboratories and the associated normal ranges are to be captured in the database. In conjunction with this, a physical examination should be performed and AE information should be collected. If symptoms persist or repeat testing shows ALT or AST >3× ULN or total bilirubin >2× ULN, subjects should be closely monitored as defined below to determine whether the abnormalities are improving or worsening:

- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (eg, INR, direct bilirubin).

If close observation is not possible, study drug should be interrupted until further investigation can be performed.

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is identified and the laboratory abnormalities resolve to normal or baseline values. The Investigator and Sponsor's designated Medical Monitor must discuss and agree with any decision to rechallenge. Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug-induced.

Discontinuation of treatment should be considered if the following abnormality or group of abnormalities occur:

- 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%)

13. PHARMACOKINETICS ASSESSMENTS

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.

14. PHARMACODYNAMIC ASSESSMENTS

[redacted]

15. BASELINE CHARACTERIZATION

[redacted]

16. STATISTICS

Data summaries will use descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables and frequency and percentage for categorical and ordinal variables. Unless otherwise specified, endpoints will use the last pre-treatment value prior to the first dose of study drug as baseline. All data collected will be included in subject data listings.

A formal Statistical Analysis Plan (SAP) will be prepared and finalized before database lock. Additional statistical analysis details will be included in the SAP.

16.1. Analysis Sets

The following analysis sets will be considered:

- **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.
- **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 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.

- **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.

16.2. Estimand

Consistent with the International Council for Harmonisation (ICH) Guideline E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (FDA 2021), the definition of the attributes of the primary estimand of this study is provided in this section.

The primary estimand of the study is to assess the difference in disease activity in pruritus and hives in subjects with CSU treated with EP262 or placebo, as measured by change in weekly UAS7 after 6 weeks of randomized treatment, regardless of treatment discontinuation and use of prohibited and/or rescue medications.

The population targeted by the scientific question is 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.

Premature discontinuation from study drug and use of prohibited and/or rescue medications are the primary potential intercurrent events that could occur. The treatment policy strategy is used for the primary estimand, consistent with the intent-to-treat principle.

16.3. Endpoints

16.3.1. Primary Efficacy Endpoint

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

16.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Change from baseline in ISS7 at Visit 4 (Week 6)
- Change from baseline in HSS7 at Visit 4 (Week 6)

16.3.3. Exploratory Endpoints

[redacted]

16.4. Sample Size Considerations

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%.

With an estimated early withdrawal rate of approximately 10%, the planned enrollment of 38 subjects per treatment group (50 mg EP262, 150 mg EP262, and placebo) in Part 1 and 40 subjects (30 subjects in 25 mg EP262 and 10 subjects in placebo) in Part 2 will ensure adequate sample size to complete the 6-week treatment period.

16.5. Subject Disposition

Disposition of subjects will be summarized by treatment group and overall. Completion status and reasons for discontinuation will also be summarized.

The number and percentage of subjects in each analysis set will be summarized.

16.6. Demographics and Baseline Characteristics

Demographic data and baseline characteristics for each analysis set will be summarized by treatment group and overall using descriptive statistics.

16.7. Study Drug Usage and Compliance

Compliance rate will be computed for each subject and will be summarized for the Safety Analysis Set using summary statistics by treatment group and overall.

Duration of treatment will also be summarized.

16.8. Efficacy and Pharmacodynamic Analysis

Efficacy and PD analyses will be based on the FAS. The primary and secondary endpoint analyses will also be repeated in the PP Set as supportive analyses.

Efficacy analyses will compare placebo and each EP262 dose separately. Subjects who receive placebo in Parts 1 and 2 will be pooled for analysis. Additional analysis comparing placebo and all EP262 doses combined may be performed as appropriate. Statistical testing will be performed as a 2-sided test with a statistical significance level of 0.10.

For UAS, a weekly score will be computed as the sum of the daily UAS over the 7 days prior to the timepoint of interest. 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 timepoint.

All changes from baseline endpoints are defined as absolute change. For select endpoints, percent change from baseline will also be summarized.

16.8.1. Primary Efficacy Analysis

The UAS7 will be analyzed using a mixed effects model for repeated measures based on the data from each week up to Week 6. The model will include treatment, week, and treatment by week interaction as fixed effects. Additional model covariates will include baseline UAS7 score and randomization strata. The treatment effect will be the contrast between EP262 and placebo least-squares (LS) means.

16.8.2. Additional Efficacy and Pharmacodynamic Analyses

All efficacy and PD endpoints described in Section 16.3.2 and Section 16.3.3 will be summarized. 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.

16.8.3. Primary and Sensitivity Analyses 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 (Rubin 1987). The SAP will provide full detail of the methodologies that will be used.

16.9. Safety Analysis

The Safety Analysis Set will be used for the summaries of the safety data. Safety data will be summarized by treatment group and overall.

The safety and tolerability of EP262 will be assessed by comparing the frequency, causality, and severity of AEs as well as treatment discontinuations due to AEs. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class and preferred term. AEs that begin after the first administration of study drug, or existing AEs that worsen after the first dose of study drug, are considered treatment emergent. All AE summaries will include TEAEs, and all AEs will be presented in data listings.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized descriptively by Anatomic Therapeutic Chemistry (ATC) class using counts and percentages. Medications started prior to the first dose of study drug will be indicated in the data listings. Use of rescue medications will also be summarized.

Changes in vital signs, standard 12-lead ECGs, and laboratory evaluations will be summarized descriptively.

16.10. Pharmacokinetic Analysis

The PK Set will be used for the summaries of plasma concentrations of EP262. A descriptive summary of the observed plasma concentrations will be displayed by time and by treatment group.

16.11. Subgroup Analyses

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

16.12. Multiple Comparison/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.

16.13. Interim Analysis

Given the hypothesis-generating nature of this study, an optional interim analysis may be conducted to support business needs. The interim analysis would evaluate the effects of EP262 on UAS7, other select efficacy 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. Additional details about the interim analysis, if applicable, will be provided in the SAP, which is to be finalized before the database lock and unblinding of the study data, as applicable. 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.

17. QUALITY CONTROL AND DATA MANAGEMENT

17.1. Data Quality Assurance

The following measures will be implemented to ensure accuracy, consistency, completeness, and reliability of data:

- Investigator discussions
- Site initiation training
- Early site visits following enrollment
- Routine site management
- Ongoing site communication and training
- Periodic site monitoring
- Review of the eCRF against source data for all subjects
- Data management quality control (QC) checks
- Statistical QC checks

17.2. Data Management

A database will be designed and built based on the final eCRFs. A Data Management Plan will be written specifying the procedures that will be used for medical coding, SAE reconciliation,

QC, laboratory data, and data cleaning that will occur for the study. A Data Validation Specifications document will be written and edit checks will be programmed and validated.

17.3. Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the ICH Guideline for GCP, and applicable regional regulations and guidelines.

A monitor (or monitors) will review and verify protocol compliance with a focus on AE/SAE reporting, eCRF data, source documentation, ICFs, and any other study-related documentation, including review of site pharmacy procedures, drug accountability documentation, and drug storage facilities and records.

Monitoring will be on an ongoing basis. Before database lock, 100% eCRF data verification will be performed against the source documents. The Investigator will agree to the monitor(s) making periodic site visits during the study. The monitor(s) and the site staff will agree upon the timing of these visits.

Centralized monitoring, which consists of remote review of accumulating data from all sites, will be performed as detailed in the Centralized Monitoring Plan.

17.4. Confidentiality and Auditing

The Investigator, the Sponsor, and the Sponsor's representatives will preserve the confidentiality of all subjects participating in this study, in accordance with ICH GCP, local regulations, and institutional requirements. Only year of birth, age at Screening, and study subject number will be used to identify subjects on the eCRFs and other study-related documents submitted to the Sponsor (or designee). Documents that are not submitted to the Sponsor (eg, ICFs) should be kept in strict confidence by the investigative staff.

In compliance with ICH GCP, it is required that the Investigator and institution permit authorized representatives of the Sponsor, the IRB/IEC, the United States (US) Food and Drug Administration (FDA), the European Medicines Agency, and other appropriate regulatory authority or health authority inspectors direct access to all study-related sites, source data, documents, and reports for verification of study records and data. Direct access is the permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study. The Investigator is obligated to inform and obtain consent from the subject to permit these representatives to have access to their study-related records for this verification. Any party (eg, domestic and foreign regulatory authorities, Sponsors, auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects.

In case of data security breach, measures to mitigate possible adverse effects for subjects will be applied as per the CRO's standard operating procedure (SOP).

17.5. Case Report Forms

eCRFs will be used for this study. Site personnel will receive training on eCRF completion. Each eCRF is to be reviewed and approved by the Investigator.

During periodic monitoring visits, the eCRFs will be made available to the study monitor so that he or she may verify the data entries with the source documentation.

17.6. Source Documents

The Investigator will prepare and maintain adequate and accurate source documents (eg, medical records, 12-lead ECG results, raw data collection forms) to record all observations and other pertinent data for each subject enrolled into the study. The data recorded on the eCRFs will be derived from these source documents. The Investigator will ensure that data on the eCRFs and completed queries are accurate, consistent with source documentation, and submitted to the Sponsor in a timely manner. The Investigator will also ensure that all data on required study logs are accurate and kept up to date.

17.7. Records Retention

The Investigator must maintain essential study documents (protocol and amendments, completed eCRFs, source documentation, signed ICFs, relevant correspondence and approvals, and all other supporting documentation) until notified by the Sponsor. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period and stored separately. Custody of the records may be transferred to another responsible party, acceptable to the Sponsor, which agrees to abide by the retention policies. Written notice of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor before disposing of any study records.

Records retention will follow the data protection requirements in each country.

17.8. Informed Consent

Written informed consent will be obtained from each subject before any study-related procedures are performed. The Investigator has an ethical and legal responsibility to ensure each subject being considered for inclusion in the study is given a full explanation of the study. The Investigator, or his/her designee, shall inform each subject, in writing, of all aspects pertaining to participation in the study, including (but not limited to) aims, methods, anticipated benefits, and potential risks. Subjects will have the opportunity to inquire about details of the study and to decide whether to participate. Subjects should understand that they are free to refuse to participate in, or to withdraw from, the study at any time without prejudice or loss of medical care to which they are otherwise entitled. Each subject must personally sign and date a study-specific ICF to be a subject in the study. The ICF must be countersigned by the site Investigator (or designee) who conducted the informed consent discussion. This will be documented on a written ICF. Each ICF will include the elements required by US 21 Code of Federal Regulations (CFR) 50 and ICH E6, Section 4.8, Regulation (European Union [EU]) No 536/2014, Chapter V, and General Data Protection Regulation (EU) 2016/679 (GDPR). The Investigator agrees to obtain approval from the Sponsor of any written informed consent for use in the study before submission to the IRB/IEC.

Each subject who provides written informed consent for the study (by signing and dating the ICF), will be given a copy of the signed ICF. The original will be kept in the subject's medical record or study chart as permitted by the institution. The Investigator will inform subjects of new

information that may be relevant to the subjects' willingness to continue participation in the study according to local ethics requirements.

It is important to obtain complete follow-up for all subjects. Every attempt should be made to undertake all protocol-specified assessments and complete the eCRFs except for those subjects who specifically withdraw consent for release of such information.

17.9. Ethical Conduct of the Study

This study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP, ICH guidelines, other applicable regulatory requirements (eg, local requirements), the study protocol, and where applicable, Sponsor and/or CRO SOPs.

17.10. Institutional Review Board/Independent Ethics Committee

The Investigator will not begin the study until the protocol and ICF have been approved by the appropriate independent IRB/IEC. Any amendments to the protocol must also be approved in writing by the Sponsor and IRB/IEC, before implementation by the Investigator, except where necessary to eliminate an immediate hazard to subjects.

All IRB/IEC correspondence, including progress reports, will be retained on file at the site.

18. STUDY MANAGEMENT

18.1. Protocol Deviations

The Investigator is not permitted to deviate from the protocol in any major way without proper notification to the Sponsor (or designee). Only the Sponsor may revise the protocol. Any change in study conduct considered necessary by the Investigator will be made only after consultation with the Sponsor, who will then issue a formal protocol revision to implement the change and obtain regulatory and ethic approval. The only exception is when the Investigator considers a subject's safety to be compromised if immediate action is not taken.

In the event of an important deviation from the protocol, the Investigator or designee must contact the Sponsor or representative at the earliest possible time. This will allow an early joint decision regarding the subject's continuation in the study.

Examples of important deviations include:

- Subject did not give appropriate informed consent
- Inclusion or exclusion criteria not satisfied
- Non-permitted concomitant medications that may meaningfully impact efficacy or safety outcomes
- Meaningful dosing error
- Randomization error

The Investigator and Sponsor will both document this decision. The IRB/IEC will be informed of all important protocol deviations by the Investigator in accordance with established procedures.

18.2. Publications

No publication of the results shall take place without the Sponsor's written consent. All publication or presentation rights for the findings of the clinical investigation under this protocol shall be governed by the appropriate terms of the clinical research agreement between the Investigator, the investigational site, and the Sponsor.

This study will be registered on https://clinicaltrials.gov and https://euclinicaltrials.eu prior to the first subject being dosed.

A summary of the results of the clinical study, together with a summary that is understandable to a layperson, will be made available within 1 year from the end of the clinical study.

18.3. Change in Clinical Site Staff

In the event that the Principal Investigator at a site is unable to continue the study, another suitable person will be designated as the Investigator, and documentation testifying to this will be submitted to the Sponsor or its designee within 10 days, who must approve the change along with the IRB/IEC before the study can be continued at that investigative site.

19. LIST OF REFERENCES

Azimi E, Reddy VB, Lerner EA. Brief Communication: MRGPRX2, Atopic Dermatitis and Red Man Syndrome. Itch (Phila). 2017;2(1):e5.

Babina M. The Pseudo-Allergic/Neurogenic Route of Mast Cell Activation via MRGPRX2: Discovery, Functional Programs, Regulation, Relevance to Disease, and Relation with Allergic Stimulation. Itch. 2020;5(2):e32.

Baiardini I, Pasquali M, Braido F, et al. A New Tool to Evaluate the Impact of Chronic Urticaria on Quality of Life: Chronic Urticaria Quality of Life Questionnaire (CU-QoL). Allergy. 2005;60(8):1073-8.

Bernstein JA, Lang DM, Khan DA, et al. The Diagnosis and Management of Acute and Chronic Urticaria: 2014 Update. J Allergy Clin Immunol. 2014;133(5):1270-7.

Bossi F, Frossi B, Radillo O, et al. Mast Cells are Critically Involved in Serum-Mediated Vascular Leakage in Chronic Urticaria Beyond High-Affinity IgE Receptor Stimulation. Allergy. 2011;66(12):1538-45.

Corbiere A, Loste A, Gaudenzio N. MRGPRX2 Sensing of Cationic Compounds-A Bridge Between Nociception and Skin Diseases? Exp Dermatol. 2021;30(2):193-200.

FDA. Guidance for Industry: E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. FDA Maryland; 2021. p. 1-19.

Fok JS, Kolkhir P, Church MK, et al. Predictors of Treatment Response in Chronic Spontaneous Urticaria. Allergy. 2021;76(10):2965-81.

Folci M, Heffler E, Canonica GW, et al. Cutting Edge: Biomarkers for Chronic Spontaneous Urticaria. J Immunol Res. 2018;2018:5615109.

Fujisawa D, Kashiwakura J, Kita H, et al. Expression of Mas-Related Gene X2 on Mast Cells is Upregulated in the Skin of Patients with Severe Chronic Urticaria. J Allergy Clin Immunol. 2014;134(3):622-33 e9.

Green DP, Limjunyawong N, Gour N, et al. A Mast-Cell-Specific Receptor Mediates Neurogenic Inflammation and Pain. Neuron. 2019;101(3):412-20 e3.

HHS. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017. p. 1-146.

Kapp A, Czech W, Krutmann J, et al. Eosinophil Cationic Protein in Sera of Patients with Atopic Dermatitis. J Am Acad Dermatol. 1991;24(4):555-8.

Kulthanan K, Chularojanamontri L, Rujitharanawong C, et al. Angioedema Quality of Life Questionnaire (AE-QoL) - Interpretability and Sensitivity to Change. Health Qual Life Outcomes. 2019;17(1):160.

Mathias SD, Crosby RD, Zazzali JL, et al. Evaluating the Minimally Important Difference of the Urticaria Activity Score and Other Measures of Disease Activity in Patients with Chronic Idiopathic Urticaria. Ann Allergy Asthma Immunol. 2012;108(1):20-4.

Maurer M, Gimenez-Arnau A, Ensina LF, et al. Chronic Urticaria Treatment Patterns and Changes in Quality of Life: AWARE Study 2-Year Results. World Allergy Organ J. 2020;13(9):100460.

Maurer M, Raap U, Staubach P, et al. Antihistamine-Resistant Chronic Spontaneous Urticaria: 1-Year Data From the AWARE Study. Clin Exp Allergy. 2019;49(5):655-62.

Meixiong J, Anderson M, Limjunyawong N, et al. Activation of Mast-Cell-Expressed Mas-Related G-Protein-Coupled Receptors Drives Non-histaminergic Itch. Immunity. 2019;50(5):1163-71 e5.

Metz M, Krull C, Hawro T, et al. Substance P is Upregulated in the Serum of Patients with Chronic Spontaneous Urticaria. J Invest Dermatol. 2014;134(11):2833-6.

Morita H, Yamamoto K, Kitano Y. Elevation of Serum Major Basic Protein in Patients with Atopic Dermatitis. J Dermatol Sci. 1995;9(3):165-8.

Nakamura Y, Oscherwitz J, Cease KB, et al. Staphylococcus Delta-Toxin Induces Allergic Skin Disease by Activating Mast Cells. Nature. 2013;503(7476):397-401.

Nattkemper LA, Tey HL, Valdes-Rodriguez R, et al. The Genetics of Chronic Itch: Gene Expression in the Skin of Patients with Atopic Dermatitis and Psoriasis with Severe Itch. J Invest Dermatol. 2018;138(6):1311-7.

Ogasawara H, Furuno M, Edamura K, et al. Peptides of Major Basic Protein and Eosinophil Cationic Protein Activate Human Mast Cells. Biochem Biophys Rep. 2020;21:100719.

Quan P, Guo Y, Sabate-Bresco M, et al., editors. Silencing MRGPRX2 in LAD2 Mast Cells Reduces Degranulation Responses Induced In Vitro by Sera from Patients with Chronic Spontaneous Urticaria. European Academy of Allergy and Clinical Immunology Congress; 2022; Prague, Czech Republic.

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York Wiley; 1987.

Serhan N, Basso L, Sibilano R, et al. House Dust Mites Activate Nociceptor-Mast Cell Clusters to Drive Type 2 Skin Inflammation. Nat Immunol. 2019;20(11):1435-43.

Shtessel M, Limjunyawong N, Oliver ET, et al. MRGPRX2 Activation Causes Increased Skin Reactivity in Patients with Chronic Spontaneous Urticaria. J Invest Dermatol. 2021;141(3):678-81 e2.

Subramanian H, Gupta K, Ali H. Roles of MAS-Related G Protein-Coupled Receptor-X2 (MRGPRX2) on Mast Cell-Mediated Host Defense, Pseudoallergic Drug Reactions and Chronic Inflammatory Diseases. J Allergy Clin Immunol. 2016;138(3):700-10.

Thapaliya M, Chompunud Na Ayudhya C, Amponnawarat A, et al. Mast Cell-Specific MRGPRX2: A Key Modulator of Neuro-Immune Interaction in Allergic Diseases. Curr Allergy Asthma Rep. 2021;21(1):3.

Wang Z, Babina M. MRGPRX2 Signals its Importance in Cutaneous Mast Cell Biology: Does MRGPRX2 Connect Mast Cells and Atopic Dermatitis? Exp Dermatol. 2020;29(11):1104-11.

Weller K, Groffik A, Church MK, et al. Development and Validation of the Urticaria Control Test: a Patient-Reported Outcome Instrument for Assessing Urticaria Control. J Allergy Clin Immunol. 2014;133(5):1365-72, 72 e1-6.

Weller K, Groffik A, Magerl M, et al. Development, Validation, and Initial Results of the Angioedema Activity Score. Allergy. 2013;68(9):1185-92.

Weller K, Zuberbier T, Maurer M. Chronic Urticaria: Tools to Aid the Diagnosis and Assessment of Disease Status in Daily Practice. J Eur Acad Dermatol Venereol. 2015;29 Suppl 3:38-44.

Youngblood S, Tomasevic K. Atopic Dermatitis Skin Biopsies Have High Numbers of Activated Mast Cells that are Inhibited by AK002 after Stimulation Ex Vivo. J Allergy Clin Immunol. 2020;145(2):AB198.

Zheng W, Wang J, Zhu W, et al. Upregulated Expression of Substance P in Basophils of the Patients with Chronic Spontaneous Urticaria: Induction of Histamine Release and Basophil Accumulation by Substance P. Cell Biol Toxicol. 2016;32(3):217-28.

Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The International EAACI/GA(2)LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis, and Management of Urticaria. Allergy. 2022;77(3):734-66.

APPENDIX A. SCHEDULE OF ASSESSMENTS

Assessment	**Screening**	**Double-Blind Treatment**			**Safety Follow-Up**	**Early Tx Term**[a]	**Notes**
Visit	**Visit 1**[b]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**[c]		
Study Day	Days -30 to -14	Day 1	Day 22	Day 43	Day 71	≤2 days after last dose	
Study Week		Week 0	Week 3	Week 6	Week 10		
Visit Window	None	None	±3 days	±3 days	±3 days		
Screening or General Assessments							
Informed consent	X						
Medical history	X						Includes CSU disease history.
Height	X						Should be measured using a stadiometer with no shoes.
Body weight	X			X	X	X	Should be measured with no shoes and heavy clothing (outdoor clothing such as coats) on and using a calibrated scale.
HIV, HBV, HCV serology	X						
Eligibility check	X	X					
Randomization		X					In Part 1, subjects will be randomized via IWRS in a 1:1:1 ratio to 50 mg EP262, 150 mg EP262, or placebo. In Part 2, subjects will be randomized via IWRS in a 3:1 ratio to 25 mg EP262 or placebo.
Dispense study drug / administer dose at site		X	X				Administer orally QD as intact capsules with approximately 240 mL (8 fluid ounces) of water on an empty stomach.
Collect study drug / assess study drug accountability and compliance			X	X		X	Subjects will record self-administration of study drug daily in a dosing diary that will be reviewed at each clinic visit during the Double-Blind Treatment Period following Visit 2 by clinical site staff.
Provide electronic device/app training	X						

Assessment	Screening	Double-Blind Treatment			Safety Follow-Up	Early Tx Term[a]	Notes
Visit	**Visit 1**[b]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**[c]		
Study Day	Days -30 to -14	Day 1	Day 22	Day 43	Day 71	≤2 days after last dose	
Study Week		Week 0	Week 3	Week 6	Week 10		
Visit Window	None	None	±3 days	±3 days	±3 days		
Efficacy/Pharmacodynamic Assessments							
UAS	X	X	X	X	X	X	To be completed daily, in the morning before dosing (as applicable),
[redacted]							
Safety Assessments							
Serum pregnancy testing	X						Required for all females.
Urine pregnancy testing		X	X	X	X	X	Required for all females.
Physical examination	X						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.

Assessment	Screening	Double-Blind Treatment			Safety Follow-Up	Early Tx Term[a]	Notes
Visit	**Visit 1**[b]	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**[c]		
Study Day	Days -30 to -14	Day 1	Day 22	Day 43	Day 71	≤2 days after last dose	
Study Week		Week 0	Week 3	Week 6	Week 10		
Visit Window	None	None	±3 days	±3 days	±3 days		
Standard 12-lead ECG	X	X		X	X	X	To be performed predose (as applicable) in a supine position after ≥5 min of rest.
Vital signs	X	X	X	X	X	X	Includes sitting systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate, measured predose (as applicable) after ≥5 min of rest.
Chemistry, hematology, and urinalysis	X	X	X	X	X	X	Drawn after an overnight fast (≥8 hours) and predose (as applicable).
Coagulation	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	Record any prior use of omalizumab. Record all medications taken to treat CSU beginning from the date of diagnosis and all other medications taken within 14 days before Screening. Record any use of rescue medications.
AE assessment	X	X	X	X	X	X	To be documented from the signing of the Informed Consent Form until the end of study participation.
Pharmacokinetic Assessments							
Blood sampling for PK		X	X	X	X	X	Samples will be collected predose as applicable.
Baseline Characterization							
[redacted]							

[redacted]; AE = adverse event; [redacted]; app = application; CSU = chronic spontaneous urticaria; [redacted]e; ECG = electrocardiogram; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IWRS = Interactive Web Response System; PK = pharmacokinetic; QD = once daily; Term = termination; Tx = treatment; UAS = Urticaria Activity Score; [redacted] UGT1A1 = uridine 5'-diphospho-glucuronosyltransferase 1A1.

Subjects should fast for at least 8 hours before study visits that require a blood sample for assessment of clinical chemistry. Water is acceptable in the morning of site visits to ensure the subject is hydrated for laboratory sample collection. Subjects should fast at least 4 hours before administration of each dose of study drug and refrain from eating for at least 2 hours postdose. Each dose of study drug is to be taken with approximately 240 mL (8 fluid ounces) of water on an empty stomach.

[a] Early Treatment Termination Visit: Should be conducted as soon as possible after the last dose of study drug, ideally within 2 days after the last dose of study drug.

[b] Screening: May be conducted over more than 1 day but must be completed between Day -30 and Day -14 (inclusive).

[c] 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.

APPENDIX B. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The Common Terminology Criteria for Adverse Events (CTCAE) is widely accepted as the standard classification and severity grading scale for adverse events in cancer therapy, clinical trials, and other oncology settings. Version 5.0 is the most updated document (November 27, 2017), and may be accessed using the following link:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

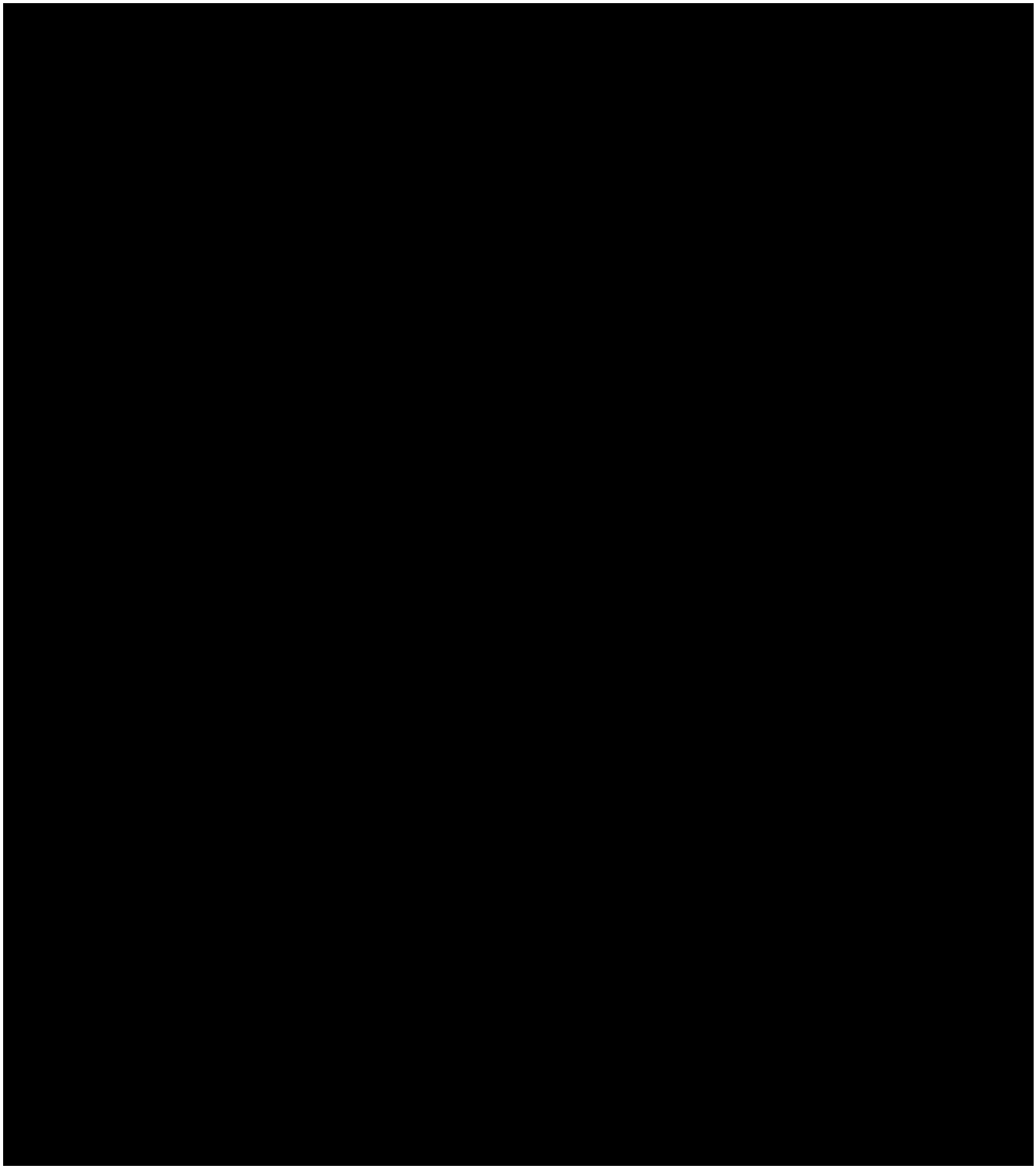
APPENDIX C. URTICARIA ACTIVITY SCORE – EXAMPLE ONLY

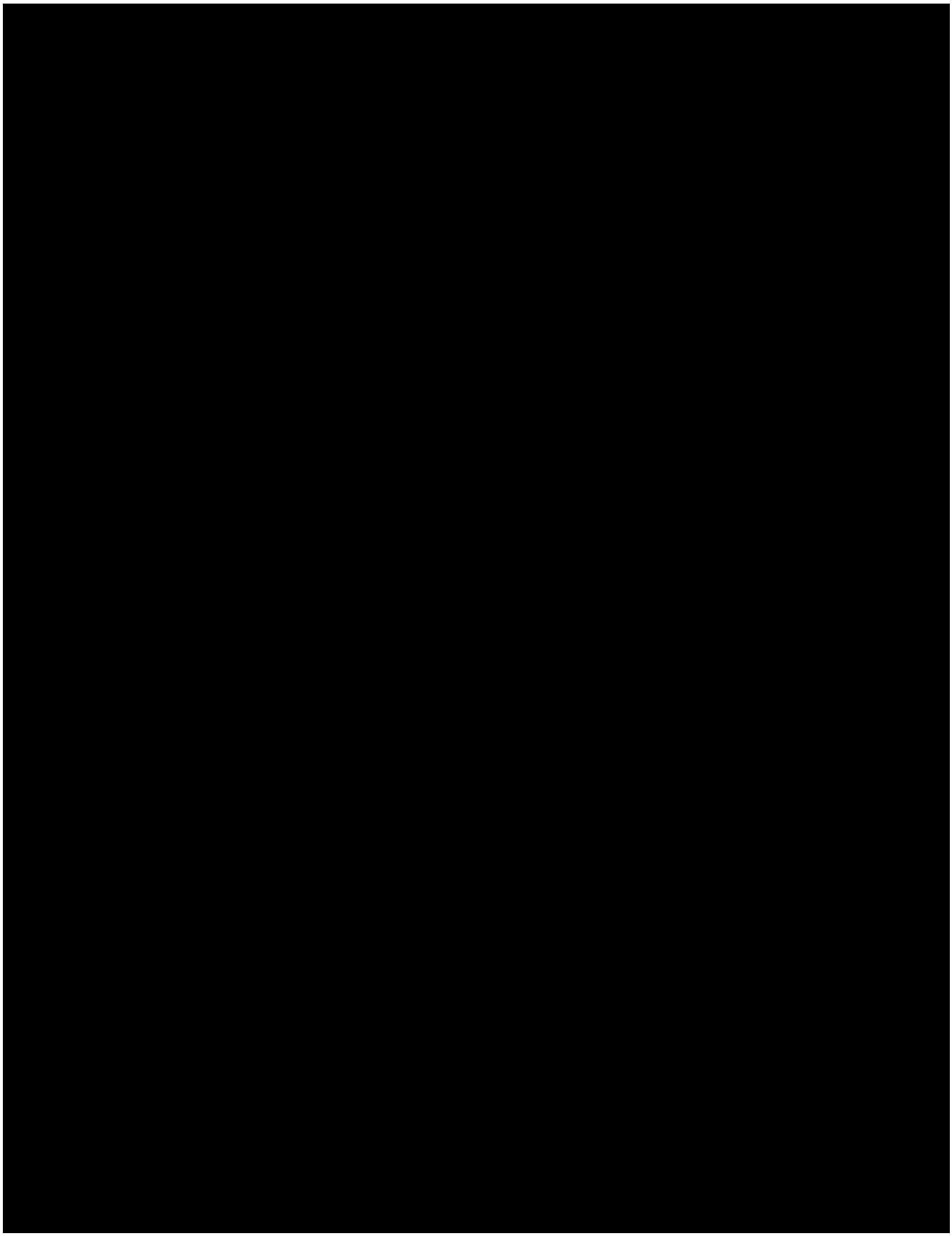
Please select the score that represents the intensity of your itch over the past **24 hours**.

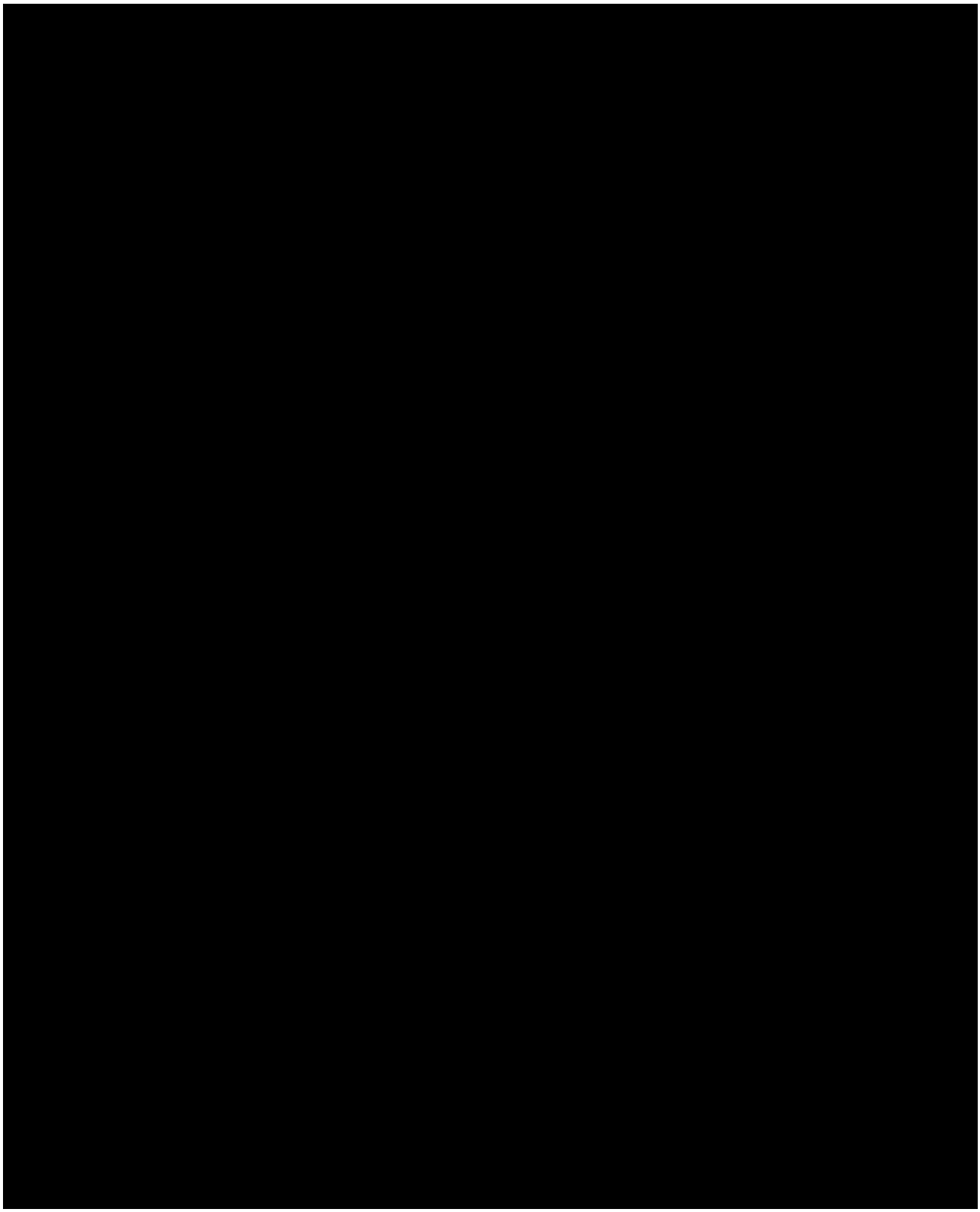
Itch Severity Score	**Itch Severity**
0	None
1	Mild (present but not annoying or troublesome)
2	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (interferes with normal daily activity or sleep)

Please select the score that corresponds to the number of wheals you have had over the past **24 hours**.

Hives Severity Score	**Hives Severity**
0	None
1	<20
2	20-50
3	>50







APPENDIX H. SUMMARY OF CHANGES BY AMENDMENT

Summary of Changes for Amendment 4.0 Dated 26 July 2024

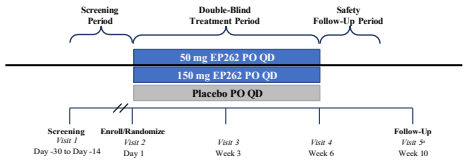
Protocol EP-262-201 has been amended primarily to further characterize the therapeutic dose range. The study will be conducted in 2 parts: Part 1 will assess 50 mg and 150 mg doses of EP262 and Part 2 will assess a 25 mg dose of EP262. Part 2 will begin after the last subject is randomized in Part 1, with approximately 40 subjects randomized in a 3:1 ratio to receive either 25 mg of EP262 or placebo.

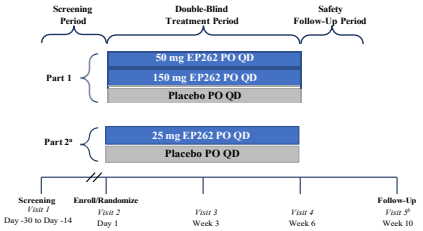
Other changes to the protocol include:

- Correcting the definition of minimal disease activity for UAS7.
- Clarifying that any interim analysis will be optional.
- Updating the name of the Medical Monitor.
- Reflecting that the Sponsor, Escient Pharmaceuticals, Inc., is now a wholly owned subsidiary of the Incyte Corporation.

Notable changes are included below in the summary table. Revised text in Amendment 4.0 is bolded, and text deleted from Amendment 3.0 is crossed out in the table below. Italicized text is used to describe a change. Minor/editorial changes are not listed individually in the summary table.

Section	Amendment 3.0	Amendment 4.0	Reason for Change
Global	*The Sponsor was referred to as Escient Pharmaceuticals, Inc.*	*The Sponsor is now referred to as Escient Pharmaceuticals, Inc., an Incyte company*	Revised to note that Escient Pharmaceuticals, Inc. became a wholly owned subsidiary of the Incyte Corporation.
Title Page	[redacted]		The name of the Medical Monitor was changed to reflect an update in the assignment of responsibilities within the study team.

Section	Amendment 3.0	Amendment 4.0	Reason for Change
Sponsor Statement	[redacted]		The name of the Medical Monitor was changed to reflect an update in the assignment of responsibilities within the study team.
Synopsis, Exploratory Objectives 6 Trial Objectives and Purpose 16.3.3 Exploratory Endpoints	[redacted]		
Synopsis, Methodology 7.1 Overall Study Design	~~The study~~ includes a Screening Period of at least 2 weeks and up to 30 days to assess subject eligibility that includes collection of the daily 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. ~~A~~approximately 114 subjects will be randomized in a 1:1:1 ratio to receive ~~either~~ a 150 mg dose of EP262, 50 mg dose of EP262, or placebo orally (PO), once daily (QD) during the 6-week Double-Blind Treatment Period. Enrollment of subjects with prior omalizumab use will be limited to 15 subjects. EP-262-201 Study Design  PO = oral; QD = once daily.	**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. Part 2 will begin after the last subject is randomized into Part 1. Part 1 and Part 2 are identical in terms of their visit structure, procedures conducted, and the populations being studied. The primary difference between the 2 parts is the EP262 dose levels being assessed.** **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 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. **In Part 1, a**pproximately 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 orally (PO), once daily (QD) during the 6-week	Revised to reflect the addition of Part 2.

Section	Amendment 3.0	Amendment 4.0	Reason for Change
	[a] 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.	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**. **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.	
Synopsis, Double-Blind Treatment Period 7.1.2 Double-Blind Treatment Period	~~S~~subjects will be randomized in a 1:1:1 ratio to receive ~~either~~ a 150 mg dose of EP262, 50 mg dose of EP262, or placebo PO, QD.	**In Part 1, s**ubjects 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.**	Revised to reflect the addition of Part 2.

Section	Amendment 3.0	Amendment 4.0	Reason for Change
Synopsis, Number of Subjects (Planned) 7.4 Number of Subjects	Approximately 114 subjects with CSU will be randomized ~~in the~~ study. Enrollment of subjects with prior omalizumab use will be limited to ~~15~~ subjects.	Approximately **154** subjects with CSU will be randomized **into this** study**. Approximately 114 subjects will be randomized in Part 1 and approximately 40 subjects will be randomized in Part 2.** Enrollment of subjects with prior omalizumab use will be limited to **20** subjects **(15 subjects in Part 1 and 5 subjects in Part 2)**.	Revised to reflect the addition of Part 2.
Synopsis, Study Drug 10.1 Study Drug	~~C~~apsules 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.	**In Part 1, c**apsules 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. **In Part 2, capsules containing 25 mg of EP262 or placebo will be supplied in bottles in a manner to ensure the study blind. Each subject will take 1 capsule per dose.**	Revised to reflect the addition of Part 2.
Synopsis, [redacted] 11.1 [redacted]	Well-controlled urticaria is defined as a [redacted] score ~~<~~6.	Well-controlled urticaria is defined as a [redacted] score ≤6.	Corrected the definition of minimal disease activity for [redacted]
Synopsis, Statistical Methods 16.8 Efficacy and Pharmacodynamic Analysis	Additional analysis comparing placebo and ~~both~~ EP262 doses combined may be performed as appropriate.	**Subjects who receive placebo in Parts 1 and 2 will be pooled for analysis.** Additional analysis comparing placebo and **all** EP262 doses combined may be performed as appropriate.	Revised to reflect the addition of Part 2.
Synopsis, Sample Size Considerations 16.4 Sample Size Considerations	The study will enroll approximately 114 subjects~~,~~ randomized in 1:1:1 ratio to receive 50 mg EP262, 150 mg EP262, or placebo. ~~A~~ sample size of 34 subjects per treatment group will provide 80% power to	The study will enroll approximately **154 subjects.**	Revised to reflect the addition of Part 2.

Section	Amendment 3.0	Amendment 4.0	Reason for Change
	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%. With an estimated early withdrawal rate of approximately 10%, the planned enrollment of 38 subjects per treatment group (50 mg EP262, 150 mg EP262, and placebo) will ensure ~~that at least 34 subjects per treatment group~~ complete the 6-week treatment period.	**In Part 1, approximately** 114 subjects **will be** randomized in **a** 1:1:1 ratio to receive 50 mg EP262, 150 mg 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%.** With an estimated early withdrawal rate of approximately 10%, the planned enrollment of 38 subjects per treatment group (50 mg EP262, 150 mg EP262, and placebo) **in Part 1 and 40 subjects (30 subjects in 25 mg EP262 and 10 subjects in placebo) in Part 2** will ensure **adequate sample size to** complete the 6-week treatment period.	

Section	Amendment 3.0	Amendment 4.0	Reason for Change
5.3 EP262 Dose Rationale	The 150 mg and 50 mg EP262 dose levels to be evaluated in Study EP-262-201 were selected based on a variety of factors to explore efficacy without adversely impacting safety, including results from nonclinical pharmacology studies, nonclinical toxicology studies, and preliminary results from Study EP-262-101, a Phase 1 first in human clinical study in healthy subjects.	The 150 mg and 50 mg EP262 dose levels to be evaluated in **Part 1 of** Study EP-262-201 were selected based on a variety of factors to explore efficacy without adversely impacting safety, including results from nonclinical pharmacology studies, nonclinical toxicology studies, and preliminary results from Study EP-262-101, a Phase 1 first-in-human clinical study in healthy subjects.	Revised to reflect the addition of Part 2.
5.3 EP262 Dose Rationale	Thus, it ~~is~~ assumed that EP262 trough concentrations of 2000 nM or higher will likely be necessary for maximum clinical efficacy. Consequently, Study EP-262-201 ~~will~~ assess 2 dose levels:	Thus, it **was** assumed that EP262 trough concentrations of [redacted] nM or higher will likely be necessary for maximum clinical efficacy. Consequently, **Part 1 of** Study EP-262-201 **was designed to** assess 2 dose levels:	Revised to reflect the addition of Part 2.
5.3 EP262 Dose Rationale	*New text.*	**To further characterize the therapeutic dose range, Part 2 was added to the protocol to evaluate a lower 25 mg EP262 dose level. The 25 mg dose level will target EP262 trough concentrations between [redacted] and [redacted] nM. Pharmacologic activity from this lower dose is expected to widen the span for the exposure-response relationship when analyzed with the responses from the higher dose levels, thus enhancing the calculation of the therapeutic dose range.**	Revised to reflect the addition of Part 2.
9.1 Treatment Assignment	~~A~~pproximately 114 subjects will be randomized in a 1:1:1 ratio to receive ~~either~~ a 50 mg dose of EP262, 150 mg dose of EP262, or placebo PO, QD during the 6-week Double-Blind Treatment Period.	**In Part 1, a**pproximately 114 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 during the 6-week Double-Blind Treatment Period. **In Part 2 of the study, approximately 40 subjects will be randomized in a**	Revised to reflect the addition of Part 2.

Section	Amendment 3.0	Amendment 4.0	Reason for Change
		3:1 ratio to receive either a 25 mg dose of EP262 or placebo PO, QD, during the 6-week Double-Blind Treatment Period.	
9.3.1 Randomization	~~S~~ubjects will be randomized in a 1:1:1 ratio to receive ~~either~~ a 50 mg dose of EP262, 150 mg dose of EP262, or placebo PO, QD for 6 weeks during the Double-Blind Treatment Period ~~beginning at Visit 2 (Day 1)~~.	**Beginning at Visit 2 (Day 1), s**ubjects 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.	[redacted]
9.3.1 Randomization	The master randomization list will be kept secured until the study blind is broken ~~at the end of study~~.	**Separate randomization lists will be utilized for each part of the study.** The master randomization list**s** will be kept secured until the study blind is broken **as specified in the study-specific blinding and unblinding plan**.	[redacted]
9.4.2.1 Visit 2 (Day 1) – Enrollment and Randomization	• Randomization to 50 mg EP262, 150 mg EP262, or placebo in a 1:1:1 ratio ~~via IWRS~~	• Randomization to **study drug treatment assignment via IWRS:** - **Part 1:** 50 mg EP262, 150 mg EP262, or placebo in a 1:1:1 ratio [redacted]	[redacted]
16.13 Interim Analysis	Given the hypothesis-generating nature of this study, an interim analysis may be conducted to support business needs.	Given the hypothesis-generating nature of this study, an **optional** interim analysis may be conducted to support business needs.	Added to clarify the nature of the interim analysis.
Appendix A Schedule of Assessments *(Randomization row)*	~~S~~ubjects will be randomized via IWRS in a 1:1:1 ratio to 50 mg EP262, 150 mg EP262, or placebo.	**In Part 1, s**ubjects will be randomized via IWRS in a 1:1:1 ratio to 50 mg EP262, 150 mg EP262, or placebo. [redacted]	[redacted]

Summary of Changes for Amendment 3.0 Dated 05 April 2024

Protocol EP-262-201 was amended to extend (from 60 days to 84 days [12 weeks]) the duration after the last dose of study drug during which subjects with reproductive capability are restricted from egg/sperm donation and are to use acceptable forms of contraception. This modification is based on preliminary trends in emerging EP262 pharmacokinetic data from the ongoing clinical studies. The extension will remain in effect as a safety precaution until results from definitive reproductive and development toxicity studies of EP262 are available.

This protocol amendment also includes an update regarding excluded medications and clarifies that only female subjects with a negative serum pregnancy test at Screening are eligible for participation in the study.

Notable changes are included below in the summary table. Revised text in Amendment 3.0 is bolded, and text deleted from Amendment 2.0 is crossed out in the table below. Italicized text is used to describe a change. Minor/editorial changes are not listed individually in the summary table.

Section	Amendment 2.0	Amendment 3.0	Reason for Change
Synopsis, Inclusion Criteria 8.1. Subject Inclusion Criteria	6. If female, have a negative serum pregnancy test at Screening[4]**,** be willing to not donate eggs from Screening until ~~60 days~~ after the last dose of study drug, and: a. Is surgically sterile; or b. Has been amenorrhoeic for ≥1 year without an alternative medical cause; or c. If of childbearing potential[5], must agree to use 2 forms of contraception, which includes at least 1 form of highly effective and 1 effective method[6] of contraception from Screening until ~~60 days~~ after the last dose of study drug. [4] ~~In instances when a serum pregnancy test result is confirmed to be indeterminate, the result should be discussed with the Escient medical team and interpreted by the Investigator using clinical judgment; it should not automatically result in screen failure.~~	6. If female, **must** have a negative serum pregnancy test at Screening**,** be willing to not donate eggs from Screening until **12 weeks** after the last dose of study drug, and: a. Is surgically sterile; or b. Has been amenorrhoeic for ≥1 year without an alternative medical cause; or c. If of childbearing potential[3], must agree to use 2 forms of contraception, which includes at least 1 form of highly effective and 1 effective method[4] of contraception from Screening until **12 weeks** after the last dose of study drug.	Modified the duration after the last dose of study drug during which subjects with reproductive capability are restricted from egg/sperm donation and are to use acceptable forms of contraception based on preliminary trends in emerging EP262 pharmacokinetic data from the ongoing clinical studies. To clarify that only female subjects with a negative serum pregnancy test at Screening are eligible for participation in the study.

Section	Amendment 2.0	Amendment 3.0	Reason for Change
Synopsis, Inclusion Criteria 8.1. Subject Inclusion Criteria	7. If male and is not confirmed surgically sterile, must be willing to not donate sperm and must agree to use a barrier method of contraception (eg, condom with spermicide) during intercourse and at least 1 other acceptable contraceptive measure for his female partner(s) (eg, hormonal contraceptives, intrauterine device, female surgical sterilization, abstinence) from Screening through ~~60 days~~ after the last dose of study drug	7. If male and is not confirmed surgically sterile, must be willing to not donate sperm and must agree to use a barrier method of contraception (eg, condom with spermicide) during intercourse and at least 1 other acceptable contraceptive measure for his female partner(s) (eg, hormonal contraceptives, intrauterine device, female surgical sterilization, abstinence) from Screening through **12 weeks** after the last dose of study drug	Modified the duration after the last dose of study drug during which subjects with reproductive capability are restricted from egg/sperm donation and are to use acceptable forms of contraception based on preliminary trends in emerging EP262 pharmacokinetic data from the ongoing clinical studies.
Synopsis, Exclusion Criteria 8.2. Subject Exclusion Criteria	4. Use of the following prohibited treatments: a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), ~~fluoroquinolones (eg, ciprofloxacin, levofloxacin),~~ vancomycin, ~~certain antidepressants/antipsychotics/antispasmodics (eg, paroxetine, clozapine, benztropine),~~ or nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium) within 14 days before Screening	4. Use of the following prohibited treatments: a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), vancomycin, **clomipramine,** or nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium) within 14 days before Screening	Revised the list of excluded agonists at the MRGPRX2 receptor based on emerging data to remove those that are weak agonists of MRGPRX2.

Summary of Changes for Amendment 2.0 Dated 11 March 2024

Protocol EP-262-201 was amended to address the following changes:

- Increase the number of subjects participating in the study from 90 to 114
- Provide guidance regarding confirmed indeterminant pregnancy test results at Screening
- Update excluded medications
- Update the time to reach the maximum observed concentration and half-life of EP262 based on results from Study EP-262-101
- Update text to better reflect how the [redacted] will be administered for this study

Notable changes are included below in the summary table. Revised text in Amendment 2.0 is bolded, and text deleted from Amendment 1.0 is crossed out in the table below. Italicized text is used to describe a change. Minor/editorial changes are not listed individually in the summary table.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
Synopsis, Methodology 7.1. Overall Study Design	Approximately ~~90~~ subjects will be randomized in a 1:1:1 ratio to receive either a 150 mg dose of EP262, 50 mg dose of EP262, or placebo PO, once daily (QD) during the 6-week Double-Blind Treatment Period. Enrollment of subjects with prior omalizumab use will be limited to ~~12~~ subjects.	Approximately **114** subjects will be randomized in a 1:1:1 ratio to receive either a 150 mg dose of EP262, 50 mg dose of EP262, or placebo PO, once daily (QD) during the 6-week Double-Blind Treatment Period. Enrollment of subjects with prior omalizumab use will be limited to **15** subjects.	In recent studies evaluating Bruton's tyrosine kinase inhibitors, a key class of competitor compounds, placebo-corrected UAS7 reductions of <9 was observed. Thus, the effect size was decreased for the sample size calculation and the number of subjects allowed to participate in the study was increased.
Synopsis, Number of Subjects (Planned) 7.4. Number of Subjects	Approximately ~~90~~ subjects with CSU will be randomized in the study. Enrollment of subjects with prior omalizumab use will be limited to ~~12~~ subjects.	Approximately **114** subjects with CSU will be randomized in the study. Enrollment of subjects with prior omalizumab use will be limited to **15** subjects.	In recent studies evaluating Bruton's tyrosine kinase inhibitors, a key class of competitor compounds, placebo-corrected UAS7 reductions of <9 was observed. Thus, the effect size was decreased for the sample size calculation and the number of subjects allowed to participate in the study was increased.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
Synopsis, Inclusion Criteria 8.1 Subject Inclusion Criteria	6. If female, ~~must~~ have a negative serum pregnancy test at Screening ~~and~~ be willing to not donate eggs from Screening until 60 days after the last dose of study drug and:	6. If female, have a negative serum pregnancy test at Screening**[4],** be willing to not donate eggs from Screening until 60 days after the last dose of study drug**,** and: **[4] In instances when a serum pregnancy test result is confirmed to be indeterminate, the result should be discussed with the Escient medical team and interpreted by the Investigator using clinical judgment; it should not automatically result in screen failure.**	Guidance was provided to potentially allow women with a confirmed indeterminate result the opportunity to participate in the study, based on the Investigator's clinical judgement. For instance, an indeterminant pregnancy test result in a surgically sterile or postmenopausal subject would not necessarily result in her inability to participate in the study.
Synopsis, Exclusion Criteria 8.2 Subject Exclusion Criteria	4. Use of the following prohibited treatments: a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), fluoroquinolones (eg, ciprofloxacin, levofloxacin), vancomycin, certain antidepressants/antipsychotics/ antispasmodics (eg, ~~doxepin,~~ paroxetine, clozapine, benztropine), or nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium)within 14 days before Screening	4. Use of the following prohibited treatments: a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), fluoroquinolones (eg, ciprofloxacin, levofloxacin), vancomycin, certain antidepressants/antipsychotics/ antispasmodics (eg, paroxetine, clozapine, benztropine), or nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium) within 14 days before Screening	Doxepin was removed from the list of example antidepressants/ antipsychotics/antispasmodics given that it is a very weak agonist with a C_{max} below the concentration needed to activate MRGPRX2.
Synopsis, Urticaria Control Test Over a 7-Day Period (UCT7) 11.2. Urticaria Control Test Over a 7-Day Period (UCT7) Appendix A. Schedule of Assessments (*UCT7 row*)	For entries that coincide with ~~a study visit, the questionnaire is to be completed in the morning before the visit~~.	For entries that coincide with **Visit 2 (Day 1), Visit 4 (Week 6), and Visit 5 (Week 10), and the Early Treatment Termination Visit (if applicable), the questionnaire is to be completed in the morning at study visits before other procedures are performed**.	The text was updated to better reflect how the UCT7 will be administered for this study.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
Synopsis, Sample Size Considerations 16.4. Sample Size Considerations	The study will enroll approximately ~~90~~ subjects, randomized in 1:1:1 ratio to receive 50 mg EP262, 150 mg EP262, or placebo. A sample size of ~~27~~ subjects per treatment group will provide 80% power to detect ~~a 9~~-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%. With an estimated early withdrawal rate of approximately 10%, the planned enrollment of ~~30~~ subjects per treatment group (50 mg EP262, 150 mg EP262, and placebo) will ensure that at least ~~27~~ subjects per treatment group complete the 6-week treatment period.	The study will enroll approximately **114** subjects, randomized in 1:1:1 ratio to receive 50 mg EP262, 150 mg EP262, or placebo. 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%. With an estimated early withdrawal rate of approximately 10%, the planned enrollment of **38** subjects per treatment group (50 mg EP262, 150 mg EP262, and placebo) will ensure that at least **34** subjects per treatment group complete the 6-week treatment period.	In recent studies evaluating Bruton's tyrosine kinase inhibitors, a key class of competitor compounds, placebo-corrected UAS7 reductions of <9 was observed. Thus, the effect size was decreased for the sample size calculation and the number of subjects allowed to participate in the study was increased.
5.2. EP262 and Study Rationale	The time to reach the maximum EP262 observed concentration (T_{max}) was achieved on average at approximately [redacted] hours postdose with a half-life ($t_{1/2}$) of approximately [redacted] hours, driven by [redacted]	The time to reach the maximum EP262 observed concentration (T_{max}) was achieved on average at approximately [redacted] hours postdose with a half-life ($t_{1/2}$) of approximately [redacted] hours **for the [redacted] mg dose**, driven by [redacted]	The time to reach the maximum observed concentration and half-life of EP262 was updated based on results from Study EP-262-101.
9.1. Treatment Assignment	Approximately ~~90~~ subjects will be randomized in a 1:1:1 ratio to receive either a 50 mg dose of EP262, 150 mg dose of EP262, or placebo PO, QD during the 6-week Double-Blind Treatment Period.	Approximately **114** subjects will be randomized in a 1:1:1 ratio to receive either a 50 mg dose of EP262, 150 mg dose of EP262, or placebo PO, QD during the 6-week Double-Blind Treatment Period.	In recent studies evaluating Bruton's tyrosine kinase inhibitors, a key class of competitor compounds, placebo-corrected UAS7 reductions of <9 was observed. Thus, the effect size was decreased for the sample size calculation and the number of subjects allowed to participate in the study was increased.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
9.4.1.1. Visit 1 (Day -30 to Day -14 [inclusive])	For all other days that coincide with a study visit (for Visit 2 and beyond), the questionnaires are to be completed in the morning before the visit.	For all other days that coincide with a study visit (for Visit 2 and beyond), the questionnaires are to be completed in the morning before the visit**, unless specified otherwise**.	The text was updated to better reflect how the UCT7 will be administered for this study.
9.4.2.1. Visit 2 (Day 1) – Enrollment and Randomization	The following assessments will be performed during Visit 2 (Day 1): • Complete [redacted] • Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 2 (Day 1) • ~~Confirm that the [redacted] was completed the morning of Visit 2 (Day 1)~~	The following assessments will be performed during Visit 2 (Day 1): • Complete [redacted] • Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 2 (Day 1)	The text was updated to better reflect how the [redacted] will be administered for this study.
9.4.2.2. Visit 3 (Week 3)	The following assessments will be performed during Visit 3 (Week 3): • Complete [redacted] • Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 3 (Week 3) • Confirm that the [redacted] was completed weekly from the last visit through ~~the morning of~~ Visit 3 (Week 3)	The following assessments will be performed during Visit 3 (Week 3): • Complete [redacted] • Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 3 (Week 3) • Confirm that the [redacted] was completed weekly from the last visit through Visit 3 (Week 3)	The text was updated to better reflect how the [redacted] will be administered for this study.
9.4.2.3. Visit 4 (Week 6)	The following assessments will be performed during Visit 4 (Week 6): • Complete [redacted] • Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 4 (Week 6) • Confirm that the [redacted] was completed weekly from the last visit through ~~the morning of Visit 4 (Week 6)~~	The following assessments will be performed during Visit 4 (Week 6): • Complete [redacted] • Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 4 (Week 6) • Confirm that the [redacted] was completed weekly from the last visit through **Week 5**	The text was updated to better reflect how the [redacted] will be administered for this study.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
9.4.3.1. Visit 5 (Week 10)	The following assessments will be performed during the Safety Follow-Up Visit, approximately 4 weeks after the last dose of study drug: • Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 5 (Week 10) • Confirm that the [redacted] was completed weekly from the last visit through ~~the morning of Visit 5 (Week 10)~~	The following assessments will be performed during the Safety Follow-Up Visit, approximately 4 weeks after the last dose of study drug: • Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of Visit 5 (Week 10) • Confirm that the [redacted] was completed weekly from the last visit through **Week 9**	The text was updated to better reflect how the [redacted] will be administered for this study.
9.4.4. Early Treatment Termination Visit	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 following assessments will be performed during the Early Treatment Termination Visit: • Complete [redacted] • Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of the Early Treatment Termination Visit • Confirm that the [redacted] was completed weekly from the last visit through the ~~morning of the~~ Early Treatment Termination Visit	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 following assessments will be performed during the Early Treatment Termination Visit: • Complete [redacted] • Confirm that the UAS and [redacted] were completed daily from the last visit through the morning of the Early Treatment Termination Visit • Confirm that the [redacted] was completed weekly from the last visit through the Early Treatment Termination Visit	The text was updated to better reflect how the [redacted] will be administered for this study.

Summary of Changes for Amendment 1.0 Dated 29 November 2023

Protocol EP-262-201 was amended to address the following changes:

- Clarify the mandatory reasons for study termination, discontinuation of study drug, and discontinuation from the study
- Exclude the use of nondepolarizing neuromuscular blocking agents that are agonists at the MRGPRX2 receptor
- Add a list of permitted medications
- Provide a rationale for conducting an interim analysis
- Clarify that only the use of antidepressants/antipsychotics/antispasmodics that are agonists at the MRGPRX2 receptor are excluded
- Add glucose to the chemistry panel, remove urine albumin from the urinalysis panel, and clarify that dipsticks will not be used for urinalysis
- Reword the precautions regarding sun exposure
- Expand the recording of medications to include those taken to treat CSU beginning from the date of diagnosis
- Revised the study day associated with the Week 10 visit from Day 69 to Day 71
- Introduce the study acronym CALM-CSU

Notable changes are included below in the summary table. Revised text in Amendment 1.0 is bolded, and text deleted from the original version is crossed out in the table below. Italicized text is used to describe a change. Minor/editorial changes are not listed individually in the summary table.

Section	Original	Amendment 1.0	Reason for Change
Title page Sponsor Statement	*New text*	**Study Acronym: CALM-CSU**	The study acronym was added to further denote the study title.

Section	Original	Amendment 1.0	Reason for Change
Synopsis, Exclusion Criteria 8.2 Subject Exclusion Criteria	4. Use of the following prohibited treatments: a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), fluoroquinolones (eg, ciprofloxacin, levofloxacin), vancomycin, ~~or~~ antidepressants/antipsychotics/ antispasmodics (eg, doxepin, paroxetine, clozapine, benztropine) within 14 days before Screening	4. Use of the following prohibited treatments: a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), fluoroquinolones (eg, ciprofloxacin, levofloxacin), vancomycin, **certain** antidepressants/antipsychotics/ antispasmodics (eg, doxepin, paroxetine, clozapine, benztropine)**, or nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium)** within 14 days before Screening	Revised to clarify that only the use of antidepressants/antipsychotics/ antispasmodics that are agonists at the MRGPRX2 receptor are excluded. Nondepolarizing neuromuscular blocking agents are also agonists of the MRGPRX2 receptor and were added for completeness.
5.4.2 Risk Summary	[redacted]		
5.4.3 Mitigation Strategy			

Section	Original	Amendment 1.0	Reason for Change
7.6 Criteria for Study Termination	The Sponsor ~~may~~ terminate the study at a clinical site at any time ~~(eg,~~ Good Clinical Practice ~~[~~GCP~~]~~ noncompliance ~~or p~~oor study data quality~~).~~ The entire study may also be terminated by the Sponsor or at the request of a regulatory agency, IRB, or IEC.	The Sponsor **reserves the right to** terminate the study at a clinical site at any time **for any reason at the sole discretion of the Sponsor. Potential reasons for closure of a clinical site include but are not limited to:** • Good Clinical Practice **(**GCP**)** noncompliance • **P**oor study data quality **The entire study will be terminated by the Sponsor should new information become available resulting in a clearly negative benefit/risk balance.** The entire study may also be terminated by the Sponsor **for other reasons** or at the request of a regulatory agency, IRB or IEC.	Revised to include a clearly negative benefit/risk balance as a reason for study termination.
8.3 Study Restrictions	[redacted]		
8.4. Concomitant Medications	*New text*	**In addition, all medications taken to treat CSU beginning from the date of diagnosis should also be recorded.**	Added to collect more information about the study population.
8.5.3 Permitted Medications	*New text*	**8.5.3. Permitted Medications** **Allowed second generation H1AH include bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and rupatadine. Additional H1A1 not listed above may be permitted at the discretion of the Medical Monitor.**	A list of permitted medications was added for completeness.

Section	Original	Amendment 1.0	Reason for Change
8.6.1 Discontinuation of Study Drug	~~S~~study drug ~~may be discontinued~~ in the following instances: • AE • Withdrawal of consent • Lost to follow-up • Protocol deviation • Investigator decision • Sponsor decision • Pregnancy during the study (Section 12.2.3) • ~~Other~~ ~~If a subject experiences an AE that is Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 or higher, the study drug must be discontinued. AE grading for severity using CTCAE criteria is described in Section 12.1.2.~~	**Discontinuation of s**tudy drug **for a subject occurs when the study drug is stopped earlier than the protocol planned treatment duration. Discontinuation of study drug is mandatory** in the following instances: • AE**s for which continued exposure to study drug would be detrimental, including AEs that are Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 or higher (Section 12.1.2)** • **Abnormal liver laboratory results meeting the threshold for discontinuation as listed in Section 12.10.3** • Withdrawal of consent • Lost to follow-up • Protocol deviation **that results in a significant risk to the subject's safety** • Investigator decision • Sponsor decision • Pregnancy during the study (Section 12.2.3) • **Any circumstance that results in a negative benefit:risk balance**	Clarified the circumstances that will require mandatory discontinuation of study drug.
8.6.2 Discontinuation from the Study	~~Subjects may discontinue~~ from the study ~~at any time for any of~~ the following reasons:	**Discontinuation** from the study **is mandatory** for the following reasons:	Clarified the circumstances that will require mandatory discontinuation from the study.
9.4.1.1 Visit 1 (Day -30 to Day -14 [inclusive])	• Assessment of baseline concomitant medications, including any prior use of omalizumab and all medications taken within 14 days before Screening	• Assessment of baseline concomitant medications, including **all medications taken to treat CSU beginning from the date of diagnosis,** any prior use of omalizumab**,** and all medications taken within 14 days before Screening	Added to collect more information about the study population.

Section	Original	Amendment 1.0	Reason for Change
12.8 Laboratory Evaluations of Safety	• Chemistry: sodium, albumin, alkaline phosphatase (ALP), bicarbonate, calcium, corrected calcium, chloride, bilirubin (total, indirect, and direct), AST, ALT, blood urea nitrogen, urea, creatinine, magnesium, phosphorus, potassium, creatine phosphokinase, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, lactate dehydrogenase, gamma-glutamyltransferase, and total protein	• 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-glutamyltransferase, and total protein	Added glucose to the chemistry panel for completeness and to increase the robustness of safety screening and monitoring.
12.8 Laboratory Evaluations of Safety	• Urinalysis ~~(dipstick)~~: leukocyte esterase, nitrites, pH, protein, specific gravity, glucose, occult blood, ketones, bilirubin, urobilinogen~~, and albumin~~; microscopic analysis is to be performed only if protein, leukocyte esterase, blood or nitrite is positive	• 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	Corrected text to accurately reflect that dipsticks will not be used for urinalysis. Albumin is not a standard measure in urinalysis and not required for the safety evaluations in this study.
16.13 Interim Analysis	16.13 ~~Planned~~ Interim Analysis Given the hypothesis-generating nature of this study, an interim analysis may be conducted.	16.13 Interim Analysis Given the hypothesis-generating nature of this study, an interim analysis may be conducted **to support business needs**.	Added a rationale for why an interim analysis may be conducted.
Appendix A. Schedule of Assessments *(Study Day Row)*	Day ~~69~~	Day **71**	Day 71 is a more accurate study day than Day 69 for the Week 10 visit.
Appendix A Schedule of Assessments *(Concomitant medications row)*	Record any prior use of omalizumab. Record all medications taken within 14 days before Screening.	Record any prior use of omalizumab. Record all medications **taken to treat CSU beginning from the date of diagnosis and all other medications** taken within 14 days before Screening.	Added to collect more information about the study population.