Official Title: Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of EP262 in Subjects with Atopic Dermatitis

NCT Number: NCT06144424

Document Date: EP-262-202 Protocol, Amendment 4.0 (05 April 2024)

1. TITLE PAGE

Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of EP262 in Subjects with Atopic Dermatitis

Study Acronym:	EASE
Protocol Number:	EP-262-202
IND Number:	166101
Protocol Version Number:	Amendment 4.0
Issue Date:	05 April 2024
Drug Development Phase:	Phase 2a
Sponsor:	Escient Pharmaceuticals, Inc. 10578 Science Center Drive, Suite 250 San Diego, CA 92121 USA Phone/Fax: +1 (858) 617-8220

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Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of EP262 in Subjects with Atopic Dermatitis

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Sponsor Statement

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

[redacted], MD
[redacted]
Escient Pharmaceuticals, Inc.

Date

[redacted], PhD
[redacted] of Clinical Development
Escient Pharmaceuticals, Inc.

Date

[redacted], MS
[redacted], Biometrics and Data Analytics
Escient Pharmaceuticals, Inc.

Date

Investigator's Agreement

I have read the protocol for EP-262-202 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	05 April 2024
Amendment 3.1	Regional (Canada)	10 March 2024
Amendment 3.0	Global	10 March 2024
Amendment 2.1	Regional (Canada)	14 November 2023
Amendment 2.0	Global	19 October 2023
Amendment 1.1	Regional (Canada)	10 October 2023
Amendment 1.0	Global	02 August 2023
Original Protocol	Not applicable	07 July 2023

2. Synopsis

Name of Sponsor/Company: Escient Pharmaceuticals, Inc.	
Name of Investigational Product: EP262 oral capsules	
Study Number: EP-262-202	**Phase of Development:** Phase 2a
Title of Study: Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of EP262 in Subjects with Atopic Dermatitis	
Study Center(s): Multi-center within North America	

Objectives	Endpoints
Primary Objective	
To evaluate the safety and tolerability of EP262 compared to placebo in subjects with atopic dermatitis (AD)	• Type, frequency, and severity of treatment-emergent adverse events (TEAEs) • Change from baseline in vital signs, electrocardiograms (ECGs), and clinical laboratory parameters
Secondary Objectives	
To evaluate the pharmacodynamic (PD) effects of EP262 compared to placebo in subjects with AD on skin biopsy-derived biomarkers	• Change from baseline to Week 6 in gene expression signature and skin histology (epidermal thickness, immune cell infiltration, markers of epidermal proliferation) as assessed from biopsies of lesional skin
Exploratory Objectives	
[redacted]	

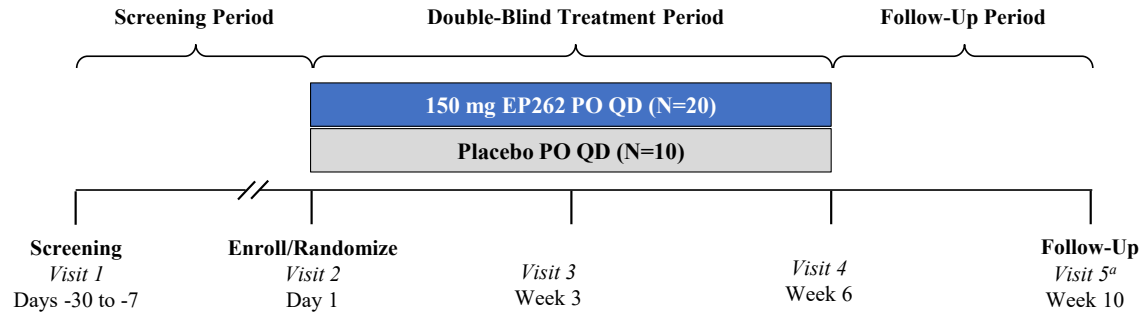
[redacted]

Methodology:

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

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

EP-262-202 Study Design



PO = oral; QD = once daily.

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

Screening Period

The Screening Period will consist of one visit (Visit 1). During this period, subjects will undergo assessments to determine study eligibility per inclusion and exclusion criteria. Visit 1 may be conducted over more than 1 day but must be completed between Day -30 and Day -7 (inclusive) to allow for collection of a baseline average PP-NRS score. Subjects are to use a protocol-permitted, non-urea-containing emollient on lesional and nonlesional skin daily for at least 1 week before Day 1 and agree to continue using that same emollient daily at the same frequency (ideally once or twice daily) throughout the study. Subjects will record emollient use in a daily diary throughout the study.

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), in a 2:1 ratio, to receive double-blind, PO, QD 150 mg doses of EP262 or placebo for 6 weeks. Randomization will be conducted centrally via an Interactive Web Response System (IWRS). 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.

Follow-Up Period

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

Number of Subjects (Planned):

Approximately 30 subjects with AD will be randomized in the study.

Main Criteria for Inclusion and Exclusion:

Subjects who do not meet the criteria for participation in this study (screen failure) may be rescreened once, if deemed acceptable by the Investigator. 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. Clinically confirmed diagnosis of active AD, according to Hanifin and Rajka criteria (Hanifin 1980), for at least 1 year, with a BSA of AD involvement of 3% to 20% (excluding palms, soles, and scalp) and a vIGA-AD score of ≥3 at Screening and Day 1. Subject should have had no significant flares in AD for at least 4 weeks before Screening (based on review of the medical chart or directly from the subject)
2. Has been using a protocol-permitted, non-urea-containing emollient on lesional and nonlesional skin daily for at least 1 week before Day 1 and agrees to continue using that same emollient daily at the same frequency (ideally once or twice daily) throughout the study
3. Aged 18 to 80 years, inclusive, at the time of consent
4. 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

[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).

- 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

5. 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
6. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study, and understand and provide written consent

<u>Exclusion Criteria</u>

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

1. Other active skin diseases associated with chronic pruritus that might confound the study evaluations and results (eg, urticaria, bullous pemphigoid, prurigo nodularis, dermatitis herpetiformis)
2. Clinically infected AD that requires antibiotic therapy
3. Tattoos or any other markings on any area of the body that might confound the study evaluations and results
4. History of an allergic reaction or significant hypersensitivity to lidocaine or other local anesthetics
5. History of hypertrophic scarring or keloid formation in scars or suture sites or has a contraindication to skin biopsies
6. Use of the following prohibited AD treatments:
    a. Dupilumab within 26 weeks before Day 1. Other monoclonal antibodies within 4 months or 5 half-lives (whichever is longer) before Day 1
    b. Systemic medications that could affect AD, such as retinoids, calcineurin inhibitors, hydroxycarbamide (hydroxyurea), azathioprine, systemic corticosteroids, oral janus kinase (JAK) inhibitors, hydroxychloroquine, methotrexate, mycophenolate, cyclosporine, or cyclophosphamide within 4 weeks before Day 1
    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed
    c. Phototherapy (ie, ultraviolet B [UVB], ultraviolet A [UVA]) or sublingual immunotherapy within 4 weeks before Day 1
    d. Topical medications that could affect AD, including corticosteroids, calcineurin inhibitors, JAK inhibitors, antibiotics and other antimicrobials, products containing urea, or phosphodiesterase inhibitors, within 1 week before Day 1. Topical antibiotics may be allowed at the skin punch biopsy site only, at the discretion of the Investigator
    e. Systemic antibiotics within 2 weeks before Day 1
    f. Hydroxyzine or diphenhydramine within 1 week before Day 1
    g. Bleach baths within 2 weeks before Day 1 or planned use during the study

h. Has had excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1 or is not willing to minimize natural and artificial sunlight exposure during the study

7. Use of the following prohibited medications within 2 weeks before Day 1:
    a. Drugs that are agonists at the mas-related G protein-coupled receptor X2 (MRGPRX2) receptor, including icatibant, opioids (eg, codeine, morphine), clomipramine, or nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium)
    b. Drugs that inhibit uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1) (eg, atazanavir, canagliflozin, pazopanib, regorafenib, sorafenib, tranilast)
    c. [redacted]
    d. [redacted]
8. 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
9. 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
10. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect subject safety
11. 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
12. 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
13. 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
14. Significant history of abuse of drugs, solvents, or alcohol within the past year
15. Participation in any clinical study with an investigational or approved drug/device within 30 days or 5 half-lives (whichever is longer) before Day 1 or is planning to participate in another clinical study while enrolled in this study
16. History of known or suspected hypersensitivity to any component of study drug
17. Female who is pregnant, nursing, or intends to become pregnant during the study
18. Had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study
19. 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

20. Is employed by Escient Pharmaceuticals, Inc., (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 Escient Pharmaceuticals, Inc.
21. Subject is, in the opinion of the Investigator, not suitable to participate in the study

Study Drug Materials and Management:

Study Drug

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

Study Drug Packaging and Labeling

Study drug will be packaged into bottles with child-resistant caps, induction sealed, 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, which will be reviewed by clinical site staff at each clinic visit during the Double-Blind Treatment Period following Visit 2.

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 during 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 Safety, Pharmacokinetic, Pharmacodynamic, and Baseline Characterization Assessments:

At specific visits outlined in the Schedule of Assessments (Appendix A), subjects will undergo 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 PD and safety, but not PK measures) will participate in the Follow-Up Visit if the last dose of study drug was administered less than 4 weeks before Visit 4 (Week 6) to ensure that at least 4 weeks of follow-up data are collected for all randomized subjects.

If a subject discontinues study drug and chooses not to complete all of the remaining study visits, the subject should have the Early Treatment Termination Visit conducted as soon as possible after the last dose of study drug, ideally within 2 days after the last dose of study drug, and a Follow-Up Visit approximately 4 weeks (±3 days) after the last dose of study drug if at least 4 weeks of follow-up data have not already been collected. If a subject fails to attend the 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

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

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.

Pharmacodynamic Assessments

Skin swabs, skin sample collection via skin tape strips, skin biopsies, [redacted] and photographs of AD lesions and sites for skin swabs, skin tape strips application, and biopsies will be performed as indicated in the Schedule of Assessments (Appendix A). It is preferred that the skin swab, tape strips, and biopsies (if applicable) come from the same lesion, if lesion size permits, or from a similar lesion in the same anatomical area.

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 a study-issued electronic device or application (app).

Skin Swabs

A cotton swab will be passed along the lesional skin of the area of worst involvement at Screening. The skin swab will be placed in aerobic culture and analyzed for the presence of *Staphylococcus aureus* (*S. aureus*). At Visits 2, 3, and 4 (Day 1, Week 3, and Week 6), skin swabs will be collected

from the same lesional site, even if the lesion has cleared, for assessment of [redacted]. Skin swabs are to be collected before skin tape strips application and biopsies when performed on the same day.

Skin Tape Strips

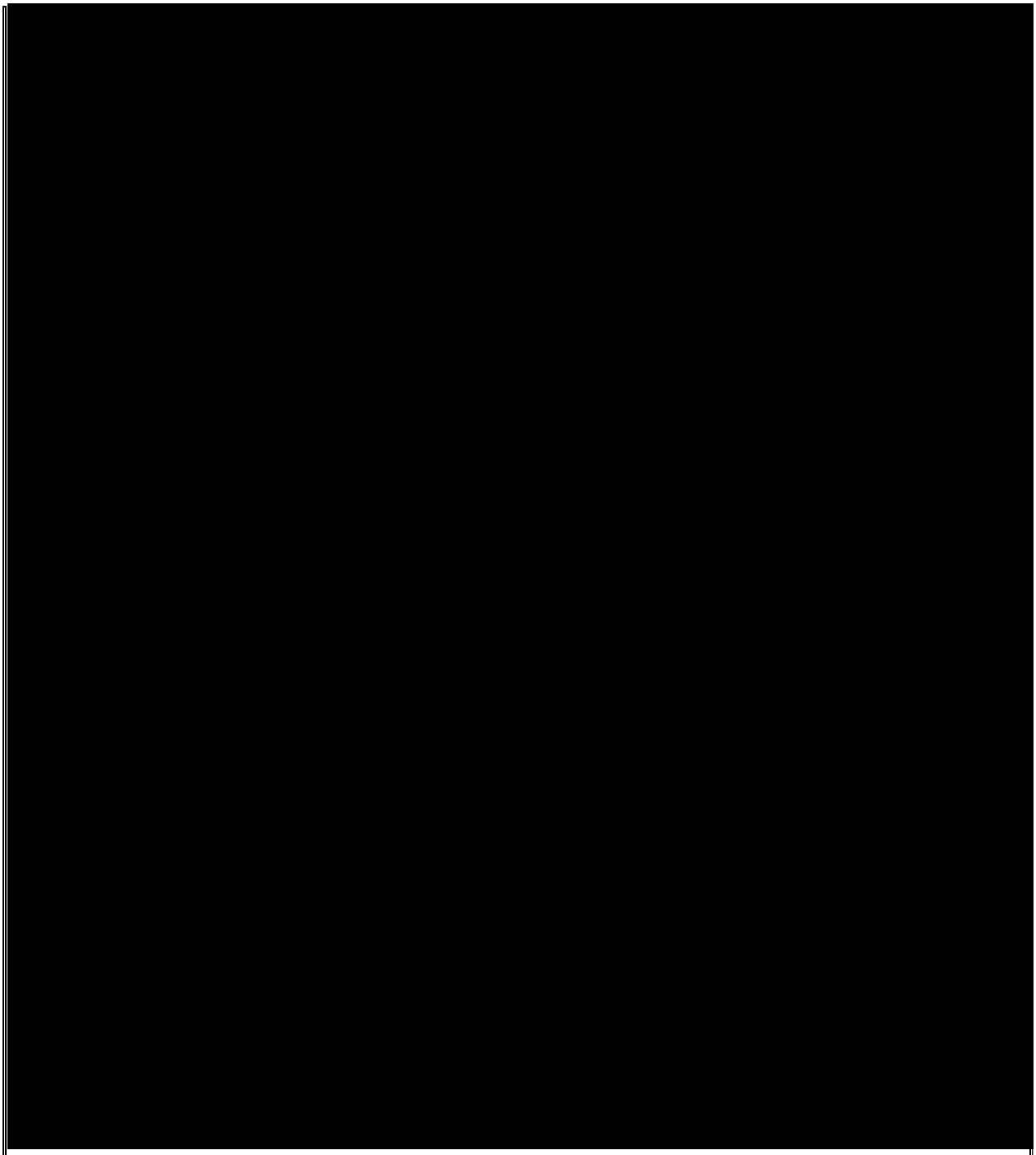
Commercially available adhesive sheets will be applied on the surface of the skin at predefined areas. This procedure will be repeated up to 20 times sequentially on the same area to collect samples from the stratum corneum for proteomic assessment. Skin tape strips will be applied to AD lesional skin on Visits 2, 3, and 4 (Day 1, Week 3, and Week 6, same location, even if the lesion has cleared), and at a nonlesional site at Visit 2 (Day 1).

Skin Punch Biopsies

Two 4.0-mm skin biopsies will be collected on Visit 2 (Day 1), one from lesional skin and one from nonlesional skin in the vicinity of the lesional skin, and one 4.0-mm skin biopsy will be collected on Visit 4 (Week 6) from the same lesional skin, at least 1 cm away from the previous scar, even if the lesions have cleared. The effect of EP262 on the gene expression signature and skin histology (epidermal thickness, immune cell infiltration, markers of epidermal proliferation) will be evaluated via histology, immunohistochemistry, and transcriptomics. The location of the biopsies will be 1 to 2 cm away from where the skin tape strips were applied, when both are to be performed on the same day. If it is not possible to collect the biopsy sample from the same lesion as the tape strips, it should be collected from a similar lesion in the same anatomical area.

Disease Severity

[redacted]



Photographs of AD Area

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

Baseline Characterization A blood sample will be collected at Visit 2 (Day 1) for measurement of house dust mite (HDM)-specific IgE. Blood samples will also be taken at Visit 2 (Day 1) for genotyping to evaluate UGT1A1 and filaggrin polymorphisms to enable pharmacogenomic analyses. Pharmacokinetic Assessment Blood sampling will be collected predose (as applicable) at Visit 2 (Day 1), and each visit thereafter to analyze trough EP262 concentrations. The EP262 metabolite profile may also be analyzed from these trough samples.
Statistical Methods: Descriptive statistics will be presented for study outcome measures, as appropriate. Details will be described in the Statistical Analysis Plan (SAP).
Sample Size Considerations: No formal sample size calculation has been made. The sample size has been selected to provide adequate information on the safety, tolerability, PK, and PD of EP262 over 6 weeks.

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

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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
AD	atopic dermatitis
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
app	application
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemistry
BCRP	breast cancer resistance protein
BSA	Body Surface Area
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
[redacted]	[redacted]
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EGF	epidermal growth factor
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HBV	hepatitis B virus
HCV	hepatitis C virus
HDM	house dust mite
HEENT	head, eyes, ears, nose, throat
HIV	human immunodeficiency virus

Abbreviation or Specialist Term	Explanation
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
IWRS	Interactive Web Response System
JAK	janus kinase
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
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
[redacted]	[redacted]
PQC	product quality complaint
QC	quality control
QD	once daily
[redacted]	[redacted]
SAE	serious adverse event
SAER	Serious Adverse Event Report
SAP	Statistical Analysis Plan
S. aureus	*Staphylococcus aureus*
SEB	*Staphylococcus aureus* Enterotoxin Type B
SOC	System Organ Class
SOP	standard operating procedure

Abbreviation or Specialist Term	Explanation
$t_{1/2}$	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
[redacted]	[redacted]
UGT1A1	uridine 5'-diphospho-glucuronosyltransferase 1A1
ULN	upper limit of normal
UVA	ultraviolet A
UVB	ultraviolet B
US	United States
[redacted]	[redacted]
WHO	World Health Organization

5. INTRODUCTION

5.1. Role of the MRGPRX2 Receptor in the Pathogenesis of Atopic Dermatitis

Atopic dermatitis (AD) is a common, chronic inflammatory skin disease characterized by impaired barrier function, eczematous dermatitis, and chronic itch (Magnifico 2020, Yu 2021). Skin thickening, lichenification of the skin from chronic scratching, erythema, and acute lesions may develop over time (Correale 1999). Disease symptoms are often exacerbated by external factors, including bacterial colonization on the skin, various environmental stimuli including heat and sweating, as well as exposure to aeroallergens such as house dust mites (HDMs). In addition to these external factors, impaired epidermal skin barrier function is believed to be an important factor in the pathogenesis of AD, including genetic mutations in filaggrin, decreased filaggrin expression, and dysregulation of the immune system leading to cellular infiltrates including dendritic cells, type 2 T helper cells (Th2), and eosinophils in the skin. The prevalence of AD in adults has been estimated to be 7% to 10% in the United States (US) and 4.4% to 7.1% in Europe (Eckert 2019, Hadi 2021).

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 (Babina 2020, Thapaliya 2021), including AD.

Mast cells and MRGPRX2 have been implicated in the pathophysiology of AD in both clinical and preclinical studies. A significant association has been observed between the number of mast cells in AD skin lesions and the disease severity (assessed by the Eczema Area and Severity Index [EASI] score) (Simon 2004). Increased expression of the MRGPRX2 agonist substance P, as well as MRGPRX2, has been reported in itchy AD patient skin versus non-itchy skin samples (Nattkemper 2018, Youngblood 2020). In addition to substance P, MRGPRX2 is also activated by multiple eosinophil granule proteins, including major basic protein and eosinophil cationic protein fragments. Elevated levels of these peptides in serum of patients with AD have been reported and are correlated to severity of disease (Kapp 1991, Morita 1995, Ogasawara 2020, Deeks 2021). An attenuated phenotype has been shown in Mrgprb2 knockout mice (the murine homolog of MGRPRX2) in a preclinical model of AD induced by treatment with delta-toxin, an MRGPRX2 agonist released by *Staphylococcus aureus* (*S. aureus*), and HDM extract including a reduction in Th2 cytokines, improved epidermal integrity, improved clinical scores, and reduced local skin inflammation (Serhan 2019). This reduction of phenotype in Mrgprb2 knockout mice was also observed in other models of dermatitis (Green 2019, Meixiong 2019, Corbiere 2021).

Collectively, these findings point to a key role of MRGPRX2 in mediating IgE-independent mast cell activation and skin inflammation, making this receptor a promising novel target for AD as

well as numerous urticarial, inflammatory, and pain conditions that are precipitated by degranulation of mast cells and not adequately addressed by available treatments.

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 AD and chronic spontaneous urticaria.

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, moderate or severe AEs, or serious AEs (SAEs) reported with EP262. 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. [redacted]

EP262 was evaluated in MRGPRX2 knock-in mice expressing the human receptor in a translational model of AD induced by cutaneous exposure to HDM extracts and *S. aureus* Enterotoxin Type B (SEB). In initial experiments, daily PO administration of EP262 significantly attenuated the development of AD relative to vehicle controls as measured by visual scoring, tissue measurements, and histopathology following exposure to HDM/SEB (Wollam 2023). As a proof-of-concept study, Study EP-262-202 aims to confirm these findings in human disease, focusing on mechanistic measures and objective assessments of early changes in lesional AD skin. Study EP-262-202 will evaluate the safety, tolerability, and pharmacodynamics (PD) of EP262 over 6 weeks of treatment in subjects with AD. The 6-week treatment duration is supported by the 6-week GLP toxicology program and deemed sufficient to demonstrate changes in PD measures and to provide trends in efficacy based on the anticipated rapid onset of action of EP262 to directly block activation of MRGPRX2.

The primary objective is to evaluate the safety and tolerability of EP262 in patients with AD, which will be measured by type, frequency, and severity of treatment-emergent AEs (TEAEs), and change from baseline in vital signs, ECGs, and clinical laboratory parameters. In addition to evaluations of safety and tolerability, changes in differentially expressed genes from biopsies of lesional skin relative to nonlesional skin will be assessed before and after treatment. The effect of EP262 on AD skin lesions will also be assessed via histology, including examinations of epidermal thickness, immune cell infiltration, and markers of epidermal proliferation and skin barrier integrity. Notably, early transcriptomic and histologic changes in lesional skin have been

demonstrated to correspond with improvements in clinical scores (Hamilton 2014, Bissonnette 2019, Pavel 2019), potentially serving as initial indicators of treatment response.

Disease severity will be evaluated [redacted] Although the study is not powered to detect significant changes in these clinical scores versus placebo, they are included to assess trends in improvement and enable analyses of the correlation between transcriptomic and clinical changes. Additionally, pruritus, disease control, and quality of life will be evaluated through the [redacted]. Other exploratory analyses include [redacted]

The study will be randomized to ensure random allocation of subjects to treatment arms and reduce bias. Because several of the PD 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 EP262 dose level to be evaluated in Study EP-262-202 was selected based on a variety of factors to maximize efficacy without adversely impacting safety, including results from nonclinical pharmacology studies, nonclinical toxicology studies, and results from Study EP-262-101, a Phase 1 first in human clinical study in healthy subjects.

[redacted]

[redacted]

5.4. Summary of Benefits and Risks

5.4.1. Benefit Summary

While it is currently uncertain whether patients with AD 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 AD.

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, moderate or severe AEs, or SAEs reported with EP262. Additionally, no adverse trends in safety laboratory measures, vital signs, or ECGs were observed.

In conventional nonclinical safety assessments, no adverse toxicological findings were observed at plasma concentrations well above those estimated to be required for robust pharmacologic activity. [redacted]

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.

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 11.10.3).

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-262-202. Importantly, there is a clear unmet need for novel treatment options for AD. The first-line therapeutic approach for management of AD includes a combination of emollients, antibiotics, anti-pruritic, and topical anti-inflammatory therapies (Sahni 2022). Dupilumab and tralokinumab, injectable monoclonal antibodies that block receptor binding of interleukin (IL)-4 and/or IL-13 (reducing Th2 response), have been approved for the treatment of moderate-to-severe AD as second-line therapy (Tameez Ud Din 2020, Blair 2022). Oral janus kinase (JAK) inhibitors (abrocitinib and upadacitinib) have recently been approved for treatment of AD, but have several serious side effects and are indicated as third-line therapy only (in adults with refractory, moderate-to-severe AD whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies

is inadvisable) (Mikhaylov 2023). If determined to be effective, EP262 may ultimately have the potential to offer a much-needed additional treatment option for patients with AD.

6. TRIAL OBJECTIVES AND PURPOSE

Objectives	Endpoints
Primary Objective	
To evaluate the safety and tolerability of EP262 compared to placebo in subjects with AD	• Type, frequency, and severity of TEAEs • Change from baseline in vital signs, ECGs, and clinical laboratory parameters
Secondary Objectives	
To evaluate the PD effects of EP262 compared to placebo in subjects with AD on skin biopsy-derived biomarkers	• Change from baseline to Week 6 in gene expression signature and skin histology (epidermal thickness, immune cell infiltration, markers of epidermal proliferation) as assessed from biopsies of lesional skin
Exploratory Objectives	
[redacted]	

7. INVESTIGATIONAL PLAN

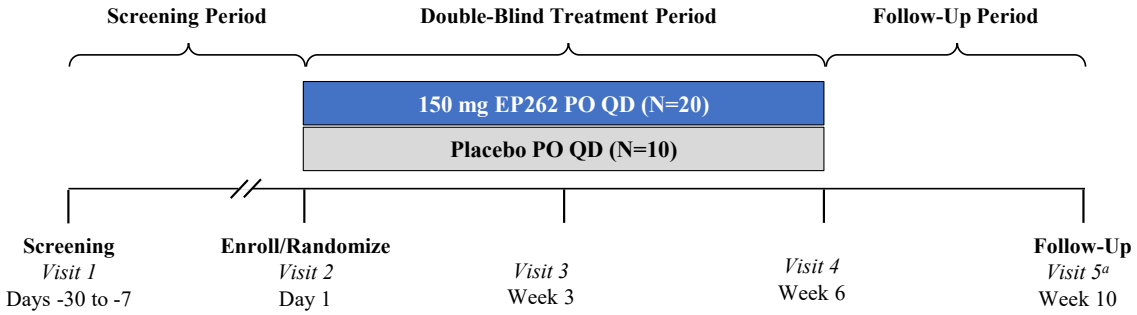
7.1. Overall Study Design

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

The study includes a Screening Period of at least a week and up to 30 days to assess subject eligibility that includes collection of daily PP-NRS scores; a 6-week Double-Blind Treatment Period; and a 4-week Follow-Up Period after administration of the last dose of study drug for a total study duration of up to approximately 14 weeks for each subject (Figure 1). Approximately

30 subjects will be randomized in a 2:1 ratio to receive either a 150 mg dose of EP262 or placebo PO, once daily (QD) during the 6-week Double-Blind Treatment Period.

Figure 1: EP-262-202 Study Design



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

7.1.1. Screening Period

The Screening Period will consist of one visit (Visit 1). During this period, subjects will undergo assessments to determine study eligibility per inclusion and exclusion criteria. Visit 1 may be conducted over more than 1 day but must be completed between Day -30 and Day -7 (inclusive) to allow for collection of a baseline average PP-NRS score. Subjects are to use a protocol-permitted, non-urea-containing emollient on lesional and nonlesional skin daily for at least 1 week before Day 1 and agree to continue using that same emollient daily at the same frequency (ideally once or twice daily) throughout the study. Subjects will record emollient use in a daily diary throughout the study.

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), in a 2:1 ratio, to receive double-blind, PO, QD 150 mg doses of EP262 or placebo for 6 weeks. Randomization will be conducted centrally via an Interactive Web Response System (IWRS). 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.

7.1.3. Follow-Up Period

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

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 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 30 subjects with AD will be randomized in the study.

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 8.5 for guidance on mandatory discontinuation of study drug due to safety findings and Section 11.10.3 for guidance on study drug interruption due to liver test abnormalities.

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 poor study data quality). The entire study may also be terminated by the Sponsor 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 8.5.2 (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 do not meet the criteria for participation in this study (screen failure) may be rescreened once, if deemed acceptable by the Investigator. 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. Clinically confirmed diagnosis of active AD, according to Hanifin and Rajka criteria (Hanifin 1980), for at least 1 year, with a BSA of AD involvement of 3% to 20% (excluding palms, soles, and scalp) and a vIGA-AD score of ≥3 at Screening and Day 1. Subject should have had no significant flares in AD for at least 4 weeks before Screening (based on review of the medical chart or directly from the subject)
2. Has been using a protocol-permitted, non-urea-containing emollient on lesional and nonlesional skin daily for at least 1 week before Day 1 and agrees to continue using that same emollient daily at the same frequency (ideally once or twice daily) throughout the study
3. Aged 18 to 80 years, inclusive, at the time of consent
4. 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),

[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).

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

5. 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
6. 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. Other active skin diseases associated with chronic pruritus that might confound the study evaluations and results (eg, urticaria, bullous pemphigoid, prurigo nodularis, dermatitis herpetiformis)
2. Clinically infected AD that requires antibiotic therapy
3. Tattoos or any other markings on any area of the body that might confound the study evaluations and results
4. History of an allergic reaction or significant hypersensitivity to lidocaine or other local anesthetics
5. History of hypertrophic scarring or keloid formation in scars or suture sites or has a contraindication to skin biopsies
6. Use of the following prohibited AD treatments:
    a. Dupilumab within 26 weeks before Day 1. Other monoclonal antibodies within 4 months or 5 half-lives (whichever is longer) before Day 1
    b. Systemic medications that could affect AD, such as retinoids, calcineurin inhibitors, hydroxycarbamide (hydroxyurea), azathioprine, systemic corticosteroids, oral JAK inhibitors, hydroxychloroquine, methotrexate, mycophenolate, cyclosporine, or cyclophosphamide within 4 weeks before Day 1
    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed
    c. Phototherapy (ie, ultraviolet B [UVB], ultraviolet A [UVA]) or sublingual immunotherapy within 4 weeks before Day 1
    d. Topical medications that could affect AD, including corticosteroids, calcineurin inhibitors, JAK inhibitors, antibiotics and other antimicrobials, products containing urea, or phosphodiesterase inhibitors, within 1 week before Day 1. Topical antibiotics may be allowed at the skin punch biopsy site only, at the discretion of the Investigator
    e. Systemic antibiotics within 2 weeks before Day 1
    f. Hydroxyzine or diphenhydramine within 1 week before Day 1
    g. Bleach baths within 2 weeks before Day 1 or planned use during the study

h. Has had excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1 or is not willing to minimize natural and artificial sunlight exposure during the study

7. Use of the following prohibited medications within 2 weeks before Day 1:
   a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), clomipramine, or nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium)
   b. Drugs that inhibit UGT1A1 (eg, atazanavir, canagliflozin, pazopanib, regorafenib, sorafenib, tranilast)
   c. [redacted]
   d. [redacted]
8. 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
9. 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
10. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect subject safety
11. 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
12. 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
13. 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
14. Significant history of abuse of drugs, solvents, or alcohol within the past year
15. Participation in any clinical study with an investigational or approved drug/device within 30 days or 5 half-lives (whichever is longer) before Day 1 or is planning to participate in another clinical study while enrolled in this study

16. History of known or suspected hypersensitivity to any component of study drug
17. Female who is pregnant, nursing, or intends to become pregnant during the study
18. Had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study
19. 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
20. Is employed by Escient Pharmaceuticals, Inc., (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 Escient Pharmaceuticals, Inc.
21. Subject is, in the opinion of the Investigator, not suitable to participate in the study

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:

- On days of study visits, do not apply topical emollients prior to attending and completing each visit.
- Do not take bleach baths.
- 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, during the study 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 30 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 AD beginning from the date of diagnosis should also be recorded.

[redacted]

8.4.1. Background Therapy

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

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

8.4.2. Rescue Medications

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

8.5. 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.

8.5.1. Discontinuation of Study Drug

Study drug may be discontinued in the following instances:

- AE
- Rescue medication use
- Withdrawal of consent
- Lost to follow-up
- Protocol deviation
- Investigator decision

- Sponsor decision
- Pregnancy during the study (Section 11.2.3)
- Other

If a subject experiences a TEAE that is Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or higher in the Cardiac Disorders System Organ Class (SOC), Grade 2 or higher in CTCAE terms of Bone marrow hypocellular, Lymphocyte count decreased, Lymphocyte count increased, or Myelodysplastic syndrome, or Grade 3 or higher in other SOCs, the study drug must be discontinued. AE grading for severity using CTCAE criteria is described in Section 11.1.2 and determination of AE causality is described in Section 11.1.3.

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 PD and safety, but not PK measures) will participate in the Follow-Up Visit if the last dose of study drug was administered less than 4 weeks before Visit 4 (Week 6) to ensure that at least 4 weeks of follow-up data are collected for all randomized subjects.

If a subject discontinues study drug and chooses not to complete all of the remaining study visits, the subject should have the Early Treatment Termination Visit conducted as soon as possible after the last dose of study drug, ideally within 2 days after the last dose of study drug, and a Follow-Up Visit approximately 4 weeks (±3 days) after the last dose of study drug if at least 4 weeks of follow-up data have not already been collected. If a subject fails to attend the 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.

8.5.2. Discontinuation from the Study

Subjects may discontinue from the study at any time for any of 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

Approximately 30 subjects with AD will be randomized in a 2:1 ratio to receive either a 150 mg dose of EP262 or placebo PO, QD 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

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

Subjects who withdraw for any reason without completing all screening evaluations successfully will be considered "screening failures". A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any 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. 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 safety, PD, baseline characterization, and PK assessments are located in Sections 11, 12, 13, and 14, respectively.

9.4.1. Screening Period

9.4.1.1. Visit 1 (Day -30 to Day -7 [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 -7 (inclusive):

- Completion of informed consent before performance of any study procedures or assessments
- Medical history, including AD disease history
- Height
- Body weight
- Vital signs
- Physical examination
- Standard 12-lead ECG

- Assessment of baseline concomitant medications, including all medications taken to treat AD beginning from the date of diagnosis and all other medications taken within 30 days before Screening
- AE assessment
- [redacted]
- Eligibility check
- Blood and/or urine sample collection for screening and safety laboratory assessments
- Lesional skin swab
- Electronic device/app training
- [redacted]

Subjects will be instructed to complete the [redacted]

Subjects will also be instructed to record emollient use in a daily diary throughout the study.

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):

- [redacted]
- [redacted]
- Vital signs
- Standard 12-lead ECG
- Concomitant medication usage assessment
- AE assessment

- [redacted]
- Eligibility check
- Photographs of AD lesions and sites for skin swabs, skin tape strips application, and biopsies
- Blood and urine sample collection for PD, safety, PK, and/or baseline characterization laboratory assessments
- Lesional skin swab
- Skin tape strips of lesional and nonlesional skin
- Skin punch biopsy of lesional and nonlesional skin
- Randomization to 150 mg EP262 or placebo in a 2:1 ratio via IWRS
- 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

Subjects will be instructed to record self-administration of study drug daily in a dosing diary throughout the Double-Blind Treatment Period.

9.4.2.2. Visit 3 (Week 3)

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

- [redacted]
- [redacted]
- Collect study drug
- Assess study drug accountability and compliance
- Vital signs
- Abbreviated, symptom directed physical examination
- Concomitant medication usage assessment
- AE assessment
- [redacted]
- Photographs of AD lesions and sites for skin swabs and skin tape strips application
- Blood and urine sample collection for PD, safety, and/or PK assessments
- Lesional skin swab
- Skin tape strips of lesional skin

- 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):

- [redacted]
- [redacted]
- Collect study drug
- Assess study drug accountability and compliance
- Body weight
- Vital signs
- Physical examination
- Standard 12-lead ECG
- Concomitant medication usage assessment
- AE assessment
- [redacted]
- Photographs of AD lesions and sites for skin swabs, skin tape strips application, and biopsy
- Blood and urine sample collection for PD, safety, and/or PK assessments
- Lesional skin swab
- Skin tape strips of lesional skin
- Skin punch biopsy of lesional skin

9.4.3. Follow-Up Period

9.4.3.1. Visit 5 (Week 10)

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

- [redacted]
- [redacted]
- Body weight

- Vital signs
- Abbreviated, symptom directed physical examination
- Standard 12-lead ECG
- Concomitant medication usage assessment
- AE assessment
- [redacted]
- Photographs of AD lesions
- Blood and urine sample collection for PD, safety, and/or PK 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:

- [redacted]
- [redacted]
- Collect study drug
- Assess study drug accountability and compliance
- Body weight
- Vital signs
- Abbreviated, symptom directed physical examination
- Standard 12-lead ECG
- Concomitant medication usage assessment
- AE assessment
- [redacted]
- Photographs of AD lesions
- Blood and urine sample collection for PD, safety, and/or PK assessments

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

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

10.2. Study Drug Packaging and Labeling

Study drug will be packaged into bottles with child-resistant caps, induction sealed, 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, which will be reviewed by clinical site staff at each clinic visit during the Double-Blind Treatment Period following Visit 2.

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 during 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. 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).

11.1. Adverse Events

11.1.1. 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 11.2.1.

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 11.1.4.1. 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.

11.1.2. 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.

11.1.3. 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.

11.1.4. 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 11.3).

11.1.4.1. 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.

11.2. Serious Adverse Events

11.2.1. 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.

11.2.2. 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.

11.2.3. 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 [redacted] Drug Safety via email at [redacted] 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.

11.3. Medical History

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

11.4. 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.

11.5. 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.

11.6. 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.

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

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

11.7. 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.

11.8. 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.

11.9. 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.

11.10. Subject Safety Guidelines

11.10.1. Potential Side Effects

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

11.10.2. 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 17.1). An overdose does not constitute an AE; however, the subject should be closely monitored for any potential AEs.

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

11.10.3. 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%)

12. PHARMACODYNAMIC ASSESSMENTS

[redacted]

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 a 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.

12.1. Skin Swabs

A cotton swab will be passed along the lesional skin of the area of worst involvement at Screening. The skin swab will be placed in aerobic culture and analyzed for the presence of *S. aureus*. At [redacted] skin swabs will be collected from

the same lesional site, even if the lesion has cleared, for assessment of [redacted]. Skin swabs are to be collected before skin tape strips application and biopsies when performed on the same day.

12.2. Skin Tape Strips

Commercially available adhesive sheets will be applied on the surface of the skin at predefined areas. This procedure will be repeated up to 20 times sequentially on the same area to collect samples from the stratum corneum for proteomic assessment. Skin tape strips will be applied to AD lesional skin on Visits 2, 3, and 4 (Day 1, Week 3, and Week 6, same location, even if the lesion has cleared), and at a nonlesional site at Visit 2 (Day 1).

12.3. Skin Punch Biopsies

Two 4.0-mm skin biopsies will be collected on Visit 2 (Day 1), one from lesional skin and one from nonlesional skin in the vicinity of the lesional skin, and one 4.0-mm skin biopsy will be collected on Visit 4 (Week 6) from the same lesional skin, at least 1 cm away from the previous scar, even if the lesions have cleared. [redacted] The location of the biopsies will be 1 to 2 cm away from where the skin tape strips were applied, when both are to be performed on the same day. If it is not possible to collect the biopsy sample from the same lesion as the tape strips, it should be collected from a similar lesion in the same anatomical area.

12.4. Disease Severity Scores

[redacted]

12.5. Pruritus

12.6. Disease Control

12.7. Quality of Life

12.9. Photographs of AD Area

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

13. BASELINE CHARACTERIZATION

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

Blood samples will also be taken at Visit 2 (Day 1) for genotyping to evaluate UGT1A1 and filaggrin polymorphisms to enable pharmacogenomic analyses.

14. PHARMACOKINETICS ASSESSMENT

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

15. 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.

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

15.2. Sample Size Considerations

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

15.3. 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.

15.4. Demographics and Baseline Characteristics

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

15.5. 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.

15.6. 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 SOC 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 protocol-permitted emollient will also be summarized descriptively.

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

15.7. Pharmacodynamic Analysis

PD analyses will be based on the FAS. Select secondary and exploratory PD endpoint analyses may also be repeated in the PP Set, if sufficiently different to the FAS, as supportive analyses.

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

For select endpoints, absolute, percent change, and/or fold-change from baseline will be summarized. Correlation analysis between responses in disease severity scores and changes in select PD parameters may be explored. Additional information will be provided in the SAP.

15.8. 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.

15.9. Subgroup Analyses

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

15.10. Multiple Comparison/Multiplicity

No adjustment for multiplicity will be performed due to the hypothesis generating nature of this study.

15.11. Planned Interim Analysis

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

The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the study files prior to conduct of the interim analysis. 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.

16. QUALITY CONTROL AND DATA MANAGEMENT

16.1. 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

16.2. 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.

16.3. Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the International Council for Harmonisation (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.

16.4. 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 US Food and Drug Administration (FDA), 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).

16.5. 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.

16.6. 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.

16.7. 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.

16.8. 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. 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.

16.9. 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.

16.10. 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.

17. STUDY MANAGEMENT

17.1. 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 PD 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.

17.2. 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.

The study will be registered on a publicly accessible website, in accordance with the applicable local laws and regulations.

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.

17.3. 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.

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APPENDIX A. SCHEDULE OF ASSESSMENTS

Assessment	**Screening**	**Double-Blind Treatment**			**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 -7	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 AD 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						
Lesional skin swab	X	X	X	X			Swab will be collected at Screening for bacterial culture to assess *S. aureus* colonization. At all other indicated visits, swabs will be collected for assessment of [redacted]
Eligibility check	X	X					
Randomization		X					Subjects will be randomized via IWRS in a 2:1 ratio to 150 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**			**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 -7	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		
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			X			
Abbreviated, symptom directed physical examination			X		X	X	Abbreviated, 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.
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 all medications taken to treat AD beginning from the date of diagnosis and all other medications taken within 30 days before Screening.
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.
Pharmacodynamic Assessments							
Skin tape strips		X	X	X			To be repeated up to 20 times sequentially at predefined areas to collect samples from the stratum corneum for proteomic assessment. To be performed on AD lesional skin at all indicated visits and at a nonlesional site at Visit 2 (Day 1).

Assessment	**Screening**	**Double-Blind Treatment**			**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 -7	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		
[redacted]							
Photographs of AD lesions		X	X	X	X	X	Representative photographs will be taken of the area of worst lesional involvement at Visit 2 (Day 1) and of the same area at Visit 3 (Week 3), Visit 4 (Week 6), and Visit 5 (Follow-Up). Photographs will also be taken of areas selected for skin swabs, skin tape strips application, and biopsies before these procedures are conducted.
Stored plasma/serum		X	X	X	X	X	To be stored for future biomarker analyses.

Assessment	Screening	Double-Blind Treatment			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 -7	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		
[redacted]							
Baseline Characterization							
Blood draw for HDM-specific IgE		X					
Genotyping		X					To evaluate UGT1A1 and filaggrin polymorphisms and enable pharmacogenomic analyses

AD = atopic dermatitis; AE = adverse event; app = application; BSA = Body Surface Area; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; HBV = hepatitis B virus; HCV = hepatitis C virus; HDM = house dust mite; HIV = human immunodeficiency virus; IgE = immunoglobulin E; IWRS = Interactive Web Response System; PK = pharmacokinetic; PP-NRS = Peak Pruritus Numeric Rating Scale; QD = once daily; RECAP = recap of atopic eczema; *S. aureus* = *Staphylococcus aureus*; Term = termination; Tx = treatment; UGT1A1 = uridine 5' diphospho-glucuronosyltransferase 1A1; vIGA-AD = validated Investigator Global Assessment for AD.

Subjects will record emollient use in a daily diary throughout the study.

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.

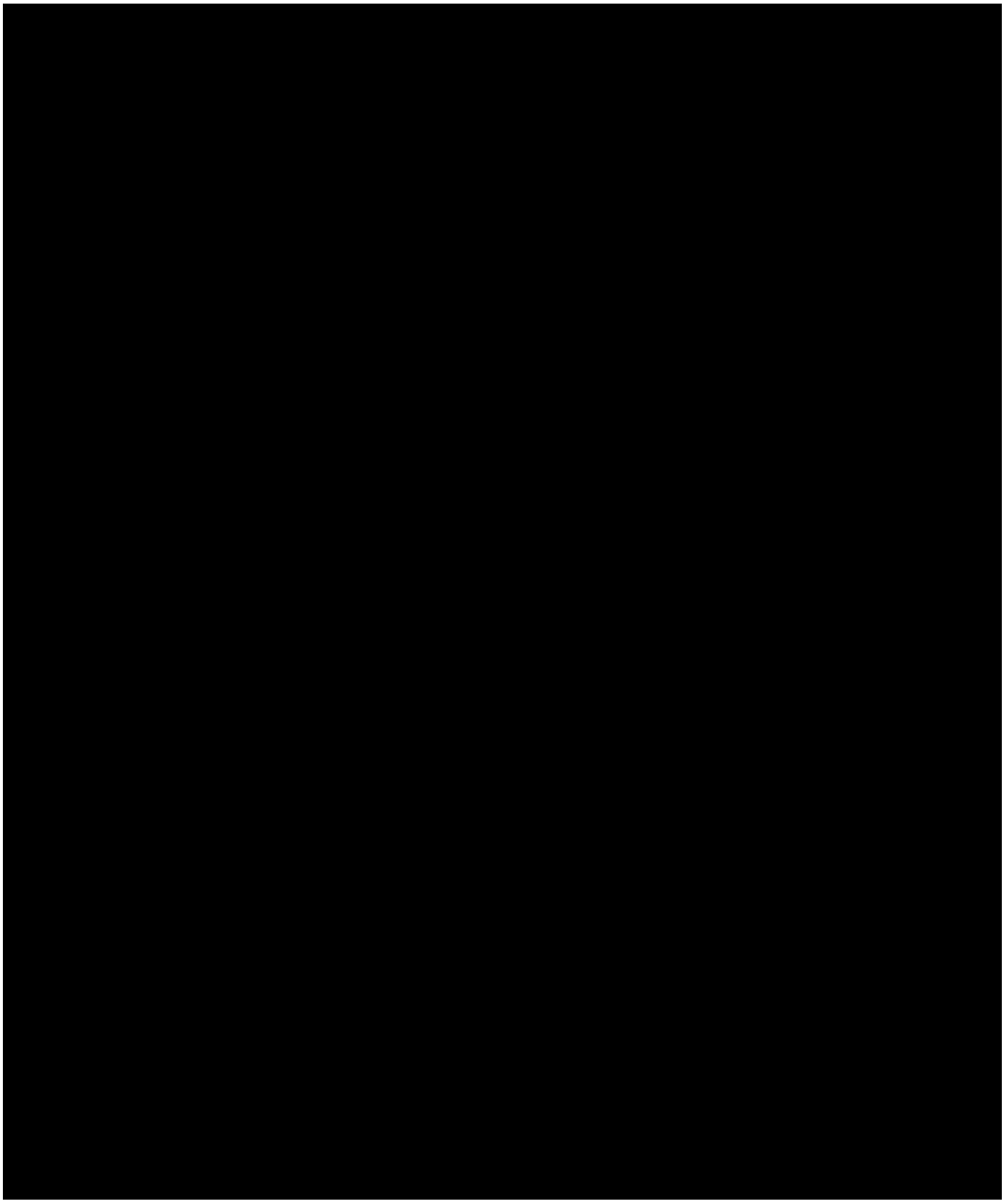
[b] Screening Visit: May be conducted over more than 1 day but must be completed between Day -30 and Day -7.

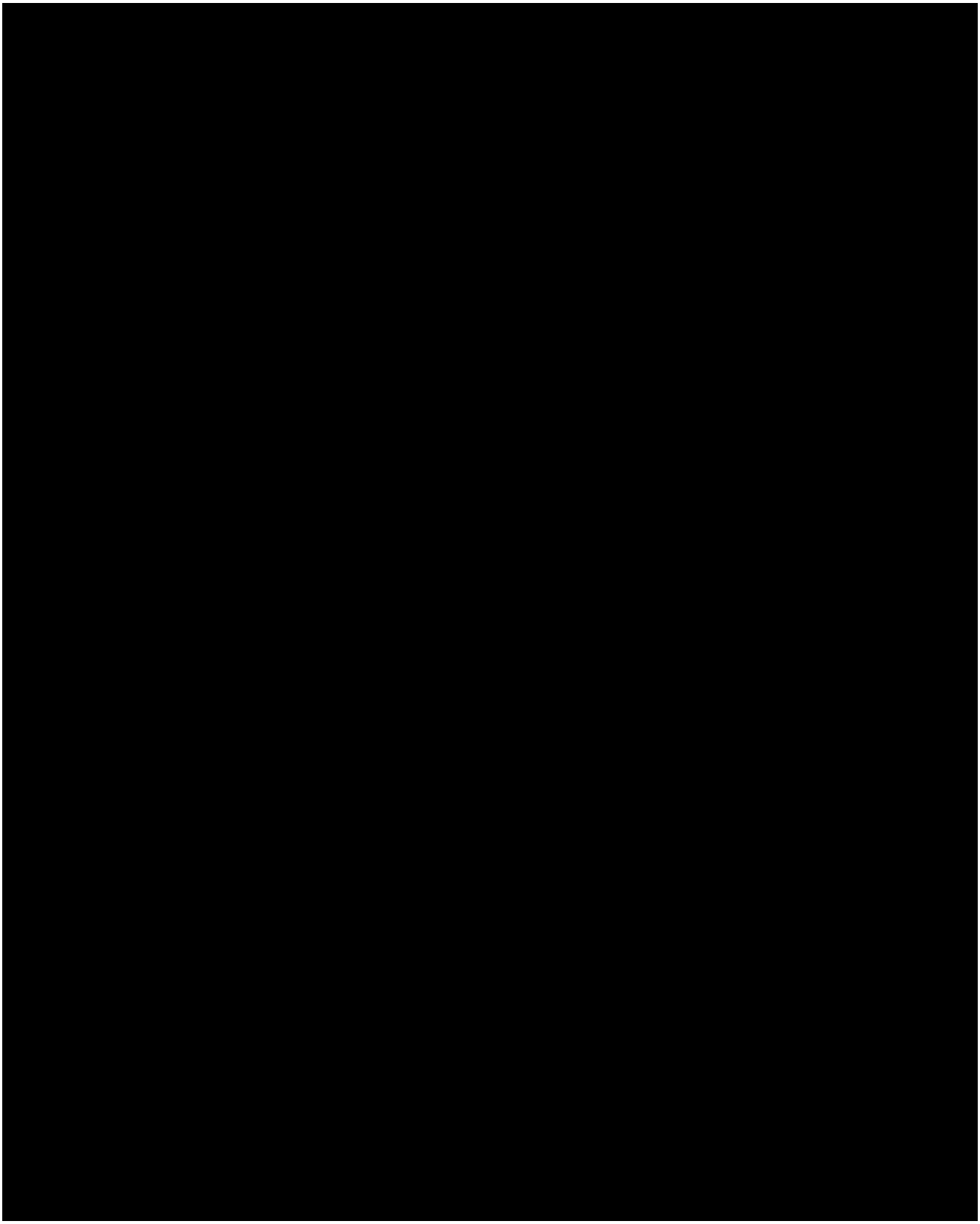
[c] Any subject who completes the Double-Blind Treatment Period or discontinues study drug (EP262 or placebo) early will have a Follow-Up Visit approximately 4 weeks (±3 days) after the last dose of study drug.

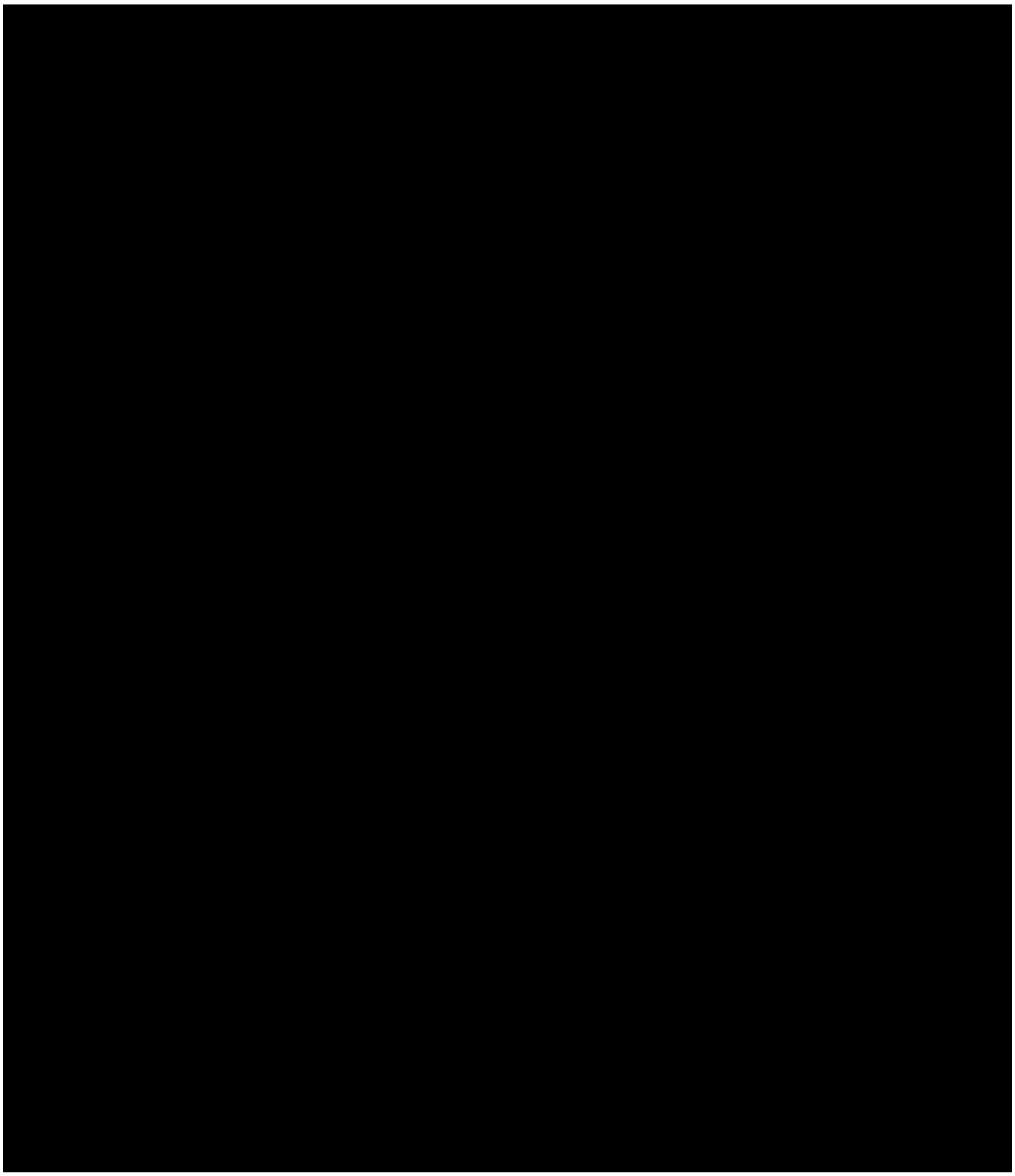
APPENDIX B. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

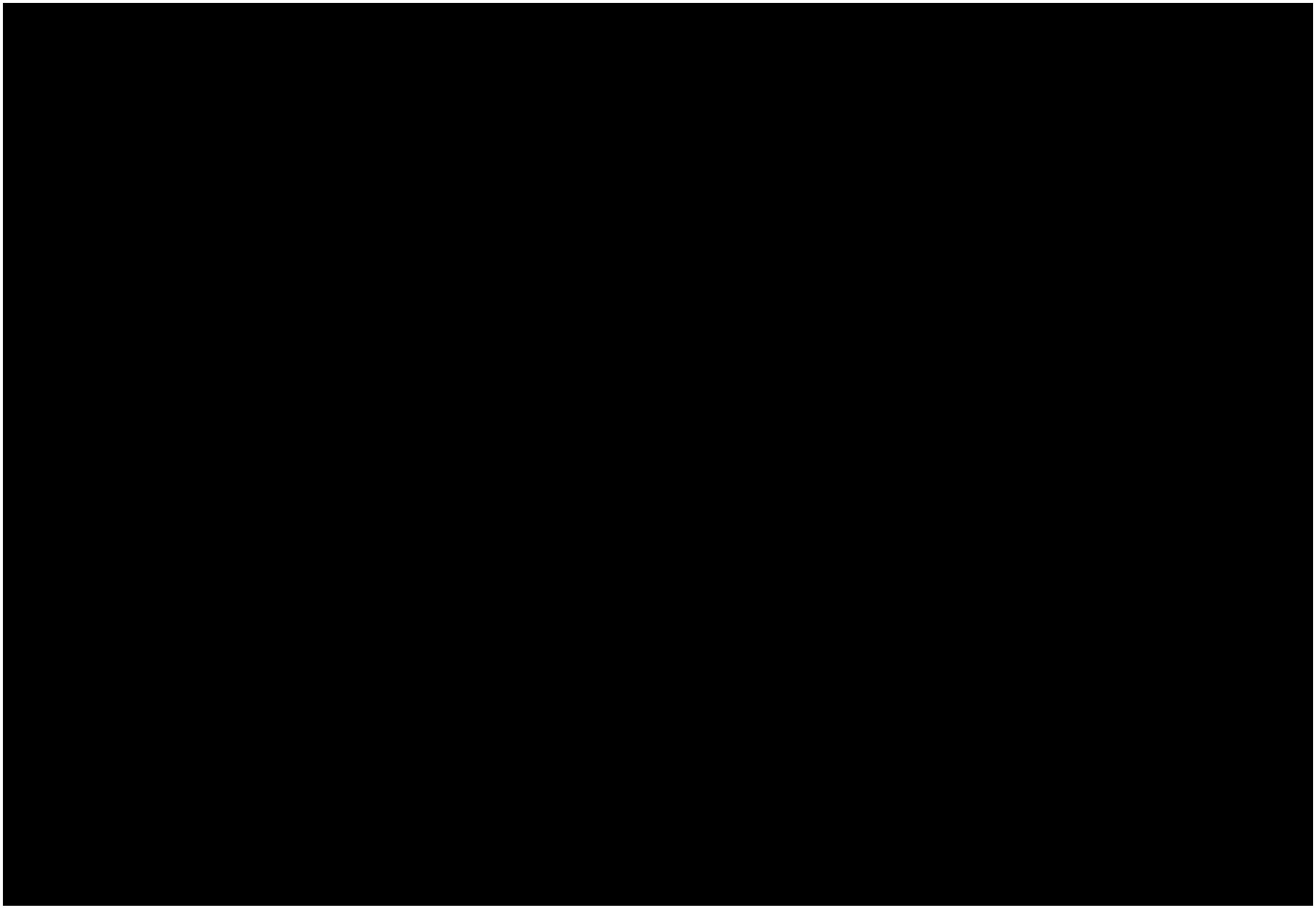
The Common Terminology Criteria for Adverse Events (CTCAE) is widely accepted as the standard classification and severity grading scale for adverse events in cancer therapy, clinical trials, and other oncology settings. Version 5.0 is the most updated document (November 27, 2017), and may be accessed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

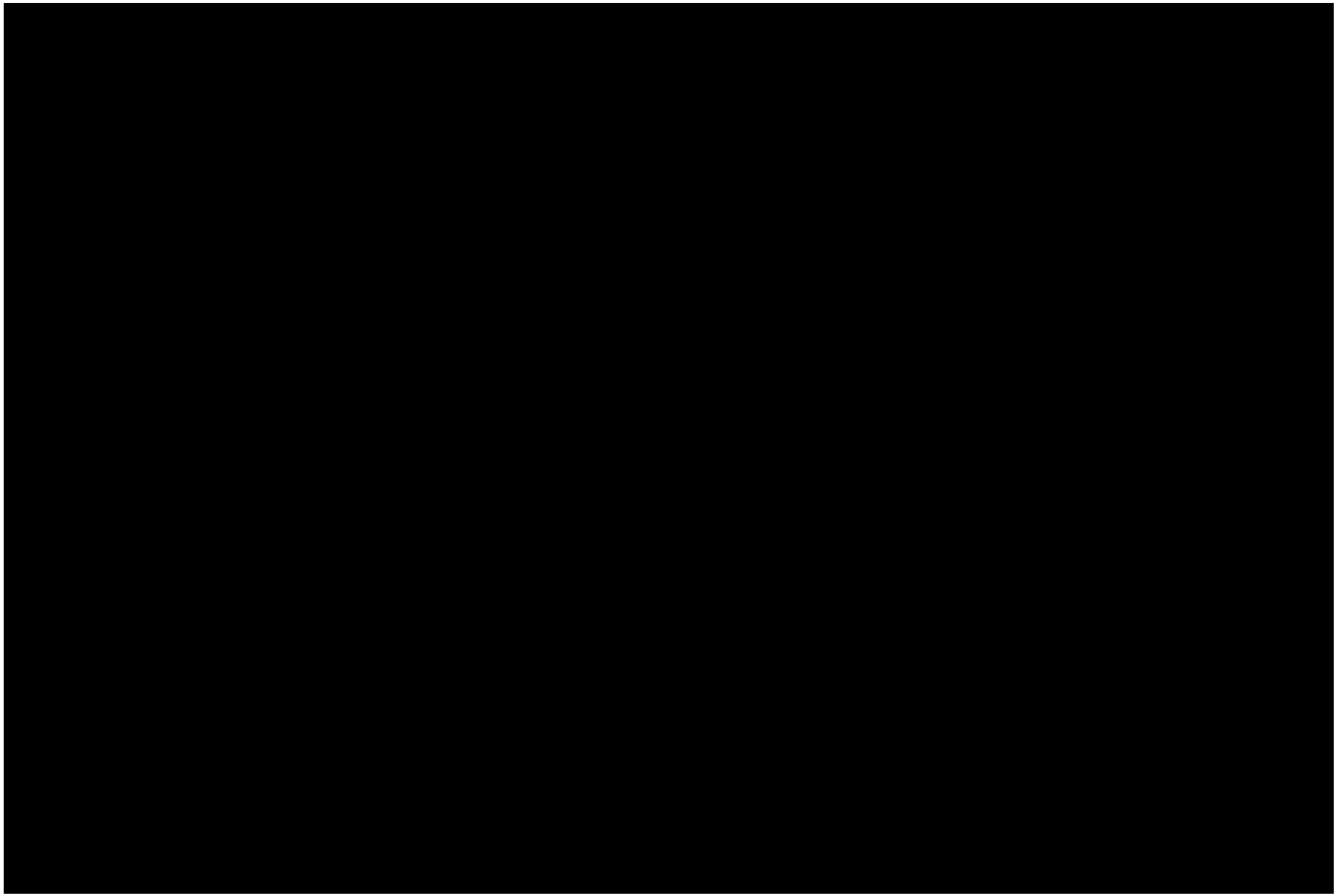
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

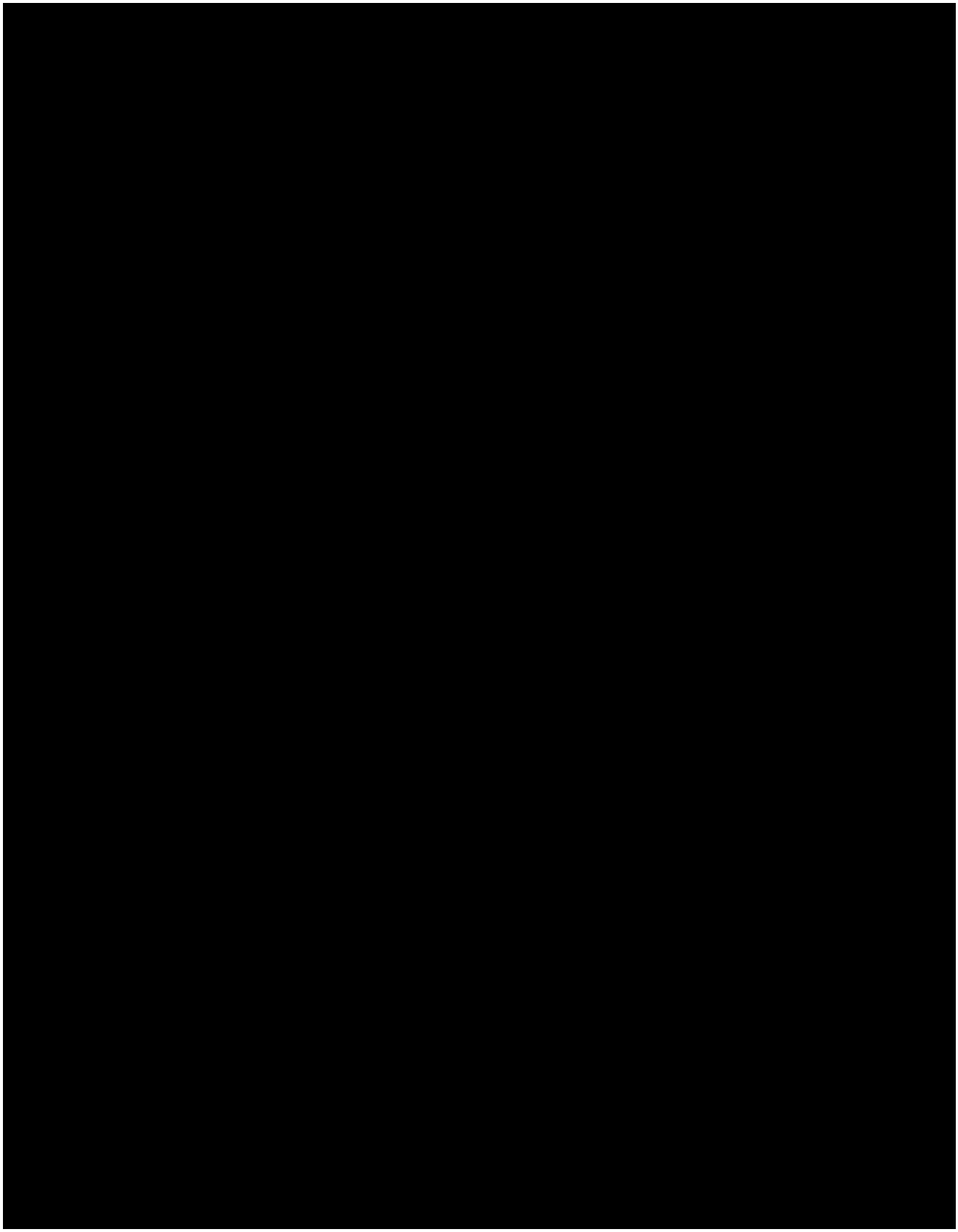












APPENDIX H. SUMMARY OF CHANGES BY AMENDMENT

Summary of Changes for Amendment 4.0 Dated 05 April 2024

Protocol EP-262-202 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 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
Synopsis, Inclusion Criteria 8.1. Subject Inclusion Criteria	4. 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.~~	4. 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.
Synopsis, Inclusion Criteria 8.1. Subject Inclusion Criteria	5. 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	5. 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.

Section	Amendment 3.0	Amendment 4.0	Reason for Change
Synopsis, Exclusion Criteria 8.2. Subject Exclusion Criteria	7. Use of the following prohibited medications within 2 weeks before Day 1: a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), ~~certain antidepressants/antipsychotics/antispasmodics (eg, paroxetine, clozapine, benztropine),~~ or nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium)	7. Use of the following prohibited medications within 2 weeks before Day 1: a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), **clomipramine,** or nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium)	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 3.0 Dated 10 March 2024

Protocol EP-262-202 was amended to address the following changes, including:

- Remove the eligibility requirement for positive colonization of *Staphylococcus aureus* at Screening
- Provide guidance regarding confirmed indeterminant pregnancy test results at Screening
- Updates to the excluded concomitant medications
- Reword the precautions regarding sun exposure

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	~~2. Positive for colonization of *S. aureus* based on culturing of lesional skin swabs at Screening~~	*Deleted text*	Although testing for *S. aureus* colonization at Screening will still occur, the removal of requiring a positive result for study participation will increase subject eligibility without impacting safety.
Synopsis, Inclusion Criteria 8.1 Subject Inclusion Criteria	5. 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:	4. 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.

Section	Amendment 2.0	Amendment 3.0	Reason for Change
Synopsis, Exclusion Criteria 8.2 Subject Exclusion Criteria	7. Use of the following prohibited medications within 2 weeks before Day 1: a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), ~~or~~ antidepressants/antipsychotics/ antispasmodics (eg, ~~doxepin,~~ paroxetine, clozapine, benztropine)	7. Use of the following prohibited medications within 2 weeks before Day 1: a. Drugs that are agonists at the MRGPRX2 receptor, including icatibant, opioids (eg, codeine, morphine), **certain** antidepressants/antipsychotics/ antispasmodics (eg, paroxetine, clozapine, benztropine)**, or nondepolarizing neuromuscular blocking agents (eg, atracurium, rocuronium, vecuronium, cisatracurium, mivacurium)**	Revised to clarify that only the use of antidepressants/antipsychotics/ antispasmodics that are agonists at the MRGPRX2 receptor are excluded. 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. Nondepolarizing neuromuscular blocking agents are also agonists of the MRGPRX2 receptor and were added for completeness.
Synopsis, Skin Swabs 12.1 Skin Swabs	A cotton swab will be passed along the lesional skin of the area of worst involvement at Screening. The skin swab will be placed in aerobic culture and analyzed for the presence of *S. aureus* ~~to determine eligibility~~.	A cotton swab will be passed along the lesional skin of the area of worst involvement at Screening. The skin swab will be placed in aerobic culture and analyzed for the presence of *S. aureus*.	Although testing for *S. aureus* colonization at Screening will still occur, the removal of requiring a positive result for study participation will increase subject eligibility without impacting safety.
[redacted]			

Section	Amendment 2.0	Amendment 3.0	Reason for Change
[redacted]			
Appendix A. Schedule of Assessments *(Lesional Skin Swab Row)*	Swab will be collected at Screening for bacterial culture to assess *S. aureus* colonization ~~for eligibility~~.	Swab will be collected at Screening for bacterial culture to assess *S. aureus* colonization.	Although testing for *S. aureus* colonization at Screening will still occur, the removal of requiring a positive result for study participation will increase subject eligibility without impacting safety.

Summary of Changes for Amendment 2.0 Dated 19 October 2023

Protocol EP-262-202 was amended to address the following changes, including:

- [redacted]
- Add abbreviated, symptom directed physical examinations at Visit 3 (Week 3), Visit 5 (Week 10), and the Early Treatment Termination Visit
- Remove the requirement to measure the designated site for swabbing the skin
- Remove the requirement to use a dedicated instrument to apply a defined pressure onto skin tape strips
- [redacted]
- [redacted]
- Add glucose to the chemistry panel and clarify that dipsticks will not be used for urinalysis
- Rearrange the rows in the scoring table for calculating the Eczema Area and Severity Index

Notable changes are included below in the summary table. Revised text in Amendment 2.0 is bolded, and text deleted from the 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
Global change	*Included lipidomic analysis of skin tape strip samples*	*Removed lipidomic analysis of skin tape strip samples*	Only proteomics will be analyzed from skin tape strip samples.
Global change	*Symptom directed physical examinations were at the discretion of the Investigator*	*Abbreviated, symptom directed physical examinations are now required at Visit 3 (Week 3), Visit 5 (Week 10), and the Early Treatment Termination Visit, and may be conducted at the discretion of the Investigator for all other visits.*	Added the required abbreviated, symptom directed physical examinations to reflect feedback received from the US FDA.
Synopsis, Skin Swabs 12.1 Skin Swabs	~~The designated site for swabbing will be measured for each subject, and the total area (cm × cm) recorded.~~	*Text was removed*	Removed text to reflect changes to the procedure for collecting microbes from skin.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
Synopsis, Skin Tape Strips 12.2 Skin Tape Strips	~~A dedicated instrument will be used to apply a defined pressure onto the skin tape strip.~~	*Text was removed*	Removed text to reflect changes to the procedure for collecting skin tape strips.
[redacted]			
11.8 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.
11.8 Laboratory Evaluations of Safety	• Urinalysis ~~(dipstick)~~: 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	• 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.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
[redacted]			

Summary of Changes for Amendment 1.0 Dated 02 August 2023

Protocol EP-262-202 was amended to address the following changes, including:

- Criteria for study drug discontinuation were updated
- Photographs will not be taken until a subject is enrolled in the study, the protocol was updated accordingly
- Urine albumin was removed from the urinalysis panel

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: EASE**	The study acronym was added to further denote the study title.
Synopsis, Study Drug Section 10.1, Study Drug	Study Drug Capsules containing 75 mg of EP262 or placebo will be supplied in bottles in a manner to ensure the study blind. Each subject will take 2 capsules per dose ~~for~~ a total of 150 mg per day.	Study Drug Capsules containing 75 mg of EP262 or placebo will be supplied in bottles in a manner to ensure the study blind. Each subject will take 2 capsules per dose**, with subjects randomized to EP262 receiving** a total of 150 mg per day.	Text was added to clarify that only subjects randomized to the EP262 group will receive active drug.
[redacted]			

Section	Original	Amendment 1.0	Reason for Change
Section 8.5.1, Discontinuation of Study Drug	If a subject experiences a TEAE that is Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or higher in the Cardiac Disorders System Organ Class (SOC) or Grade 3 or higher in other SOCs ~~and assessed as related to blinded study drug~~, the study drug must be discontinued.	If a subject experiences a TEAE that is Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or higher in the Cardiac Disorders System Organ Class (SOC), **Grade 2 or higher in CTCAE terms of Bone marrow hypocellular, Lymphocyte count decreased, Lymphocyte count increased, or Myelodysplastic syndrome**, or Grade 3 or higher in other SOCs, the study drug must be discontinued.	Incorporated per FDA recommendations on criteria for study drug discontinuation.
Section 9.4.1.1, Visit 1 (Day -30 to Day -7 [inclusive]) Schedule of Events	*Photograph of site for skin swab was included in the Screening Visit list of procedures*	*Photograph of site for skin swab was removed from Screening Visit list of procedures*	Photographs will only be taken once a subject is enrolled in the study.
Section 11.8, 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 (dipstick): 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	Albumin is not a standard measure in urinalysis and not required for the safety evaluations in this study.
[redacted]			