1. TITLE PAGE

Randomized, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of EP547 in Healthy Subjects and Subjects with Cholestatic or Uremic Pruritus

Protocol Number:	EP-547-101
Protocol Version Number:	Amendment 2.0
Issue Date:	19 February 2021
Drug Development Phase:	Phase 1
Sponsor:	Escient Pharmaceuticals, Inc. 10578 Science Center Drive, Suite 250 San Diego, CA 92121 USA Phone/Fax: +1 (858) 617-8220
	[redacted] Chief Executive Officer Escient Pharmaceuticals, Inc. [redacted]

Randomized, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of EP547 in Healthy Subjects and Subjects with Cholestatic or Uremic Pruritus

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Sponsor Statement

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

DocuSigned by:
[redacted]

[redacted]
Chief Executive Officer
Escient Pharmaceuticals, Inc.

Date

[redacted]

[redacted]
Vice President, Head of Clinical Development
Escient Pharmaceuticals, Inc.

DocuSigned by:
[redacted]

Date

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

Investigator's Agreement

I have read the protocol for EP-547-101 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

Procedures in Case of Emergency

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Primary Contact		
CRO Medical Monitor	[redacted] Medical Monitor Novotech	[redacted]
Secondary Contact		
Sponsor Medical Monitor	[redacted] Escient Pharmaceuticals, Inc.	[redacted]

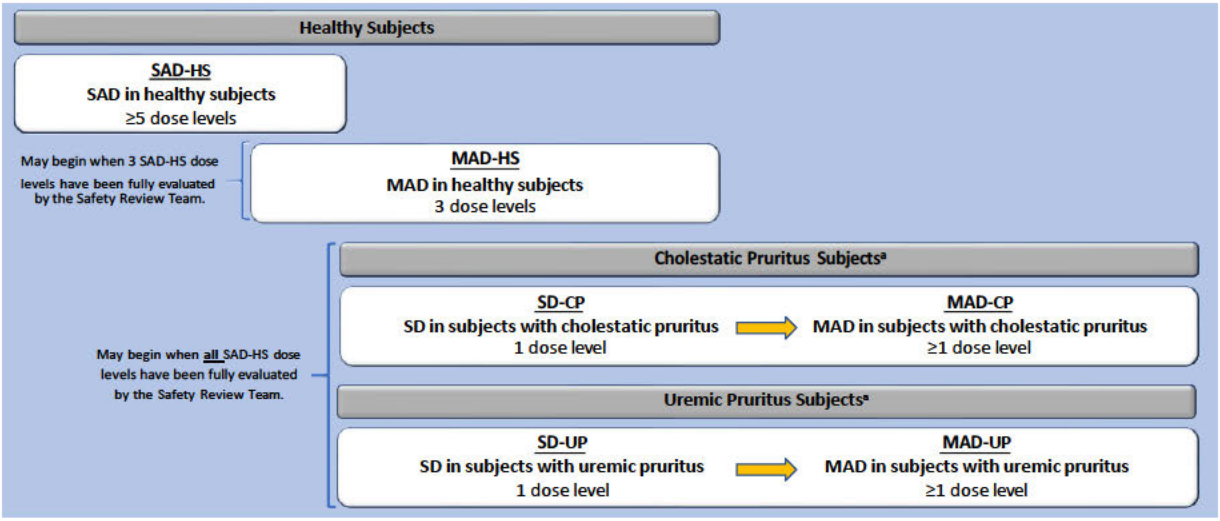
CRO = Contract Research Organization

2. SYNOPSIS

Name of Sponsor/Company: Escient Pharmaceuticals, Inc.	
Name of Investigational Product: EP547 Capsule	
Study Number: EP-547-101	**Phase of Development:** Phase 1
Title of Study: Randomized, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of EP547 in Healthy Subjects and Subjects with Cholestatic or Uremic Pruritus	
Study Center(s): Multi-center within Australia and New Zealand	
Objectives: Primary • To evaluate the safety and tolerability of single and multiple ascending doses of EP547 in healthy subjects and subjects with cholestatic or uremic pruritus Secondary • To evaluate the pharmacokinetics (PK) of single and multiple ascending doses of EP547 in healthy subjects and subjects with cholestatic or uremic pruritus • To assess QT/corrected QT (QTc) interval prolongation risk using EP547 concentration-QT/QTc modeling in healthy subjects (for use at a later development stage, not as a result of a safety signal) Exploratory [redacted]	
Methodology: This study is a first-in-human, Phase 1, randomized, single and multiple ascending dose (SAD and MAD) study with EP547 in healthy subjects and subjects with cholestatic or uremic pruritus. Each population will include a SAD or single dose (SD) segment followed by a MAD segment for a total of 6 segments (SAD-HS and MAD-HS in healthy subjects [HS]; SD-CP and MAD-CP in subjects with cholestatic pruritus [CP]; and SD-UP and MAD-UP in subjects with uremic pruritus [UP]). Each segment will evaluate at least 1 dose level. Pruritus is not a mandatory requirement for participation in SD-CP or SD-UP. Although SAD-HS and all of the MAD segments will be conducted in a blinded manner (ie, subjects, Investigator, study-site personnel, and Contract Research Organization [CRO] staff not involved in PK sample analysis or regulatory reporting will be blinded to treatment), the Sponsor, including the Sponsor Medical Monitor, will be unblinded to treatment assignment to assess safety on an ongoing basis as described in the Safety Assessments section.	

SAD-HS will evaluate at least 5 dose levels of EP547, establish the highest well-tolerated dose in healthy subjects, and guide MAD dosing in the same population. Evaluation of the first of 3 dose levels for MAD-HS may commence after 3 dose levels from SAD-HS have been fully evaluated by the Safety Review Team. When the results of all dose levels from the SAD-HS segment have been fully evaluated by the Safety Review Team, evaluation of a single dose level for SD-CP and SD-UP may commence. SD-CP and SD-UP will confirm predicted PK concentrations and guide MAD dosing in their respective populations. SD-CP and SD-UP may be conducted in parallel. Evaluation of at least 1 dose level for MAD-CP and MAD-UP may commence when the dose level from the SD segment specific to their population has been fully evaluated by the Safety Review Team. Subjects from the SD-CP and SD-UP segments may screen to determine eligibility for participation in the MAD segment specific to their population.

EP-547-101 Study Design



CP = cholestatic pruritus; HS = healthy subject; MAD = multiple ascending dose; SAD = single ascending dose; SD = single dose; UP = uremic pruritus

[a] Subjects from the SD segment may screen to determine eligibility for participation in the MAD segment specific to their population.

Dose escalation will be determined by the Safety Review Team, which will include the Investigator, Sponsor Medical Monitor, clinical and PK staff from both the site and Sponsor, and other experts for guidance as needed. The Investigator and Sponsor Medical Monitor must both indicate approval for any planned dose escalation. Dose escalation will be based on available individual chemistry, hematology, urinalysis, standard 12-lead electrocardiogram (ECG), physical examination, vital sign, adverse event (AE), and PK data through the end of Visit 2. Each dose level is expected to have a minimum of 5 evaluable subjects who receive the assigned treatment and complete study procedures. Data from all subjects will be reviewed to ensure the results meet acceptable safety and target PK profiles. Although this is a dose escalation study, a lower dose may be administered in the next groups. Further, the same dose may be tested in 2 groups or an intermediate dose may be tested to gain more information regarding safety, tolerability, and/or PK.

Study Design

Healthy Subjects

SAD-HS is anticipated to consist of 5 dose levels, with the flexibility to evaluate a sixth level. Each level will include 8 subjects. Overall, subjects will be allocated to receive EP547 or placebo as a single oral (PO) dose in a 3:1 ratio (EP547:placebo) within each dose level. The initial dose level for

SAD-HS will be 25 mg, which is 23-fold lower than the human equivalent dose (HED) of the no-observed-adverse-effect level (NOAEL) in monkeys, the most sensitive and relevant species. Following confirmation by the Safety Review Team that escalation should proceed, each subsequent dose level tested in SAD-HS will be increased by no more than 3-fold from the preceding dose level. Dose levels to be tested will not exceed 1,100 mg.

All dose levels in SAD-HS will be dosed according to a sentinel dosing design to ensure optimal safety. This means that initially, 2 subjects in each dose level will be allocated to receive EP547 or placebo. If the safety and tolerability results of the first 24 hours following dosing for the initial subjects are acceptable to the Safety Review Team, the other 6 subjects will be randomized in a 5:1 ratio (EP547:placebo) to receive EP547 or placebo.

The following treatments for SAD-HS are planned to be administered. However, fewer dose levels may be evaluated if the data from those groups can fully meet the objectives of the study.

Group 1: single PO dose of 25 mg EP547 (n = 6) or matching placebo (n = 2)

Group 2: single PO dose of EP547 that is no more than 3-fold greater than the dose in Group 1 (n = 6) or matching placebo (n = 2)

Group 3: single PO dose of EP547 that is no more than 3-fold greater than the dose in Group 2 (n = 6) or matching placebo (n = 2)

Group 4: single PO dose of EP547 that is no more than 3-fold greater than the dose in Group 3 (n = 6) or matching placebo (n = 2)

Group 5: single PO dose of EP547 that is no more than 3-fold greater than the dose in Group 4 [redacted] (n = 6) or matching placebo (n = 2)

If an additional dose level requires evaluation after conducting Group 5, Group 6 may be enrolled to evaluate a single PO dose of EP547 that is no more than 3-fold higher than the highest dose evaluated in the previous dose levels and less than or equal to 1,100 mg (n = 6) or matching placebo (n = 2).

MAD-HS can begin after 3 dose levels of SAD-HS have been fully evaluated by the Safety Review Team. Subjects who participated in SAD-HS may not participate in MAD-HS. All dose levels in MAD-HS must fall within the range of doses tested in SAD-HS that were confirmed to be well tolerated.

The initial dose level for MAD-HS will be no higher than the second dose tested in SAD-HS with predicted PK concentrations no higher than those observed in SAD-HS. Following confirmation by the Safety Review Team that escalation should proceed, each subsequent dose level tested in MAD-HS will be increased by no more than 3-fold from the preceding dose level. MAD-HS is anticipated to consist of 3 dose levels. Each level will include 8 subjects who will be randomized to receive EP547 or placebo as a daily PO dose over 7 days in a 3:1 ratio (EP547:placebo); there will be no sentinel dosing.

The following treatments for MAD-HS are planned to be administered. However, fewer dose levels may be evaluated if the data from those groups can fully meet the objectives of the study.

Group 1: daily PO dose of EP547 that is no higher than the second dose tested in SAD-HS with predicted PK concentrations no higher than those observed in SAD-HS (n = 6) or matching placebo (n = 2) over 7 days

Group 2: daily PO dose of EP547 that is no more than 3-fold greater than the dose in Group 1 (n = 6) or matching placebo (n = 2) over 7 days

Group 3: daily PO dose of EP547 that is no more than 3-fold greater than the dose in Group 2 (n = 6) or matching placebo (n = 2) over 7 days

Subjects with Cholestatic Pruritus

SD-CP may be conducted when the results from all dose levels of SAD-HS have been fully evaluated by the Safety Review Team. SD-CP is not placebo-controlled (ie, all subjects will receive EP547) and will be conducted in an unblinded manner. The dose level for SD-CP will be no higher than the third dose tested in SAD-HS. SD-CP will consist of 1 dose level. The dose level will include 6 subjects who will receive EP547 as a single PO dose.

MAD-CP can begin when the results from SD-CP have been fully evaluated by the Safety Review Team. Based on data obtained from SD-CP, the EP547 dose to be evaluated in MAD-CP must have predicted steady-state PK concentrations lower than that of the highest tolerated dose in MAD-HS. MAD-CP is anticipated to consist of 1 dose level. If an additional dose level requires evaluation after conducting the first dose level, a second dose level may be enrolled to evaluate a daily PO dose of EP547 that is no more than 3-fold greater than the dose in the previous group. Each dose level will include a minimum of 8 subjects who will be randomized to receive EP547 or placebo as a daily PO dose over 7 days in a 3:1 ratio (EP547:placebo); there will be no sentinel dosing. If additional subjects are available to participate in any MAD-CP dose level, up to 4 more subjects (for a total of 12) may be enrolled.

Subjects with Uremic Pruritus

SD-UP may be conducted when the results from all dose levels of SAD-HS have been fully evaluated by the Safety Review Team. SD-UP is not placebo-controlled (ie, all subjects will receive EP547) and will be conducted in an unblinded manner. The dose level for SD-UP will be no higher than the third dose tested in SAD-HS. SD-UP will consist of 1 dose level. The dose level will include 6 subjects who will receive EP547 as a single PO dose the day after a hemodialysis session.

MAD-UP can begin when the results from SD-UP have been fully evaluated by the Safety Review Team. Based on data obtained from SD-UP, the EP547 dose to be evaluated in MAD-UP must have predicted steady-state PK concentrations lower than that of the highest tolerated dose in MAD-HS. MAD-UP is anticipated to consist of 1 dose level. If an additional dose level requires evaluation after conducting the first dose level, a second dose level may be enrolled to evaluate a daily PO dose of EP547 that is no more than 3-fold greater than the dose in the previous group. Each dose level will include a minimum of 8 subjects who will be randomized to receive EP547 or placebo as a daily PO dose over 7 days in a 3:1 ratio (EP547:placebo) with hemodialysis occurring 4 to 6 hours after dosing on Days 1, 4, and 6; there will be no sentinel dosing. If additional subjects are available to participate in any MAD-UP dose level, up to 4 more subjects (for a total of 12) may be enrolled.

Study Schedule

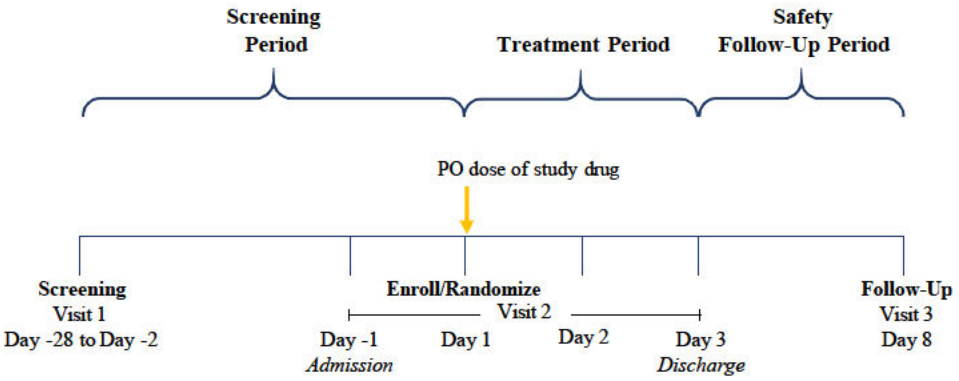
Although the number of dose levels to be evaluated in each single dose segment may differ, the overall study design amongst them is similar. The same is true for the multiple dose segments.

Subjects should fast for at least 8 hours before study days that require a blood sample for assessment of clinical chemistry, multiple blood samples for PK, [redacted] as described in the Fasting Requirements section.

Single Dose Segments

Screening:	Visit 1 (Screening) is to occur between Day -28 and Day -2.
Treatment Period:	There is 1 mandatory confinement period in the clinic (Visit 2), beginning from Day -1 (admission) to Day 3 until after the 48-hour postdose assessments are completed (discharge).
Safety Follow-Up:	Visit 3 (Follow-Up Visit) is to occur on Day 8±1 (approximately 7 days after study drug administration).

Study Schedule for the Single Dose Segments

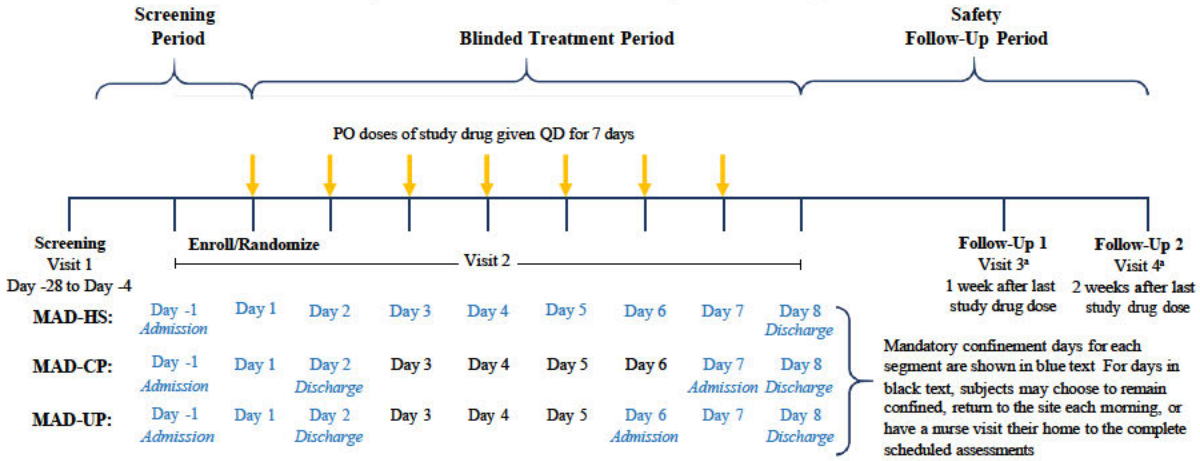


PO = oral
Shading represents the mandatory period when subjects will be confined to the study site.

Multiple Dose Segments

Screening:	Visit 1 (Screening) is to occur between Day -28 and Day -4.
Blinded Treatment Period:	There is 1 confinement period in the clinic (Visit 2), beginning from Day -1 (admission) to Day 8 until after the 24-hour post-last dose assessments are completed (discharge). The full confinement period is mandatory for MAD-HS. For Day 3 through Day 6 in MAD-CP and Day 3 through Day 5 in MAD-UP, subjects may choose to remain confined, return to the site each morning, or have a nurse visit their home to complete scheduled assessments.
Safety Follow-Up:	Visit 3 (Follow-Up Visit 1) and Visit 4 (Follow-Up Visit 2) are to occur approximately 1 and 2 weeks after the last dose of study drug, respectively. Subjects are to return to the site to complete scheduled assessments for Safety Follow-Up Visits. However, a nurse visit to their home may be permitted on a case-by-case basis with prior approval of the Sponsor.

Study Schedule for the Multiple-Dose Segments



CP = cholestatic pruritus; HS = healthy subject; MAD = multiple ascending dose; PO = oral; QD = once daily; UP = uremic pruritus
Shading represents the period when subjects may be confined to the study site.
[a] Subjects are to return to the site to complete scheduled assessments for Safety Follow-Up Visits. However, a nurse visit to their home may be permitted on a case-by-case basis with prior approval of the Sponsor.

Number of Subjects (Planned):

A total of 80 to 132 subjects are expected to participate in the study, including 64 to 72 healthy subjects, 8 to 30 subjects with cholestatic pruritus, and 8 to 30 subjects with uremic pruritus (5 to 6 groups of 8 subjects each in SAD-HS; 3 groups of 8 subjects each in MAD-HS; 1 group of 6 subjects each in SD-CP and SD-UP; 1 to 2 groups of 8 to 12 subjects each in MAD-CP and MAD-UP; up to 6 subjects each from the SD-CP and SD-UP segments will participate in the MAD segment specific to their population if they meet the requirement for pruritus).

Subjects who discontinue before completing the treatment period or are non-evaluable will be replaced in order to meet evaluable subject requirements.

Diagnosis and Main Criteria for Inclusion:

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

Healthy Subjects

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

1. Age 18 to 60 years, inclusive
2. If female, must be willing to not donate eggs from the time of informed consent until 30 days after the last dose of study drug and:
    a. Is surgically sterile; or
    b. Has been amenorrhoeic for ≥1 year and is over the age of 55 years; or
    c. Has a negative serum pregnancy test at Screening and agrees to use a barrier method (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, vasectomized partner, or abstinence) from the time of informed consent until 30 days after the last dose of study drug

Abstinence is considered a highly effective method of birth control if the subject refrains from heterosexual intercourse from the time of informed consent until 30 days after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

3. If male and is not surgically sterile for at least 3 months, must be willing to not donate sperm and must agree to use a barrier method of contraception (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, female surgical sterilization, male vasectomy, or abstinence) from Screening through 90 days after the last dose of study drug
4. Body mass index ≥19 to ≤35 kg/m^2
5. Medically healthy with no clinically significant medical history, physical examination, vital sign, standard 12-lead ECG, chemistry, hematology, urinalysis, or coagulation results at Screening as deemed by the Investigator
6. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study (including required confinement periods), and understand and provide written consent

Subjects with Cholestatic Pruritus

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

1. Age 18 to 80 years, inclusive
2. Has a cholestatic disorder as a result of one of the following conditions:
    a. Diagnosis of primary biliary cholangitis (PBC) that is consistent with American Association for the Study of Liver Diseases (AASLD) (Lindor 2019) and European Association for the Study of the Liver (EASL) Practice Guidelines (EASL 2017), defined as having ≥2 of the following 3 diagnostic factors:
        i. History of elevated alkaline phosphatase (ALP) levels for at least 6 months
        ii. Positive antimitochondrial antibody (AMA) titer or if AMA is negative or low titer (≤1:80), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (pyruvate dehydrogenase complex E2 component and 2-oxo-glutaric acid dehydrogenase complex)
        iii. Liver biopsy consistent with PBC (collected at any time before Screening)
    b. Diagnosis of primary sclerosing cholangitis (PSC) based on cholangiography at any point in time (EASL 2009, Chapman 2010)
    c. Confirmed diagnosis of chronic hepatitis B or C virus (HBV or HCV)
3. If female, must be willing to not donate eggs from the time of informed consent until 30 days after the last dose of study drug and:
    a. Is surgically sterile; or
    b. Has been amenorrhoeic for ≥1 year and is over the age of 55 years; or
    c. Has a negative serum pregnancy test at Screening and agrees to use a barrier method (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, vasectomized partner, or abstinence) from the time of informed consent until 30 days after the last dose of study drug
    Abstinence is considered a highly effective method of birth control if the subject refrains from heterosexual intercourse from the time of informed consent until 30 days after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

4. If male and is not surgically sterile for at least 3 months, must be willing to not donate sperm and must agree to use a barrier method of contraception (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, female surgical sterilization, male vasectomy, or abstinence) from Screening through 90 days after the last dose of study drug
5. No clinically relevant medical history, physical examination, vital sign, standard 12-lead ECG, chemistry, hematology, urinalysis, or coagulation results at Screening beyond what is expected for subjects with a cholestatic disorder that would place the subject at undue risk as deemed by the Investigator
6. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study (including required confinement periods), and understand and provide written consent
7. For subjects participating in MAD-CP, has experienced self-reported daily or near-daily moderate to severe pruritus for >4 weeks before Screening
8. [redacted]
9. If currently taking medications to treat the cholestatic disorder, must be on a stable dose for >12 weeks before Screening and plans to maintain the regimen throughout the study
10. If currently taking medications known to impact pruritus, must be on a stable dose for >4 weeks before Screening and plans to maintain the regimen throughout the study

Subjects with Uremic Pruritus

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

1. Age 18 to 80 years, inclusive
2. Has end-stage renal disease (ESRD) and is receiving hemodialysis 3× per week of at least 4 hours in duration for ≥3 months before Screening; hemodialysis must be adequate (ie, ≥2 urea reduction ratio measurements ≥65% on different hemodialysis days from the month before Screening to Day -1)
3. If female, must be willing to not donate eggs from the time of informed consent until 30 days after the last dose of study drug and:
    a. Is surgically sterile; or
    b. Has been amenorrhoeic for ≥1 year and is over the age of 55 years; or
    c. Has a negative serum pregnancy test at Screening and agrees to use a barrier method (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, vasectomized partner, or abstinence) from the time of informed consent until 30 days after the last dose of study drug
    Abstinence is considered a highly effective method of birth control if the subject refrains from heterosexual intercourse from the time of informed consent until 30 days after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.
4. If male and is not surgically sterile for at least 3 months, must be willing to not donate sperm and must agree to use a barrier method of contraception (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, female surgical sterilization, male vasectomy, or abstinence) from Screening through 90 days after the last dose of study drug

5. No clinically relevant medical history, physical examination, vital sign, standard 12-lead ECG, chemistry, hematology, or coagulation results at Screening beyond what is expected for subjects with ESRD that would place the subject at undue risk as deemed by the Investigator
6. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study (including required confinement periods), and understand and provide written consent
7. For subjects participating in MAD-UP, has experienced self-reported daily or near-daily moderate to severe pruritus for >4 weeks before Screening
8. [redacted]
9. If currently taking medications known to impact pruritus, must be on a stable dose for >4 weeks before Screening and plans to maintain the regimen throughout the study

Exclusion Criteria

Healthy Subjects

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

1. Any prescription medications within 14 days of Screening
2. Positive result for human immunodeficiency virus (HIV) or presence of actively replicating viral hepatitis due to HBV or HCV infection at Screening
3. 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
4. Tobacco product or electronic cigarette use within 90 days of Day -1
5. Positive drug, alcohol, or cotinine screen results at Screening or Day -1
6. Significant history of abuse of drugs, solvents, or alcohol (>3 servings or units/day on average; 1 unit = 12 ounces [350 mL] of 5% alcohol beer, 5 ounces [150 mL] of 12% wine, or 1.5 ounces [45 mL] of 80 proof distilled spirits) in the past 2 years before Screening
7. Unable or unwilling to abstain from alcohol for 48 hours before Screening and from 48 hours before Day -1 until the end of the study
8. [redacted]
9. Participation in any clinical study with an investigational or approved drug/device within 30 days before Screening or is planning to participate in another clinical study while enrolled in this study
10. Allergy to any component of study drug
11. Previously participated in another dose level group in SAD-HS or MAD-HS
12. Donated or lost >200 mL of blood within 60 days before Day -1, donated plasma within 7 days before Day -1, or plans to donate blood or plasma during the study
13. Female who is pregnant, nursing, or intends to become pregnant during the study
14. Is directly affiliated with the study at the study 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 study site
15. 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.
16. Subject is, in the opinion of the Investigator, not suitable to participate in the study

Subjects with Cholestatic Pruritus

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

1. Has a concomitant disease or a history of any medical condition that, in the opinion of the Investigator, could pose undue risk to the subject, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to:
    a. Presence of decompensated cirrhosis within 12 months before Screening
    b. Presence of cirrhosis at Screening with Child-Pugh score >6, ascites or hepatic encephalopathy within 12 months of Screening, albumin of ≤2.8 g/dL (≤28 g/L), total bilirubin ≥3 mg/dL (≥51.3 µmol/L), or international normalized ratio (INR) ≥1.8
    c. Presence of drug-induced cholestasis
2. Recent, current, or planned use of any new medications or adjustments to current medications within 14 days of Screening until the end of the study
3. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× upper limit of normal (ULN) at Screening
4. Screening platelet count <100,000/µL
5. Screening total bilirubin ≥3 mg/dL (≥51.3 µmol/L) (total bilirubin ≥3 mg/dL [≥51.3 µmol/L] is acceptable if bilirubin is fractionated and direct bilirubin <50%)
6. Positive result for HIV at Screening
7. 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
8. Positive drug, alcohol, or cotinine screen results at Screening or Day -1
9. Significant history of abuse of drugs, solvents, or alcohol (>3 servings or units/day on average; 1 unit = 12 ounces [350 mL] of 5% alcohol beer, 5 ounces [150 mL] of 12% wine, or 1.5 ounces [45 mL] of 80 proof distilled spirits) in the past 2 years before Screening
10. Unable or unwilling to abstain from alcohol for 48 hours before Screening and from 48 hours before Day -1 until the end of the study
11. Participation in any clinical study with an investigational or approved drug/device within 30 days before Screening or is planning to participate in another clinical study while enrolled in this study (previous participation in SD-CP is allowed)
12. Allergy to any component of study drug
13. Previously participated in another dose level group in MAD-CP
14. Donated or lost >200 mL of blood within 60 days before Day -1, donated plasma within 7 days before Day -1, or plans to donate blood or plasma during the study
15. Female who is pregnant, nursing, or intends to become pregnant during the study
16. Is directly affiliated with the study at the study 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 study site
17. 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.
18. Subject is, in the opinion of the Investigator, not suitable to participate in the study
19. Scheduled to receive a liver transplant during the study (placement on a transplant waiting list is not exclusionary)

20. Is receiving ongoing ultraviolet B (UVB) treatment or anticipates receiving such treatment during the study
21. For subjects participating in MAD-CP, pruritus is secondary to biliary obstruction
22. History or presence of hepatocellular carcinoma, hepatic abscess, or acute portal vein thrombosis

Subjects with Uremic Pruritus

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

1. Has a concomitant disease or a history of any medical condition that, in the opinion of the Investigator, could pose undue risk to the subject, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to:
    a. Significant systolic or diastolic heart failure (eg, New York Heart Association Class IV congestive heart failure
2. Recent, current, or planned use of any new medications or adjustments to current medications within 14 days of Screening until the end of the study unless modification to the hemodialysis regimen is needed or for subject safety
3. Positive result for HIV or presence of actively replicating viral hepatitis due to HBV or HCV infection at Screening
4. 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
5. Positive alcohol screen result at Screening or Day -1 or known use of drugs or tobacco at Screening
6. Significant history of abuse of drugs, solvents, or alcohol (>3 servings or units/day on average; 1 unit = 12 ounces [350 mL] of 5% alcohol beer, 5 ounces [150 mL] of 12% wine, or 1.5 ounces [45 mL] of 80 proof distilled spirits) in the past 2 years before Screening
7. Unable or unwilling to abstain from alcohol for 48 hours before Screening and from 48 hours before Day -1 until the end of the study
8. Participation in any clinical study with an investigational or approved drug/device within 30 days before Screening or is planning to participate in another clinical study while enrolled in this study (previous participation in SD-UP is allowed)
9. Allergy to any component of study drug
10. Previously participated in another dose level group in MAD-UP
11. Female who is pregnant, nursing, or intends to become pregnant during the study
12. Is directly affiliated with the study at the study 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 study site
13. 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.
14. Subject is, in the opinion of the Investigator, not suitable to participate in the study
15. Scheduled to receive a kidney transplant during the study (placement on a transplant waiting list is not exclusionary)
16. Is receiving ongoing UVB treatment or anticipates receiving such treatment during the study
17. Known noncompliance with hemodialysis treatment that, in the opinion of the Investigator, would impede completion or validity of the study

18. For subjects participating in MAD-UP, pruritus is attributed mainly to any disease unrelated to kidney disease, is only present during the hemodialysis sessions, or is attributed to a skin disorder that occurs in this population with associated itch (eg, acquired perforating dermatosis)

Outcome Measures:

Primary Safety Outcome Measures

- AEs
- Clinical laboratory assessments
- Vital signs and body weight
- Standard 12-lead ECGs
- Physical examinations

Secondary Pharmacokinetic and Cardiodynamic Outcome Measures

- Plasma EP547 and metabolites (as applicable) concentrations
- Plasma PK parameters estimated using noncompartmental analysis (NCA), as appropriate[1]:
    - SAD segments: C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{∞}, AUC_t, $\%AUC_{extra}$, CL/F, and V_z/F
    - MAD segments: C_{max}, C_{trough}, t_{max}, k_{el}, $t_{1/2}$, AUC_{τ} (as appropriate), AUC_t, CL/F, V_z/F, and R_{ss}
- Urine PK parameters estimated using NCA, as appropriate:
    - SAD-HS segment: A_e, F_e, CLr
- Skin EP547 and metabolites (as applicable) concentrations
- Holter monitoring for 12-lead ECG acquisition and subsequent cardiodynamic analysis

[redacted]

Study Drug Materials and Management:

Study Drugs

EP547 lockable capsules will be prepared by the central vendor to contain the desired amount of drug substance to meet the needs of the given dose level. Each lockable placebo capsule will contain placebo such as microcrystalline cellulose and will be manufactured in a way to ensure the study blind. Each dose may be made up of multiple capsules of the same or different capsule strengths.

Study Drug Packaging and Labeling

Just-in-time manufacturing will be used to supply the study drug, EP547 or placebo capsules, at the specified dose level selected for each segment. Each study drug kit will be labeled with a unique kit

[1] The PK parameter definitions are in Section 4.

number and will be supplied to study sites in a blinded manner. Study drug shipments will be sent to sites with code break envelope(s) containing the treatment assignment(s) that can be utilized by the site for emergency unblinding.

Study Drug Storage

The study drug capsules may be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F), with excursions to 10°C (50°F).

Study Drug Administration

Study drug is to be administered orally as intact capsules (swallowed whole, not chewed or crushed), and taken with water. During the MAD segments, doses are to be administered daily at approximately the same time of day over 7 days. There are no fasting or fed requirements for study drug administration (only for study procedures as described in the Fasting Requirements section). Subjects who routinely take a bile acid sequestrant (eg, cholestyramine, colestipol, or colesevelam) will be instructed to hold their morning dose until 2 hours after study drug administration. If their bile acid sequestrant baseline dosing regimen does not allow for a 2-hour hold, dosing of these medications must be held for a minimum of 1 hour after study drug administration. Alternatively, the bile acid sequestrant may be taken at least 4 hours prior to study drug administration.

Additional Dosing Instructions for Subjects with Uremic Pruritus

For subjects in SD-UP, Day 1 (study drug administration) must be the day after a hemodialysis session.

For subjects in MAD-UP, study drug will be administered 4 to 6 hours before the hemodialysis session on Days 1, 4, and 6 and at approximately the same time of day on Days 2, 3, 5, and 7 (days without a hemodialysis session).

Study Drug Dispensing and Accountability

All study drug is to be administered at the study site. The site staff will be responsible for documenting and maintaining study drug dispensation and accountability records.

Key Study Procedures and Safety, Pharmacokinetic, and Pharmacodynamic Evaluations:

At specific visits outlined in the Schedule of Assessments (Appendix A for the single dose segments and Appendix B for the multiple dose segments), subjects will undergo safety, PK, and pharmacodynamic (PD) assessments. Unless indicated otherwise, the assessments discussed below apply to all single and multiple dose segments. [redacted]

Key Study Procedures

Fasting Requirements

Subjects should fast for at least 8 hours before study days that require a blood sample for assessment of clinical chemistry, multiple blood samples for PK, [redacted]. Water is acceptable in the morning of site visits and each study day while confined to the study site to ensure the subject is hydrated for laboratory sample collection. On days with multiple blood samples for PK, study drug will be administered with approximately 240 mL of water, additional water will not be allowed from 1 hour predose to 1 hour postdose, and subjects will remain fasted until after the 4-hour PK blood sample is collected. If a subject with ESRD has a daily fluid restriction, study drug may be administered with a smaller volume of water at the Investigator's discretion.

Safety Assessments

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

Although SAD-HS and all of the MAD segments will be conducted in a blinded manner (ie, subjects, Investigator, study-site personnel, and CRO staff not involved in PK sample analysis or regulatory reporting will be blinded to treatment), the Sponsor, including the Sponsor Medical Monitor, will be unblinded to treatment assignment to assess safety on an ongoing basis. The SD-CP and SD-UP segments are not placebo-controlled (ie, all subjects will receive EP547) and will be conducted in an unblinded manner.

Adverse Event Collection

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

Discontinuation of Study Drug Due to an Adverse Event

Subjects may be withdrawn from the study due to an AE at any time based on the clinical judgment of the Investigator in consideration with the subject's wishes. Subjects who terminate the treatment period early should complete the early study termination evaluations as soon as possible after the last dose of study drug, ideally within 2 days after the last dose. If termination occurs during the treatment period, the subject will have a follow-up visit approximately 1 week (±1 day) after the last dose of study drug. If termination of the treatment period occurs while participating in a MAD segment, the subject will also have a follow-up visit approximately 2 weeks (±2 days) after the last dose of study drug. After the final study visit, further standard of care treatment will be determined by the subject and treating physician. Subjects who discontinue before completing the treatment period or are non-evaluable may be replaced in order to meet evaluable subject requirements.

Safety Criteria for Determining if a Dose Level is Well Tolerated

The nature of any AEs, including the number and severity of AEs, and the suspected relationship of the AEs to study drug, will be used to determine if a dose level for a given segment is considered generally well tolerated in the population in which it is being evaluated.

Safety Criteria for Stopping Dose Escalation

Dose escalation (or MAD dosing) for any segment will cease if 50% of EP547-treated subjects in the same dose level experience a treatment-related AE of severe intensity. Other signs of limited tolerability will also be considered, such as clustering of AEs within a System Organ Class that are largely moderate to severe in intensity. Additionally, all clinically significant abnormalities in chemistry, hematology, urinalysis, standard 12-lead ECG, physical examination, and vital sign results will be evaluated by the Safety Review Team before any dose escalation.

Safety Criteria for Stopping Dosing

Study drug dosing will be held for all subjects if any of the following criteria are met:

- A subject receiving EP547 experiences a serious adverse reaction (ie, a serious AE [SAE] considered at least possibly related to the study drug)
- At least 2 subjects receiving EP547 in the same dosing group experience a severe non-serious adverse reaction (ie, a severe, non-serious AE considered at least possibly related to the study drug)

Study drug dosing will only restart when all appropriate evaluations are performed to ensure subject safety and only if the Safety Review Team agrees that it is appropriate to restart. External expert opinion may be sought to assist in evaluating the risk to subjects and determining if study drug dosing should be continued.

Pharmacokinetic Criteria for Selecting, Adjusting, or Stopping Doses

PK concentrations and/or PK parameters from each dose level in each population will be evaluated by the Safety Review Team before selection of doses in the subsequent segment. Any anticipated accumulation will be considered for PK predictions of doses in the MAD segments. There are no pre-defined PK criteria to adjust or stop dosing.

Pharmacokinetic Assessments

Blood, urine, and skin samples for PK will be utilized to analyze EP547 concentrations; the metabolite profile may also be analyzed from these samples.

Blood Sampling for Pharmacokinetics

Blood sampling for PK of EP547 will be collected as follows:

- **SAD-HS, SD-CP, and SD-UP:** predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours postdose on Day 1; 18, 24, and 36 hours postdose on Day 2; 48 hours postdose on Day 3; and at follow-up on Day 8.
- **MAD-HS:** predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 18 hours postdose relative to the dose of study drug on Day 1; predose on Day 2 through Day 6; predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 24 hours postdose relative to the last dose of study drug on Day 7; and at follow-up on Day 14 and Day 21.
- **MAD-CP:** predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 18 hours postdose relative to the dose of study drug on Day 1; predose on Day 2; predose on Day 4; predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 24 hours postdose relative to the last dose of study drug on Day 7; and at follow-up on Day 14 and Day 21.
- **MAD-UP:** predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 18 hours postdose relative to the dose of study drug on Days 1, 2, and 6; predose on Day 4; predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 24 hours postdose relative to the last dose of study drug on Day 7; and at follow-up on Day 14 and Day 21.

The MAD dosing and PK blood sampling schedule is summarized in Appendix C. The assessment window for blood sample collection timepoints for the single and multiple dose segments is also included in Appendix C.

Urine Collection for Pharmacokinetics (SAD-HS Only)

Urine sampling for PK of EP547 will be collected at predose (-6 to 0 hours) and from >0 to 6, >6 to 12, and >12 to 18 hours postdose on Day 1; >18 to 24, >24 to 30, and >30 to 36 hours postdose on Day 2; and >36 to 42 and >42 to 48 hours postdose on Day 3.

Skin Biopsy for Pharmacokinetics (Last Dose Level for MAD-HS and All Dose Levels for MAD-CP and MAD-UP Only)

Given that EP547 is hypothesized to be an inverse agonist (inhibitor) of mas-related G protein-coupled receptor X4 (MRGPRX4) in the skin to reduce itch, three 3-mm biopsies of the skin from the back will be performed under local anesthesia on Day 1 at 2 hours postdose with an assessment window of +30 minutes. One biopsy will be used for PK to evaluate drug concentrations at the site of action and

the other 2 biopsies will be used for PD assessment as described in the Blood Sampling and Skin Biopsy for Metabolite Analysis section to further elucidate the mechanism of action of EP547.

Cardiodynamic Assessment

Holter Monitoring for 12-Lead ECG Acquisition and Subsequent Cardiodynamic Analysis (SAD-HS Only)

Clinical evaluation of QT/QTc interval prolongation risk and proarrhythmic potential will be conducted for EP547, which is recommended by the United States (US) Food and Drug Administration (FDA) for all new non-antiarrhythmic drugs having systemic bioavailability (FDA 2005a). Continuous digital 12-lead ECGs will be recorded from approximately 1 hour predose on Day 1 to 24 hours postdose on Day 2 under constant supervision for subjects in SAD-HS only. Subjects will rest quietly in the supine position for at least 10 minutes before each extraction timepoint and for 5 minutes during each extraction with the understanding that a full undisturbed supine period may not be possible given other assessments at competing timepoints. Twelve-lead ECG extraction timepoints will be at -30, -20, and -10 minutes predose on Day 1; at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours postdose on Day 1; and at 18 and 24 hours postdose on Day 2. Twelve-lead ECGs will be extracted from the continuous recording from a 5-minute window preceding the ECG timepoints and scheduled to end 1 to 2 minutes before the scheduled PK draw to conduct early QT assessment based on concentration-QT analysis. Subjects are to continue fasting through 4 hours postdose as food can impact the results.

[redacted]

An additional biopsy for PK analysis is described in the Pharmacokinetic Assessments section.

[redacted]

[redacted]

Statistical Methods:

Descriptive statistics will be presented for study outcome measures by treatment and study day, as appropriate.

Sample Size Considerations:

No formal sample size calculation has been made. The sample size has been selected to provide adequate information on safety, tolerability, PK, and PD following single and multiple doses of EP547.

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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 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
A_e	amount of drug excreted in urine
AE	adverse event
AASLD	American Association for the Study of Liver Diseases
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemistry
$\%AUC_{extra}$	Percentage of estimated part for the calculation of AUC_∞
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t
AUC_τ	area under the plasma concentration time curve over a dosing interval τ
AUC_∞	area under the concentration-time curve from time 0 to infinity
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CKD	chronic kidney disease
CL/F	apparent clearance
CLr	renal clearance
C_{max}	maximum (peak) plasma concentration
CP	cholestatic pruritus
CPK	creatine phosphokinase
CRO	Contract Research Organization
C_{trough}	trough plasma concentration
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form

Abbreviation or Specialist Term	Explanation
ESRD	end-stage renal disease
FDA	Food and Drug Administration
F_e	urinary recovery rate
FSH	follicle-stimulating hormone
GGT	gamma-glutamyltransferase
HED	human equivalent dose
HEENT	head, eyes, ears, nose, throat
HEK	human embryonic kidney
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-c	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HS	healthy subject
GCP	Good Clinical Practice
IC_{100}	maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgE	immunoglobulin E
INR	international normalized ratio
IP-1	inositol phosphate-1
IRB	Institutional Review Board
k_{el}	terminal elimination rate constant
LDH	lactate dehydrogenase
LDL-c	low-density lipoprotein cholesterol
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MRGPR	mas-related G protein-coupled receptor
MRSD	maximum recommended starting dose
NCA	noncompartmental analysis
NOAEL	no-observed-adverse-effect-level

Abbreviation or Specialist Term	Explanation
OTC	over-the-counter
PBC	primary biliary cholangitis
PD	pharmacodynamics
[redacted]	[redacted]
PK	pharmacokinetics
PO	oral
PQC	product quality complaint
PSC	primary sclerosing cholangitis
PT	prothrombin time
QC	quality control
QTc	corrected QT
R_{ss}	exposure ratio
SAD	single ascending dose
SAE	serious adverse event
SAER	Serious Adverse Event Report
SAP	Statistical Analysis Plan
SD	single dose
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
t_{max}	time to achieve maximum (peak) plasma concentration
ULN	upper limit of normal
UP	uremic pruritus
US	United States
UVB	ultraviolet B
V_z/F	apparent volume of distribution at terminal phase
WBC	white blood cell
WHO	World Health Organization
[redacted]	[redacted]

5. INTRODUCTION

5.1. Cholestatic and Uremic Pruritus

Patients with cholestatic liver disease, such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), often suffer from chronic itch or pruritus that is experienced by up to 70% to 80% of these patients over the course of their disease (Mittal 2016).

Uremic pruritus is common in patients with kidney failure, with prevalence rates ranging from 20% to 90% in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) receiving hemodialysis. The broad range is likely due to varying characteristics of the studied populations, the era when studies were performed, and the diagnostic instruments used to define itch (Shirazian 2017). A recent meta-analysis of 42 studies comprising 11,800 patients estimates that the overall prevalence of CKD-associated pruritus among adult hemodialysis patients is 55% (Hu 2018).

Patients with cholestatic or uremic pruritus have difficulty coping with the intense itching and develop associated stress. Pruritus also has a negative effect on patients' quality of life, sleep, emotional state, and social relations (Bassari 2015, Ibrahim 2016), and contributes to the development of skin and soft tissue lesions and/or infections (Ozen 2018).

The pathophysiology of cholestatic and uremic pruritus is not fully understood and the itch-causing pruritogen(s) and their cognate receptor(s) have remained largely elusive. Cholestatic itch is often nonresponsive to standard pharmacological treatments, including antihistamines, and instead requires physically removing the causative obstruction (such as gallstones), draining the bile, or transplanting the liver to alleviate itch (Bergasa 2014). Because these procedures are often curative, the responsible pruritogens are hypothesized to originate from the liver and bile. Numerous candidate pruritogens are present in bile and up-regulated in cholestatic patients, including opioids, lysophosphatidic acid, bilirubin, and bile acids. Therapies targeting these mechanisms, such as opioid antagonists, rifampicin, and bile acid-binding resins like cholestyramine, are frontline therapy for cholestatic itch (Bassari 2015, Mittal 2016), however, patients are poorly managed with these therapies (Bassari 2015, Mittal 2016).

Uremic pruritus is typically resistant to treatment and difficult to manage. Other than a kidney transplant, which is curative, there remains considerable uncertainty about effective treatments and optimal solutions remain poorly defined (Simonsen 2017). The initial therapy for hemodialysis patients with uremic pruritus may consist of dialysis modification, correction of phosphorus and calcium levels, hyperparathyroid treatment (if applicable), and topical treatments (Rayner 2017). Patients with continued symptoms despite initial therapy may be treated with an oral antihistamine and, if that is ineffective, gabapentin, selective serotonin reuptake inhibitors, or leukotriene receptor antagonists (Mettang 2016). For patients who are refractory to previous lines of therapy, ultraviolet B (UVB) phototherapy is a therapeutic option (Mettang 2016). UVB irradiation is effective in the treatment of uremic pruritus, however, symptoms may resume after stopping therapy.

Although a variety of interventions have been explored, the need for improved treatment of cholestatic and uremic pruritus remains high. Therefore, development of additional safe and effective therapeutic options for these conditions is essential.

5.2. Mas-Related G Protein-Coupled Receptor X4

Mas-related G protein-coupled receptors (MRGPRs) represent a family of 8 human chemosensory receptors that reside chiefly in barrier tissues, sensory neurons, and immune cells that recognize a variety of endogenous and exogenous potentially offensive stimuli.

MRGPRs mediate immune-like non-immunoglobulin E (IgE), non-histaminergic, non-eosinophilic reactions generally referred to as pseudo-allergic or autoreactive diseases.

MRGPRX4 is expressed in a subset of dorsal root ganglia neurons, skin sensory afferents, dendritic cells, melanocytes, and polymorphonuclear leukocytes and has been demonstrated to be a receptor relevant to cholestatic pruritus (Meixiong 2019a, Meixiong 2019b, Yu 2019) (data on file). Although most, if not all components of bile activate MRGPRX4 to varying degrees, bile acids and bilirubin in particular are strong agonists of MRGPRX4, and their skin accumulation in association with pruritic cholestatic diseases implicates MRGPRX4 in this disease state (data on file). Many experiments have been conducted and published in support of this, including observations that acute injection of bile acids results in itch in both mice and humans, and bile acid-modulating therapy is effective in controlling patient itch (Meixiong 2019a, Meixiong 2019b, Yu 2019). Similarly, bilirubin has been demonstrated to play a role in itch, and in vitro investigation of bilirubin and metabolites by the Sponsor has shown that a number of heme metabolites in addition to bilirubin can activate MRGPRX4 as effectively as bile acids (data on file).

Disordered bile acid metabolism is also present in patients with CKD and may contribute to pruritus. The effectiveness of UVB phototherapy for alleviating pruritus in this population is supportive of a hypothesis in which heme metabolites and specifically photosensitive renally-cleared urobilin may be accumulating in the skin, interacting with MRGPRX4, and inducing itch.

These data suggest that inhibition of MRGPRX4 may reduce or alleviate pruritus in patients that have a build-up of bile acids and/or heme metabolites and supports investigation in patients with cholestatic or uremic pruritus.

5.3. EP547

EP547 is a potent inverse agonist (low nM inhibitor) of MRGPRX4. In vitro studies have shown that EP547 antagonizes at least 18 MRGPRX4 agonists in several cell lines (overexpressing Chinese hamster ovary [CHO] and human embryonic kidney [HEK]-293 cells and in endogenously expressing SH-4 melanoma cells), utilizing an array of assay readouts (calcium mobilization, inositol phosphate-1 [IP-1] accumulation, and β-arrestin recruitment). In vivo absorption, distribution, metabolism, and excretion studies demonstrated that EP547 is highly bound to human plasma proteins, has high bioavailability with total volume of distribution similar to body water (approximately 0.8 L/kg), and biodistributes to sites of action in the skin and dorsal root ganglion. Pharmacokinetic (PK) studies in monkeys demonstrated that maximum (peak) plasma concentration (C_{max}) occurred approximately 2 hours after oral dosing with a half-life of approximately 18 hours. In vitro safety studies to date demonstrate no meaningful safety signals. [redacted]

[redacted] Additional information for these studies is provided in the Investigator's Brochure.

In view of the available nonclinical data, further development of EP547 for the treatment of cholestatic or uremic pruritus is warranted. This first-in-human study is designed to assess the safety, tolerability, PK, and pharmacodynamics (PD) of single and multiple ascending doses of EP547 in healthy subjects and subjects with cholestatic or uremic pruritus. The outcome of EP-547-101 will inform the design of future clinical studies evaluating EP547.

5.4. EP547 Dose Rationale

[redacted]

The study will consist of a single ascending dose (SAD) segment and a multiple ascending dose (MAD) segment in healthy subjects, along with a single dose segment and multiple dose segment in subjects with cholestatic or uremic pruritus. Dose escalations in the SAD segment for healthy subjects will have a maximum 3-fold increase between doses. [redacted] The MAD doses for healthy subjects must be within the range of the SAD doses tested, with the starting MAD dose level being no greater than the second SAD dose level tested with predicted PK concentrations no higher than those observed in SAD. Dose escalations in the MAD segment will have a maximum 3-fold increase between doses. The initial EP547 dose level for subjects with cholestatic or uremic pruritus (single dose) will be no higher than the third dose tested in the SAD portion conducted in the healthy subjects. The initial dose to be evaluated in the multiple dose portion for subjects with cholestatic or uremic pruritus must have predicted steady-state PK concentrations lower than the highest tolerated dose in the MAD segment conducted in healthy subjects.

Safety criteria to stop dose escalation in both single and multiple dose segments will be implemented as described in Section 7.3.3.

The use of a randomized, placebo control group in healthy subjects for both SAD and MAD assessments and in subjects with cholestatic or uremic pruritus for MAD assessments provides a reference for interpretation of endpoints. A placebo group is not included for the single dose assessment in subjects with cholestatic or uremic pruritus as the objective of that assessment is to confirm PK with acute tolerability evaluation, for which a reference group is unnecessary.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

- To evaluate the safety and tolerability of single and multiple ascending doses of EP547 in healthy subjects and subjects with cholestatic or uremic pruritus

6.2. Secondary Objectives

- To evaluate the PK of single and multiple ascending doses of EP547 in healthy subjects and subjects with cholestatic or uremic pruritus
- To assess QT/corrected QT (QTc) interval prolongation risk using EP547 concentration-QT/QTc modeling in healthy subjects (for use at a later development stage, not as a result of a safety signal)

6.3.

7. INVESTIGATIONAL PLAN

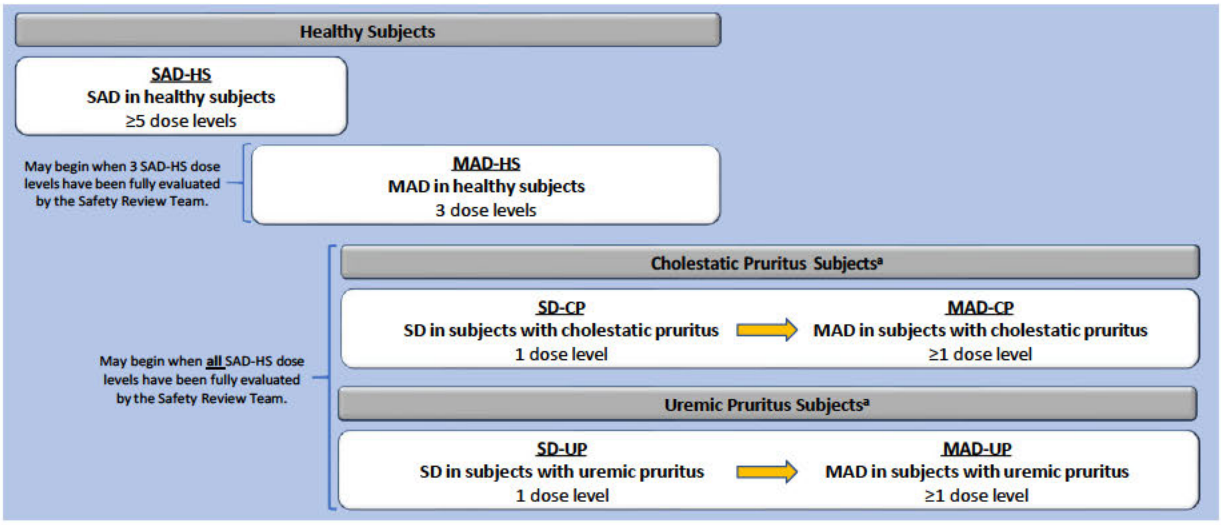
7.1. Overall Study Design

This study is a first-in-human, Phase 1, randomized, single and multiple ascending dose (SAD and MAD) study with EP547 in healthy subjects and subjects with cholestatic or uremic pruritus. As shown in Figure 1, each population will include a SAD or single dose (SD) segment followed by a MAD segment for a total of 6 segments (SAD-HS and MAD-HS in healthy subjects [HS]; SD-CP and MAD-CP in subjects with cholestatic pruritus [CP]; and SD-UP and MAD-UP in subjects with uremic pruritus [UP]). Each segment will evaluate at least 1 dose level. Pruritus is not a mandatory requirement for participation in SD-CP or SD-UP.

Although SAD-HS and all of the MAD segments will be conducted in a blinded manner (ie, subjects, Investigator, study-site personnel, and Contract Research Organization [CRO] staff not involved in PK sample analysis or regulatory reporting will be blinded to treatment), the Sponsor, including the Sponsor Medical Monitor, will be unblinded to treatment assignment to assess safety on an ongoing basis as described in Section 9.3.2.

SAD-HS will evaluate at least 5 dose levels of EP547, establish the highest well-tolerated dose in healthy subjects, and guide MAD dosing in the same population. Evaluation of the first of 3 dose levels for MAD-HS may commence after 3 dose levels from SAD-HS have been fully evaluated by the Safety Review Team. When the results of all dose levels from the SAD-HS segment have been fully evaluated by the Safety Review Team, evaluation of a single dose level for SD-CP and SD-UP may commence. SD-CP and SD-UP will confirm predicted PK concentrations and guide MAD dosing in their respective populations. SD-CP and SD-UP may be conducted in parallel. Evaluation of at least 1 dose level for MAD-CP and MAD-UP may commence when the dose level from the SD segment specific to their population has been fully evaluated by the Safety Review Team. Subjects from the SD-CP and SD-UP segments may screen to determine eligibility for participation in the MAD segment specific to their population.

Figure 1: EP-547-101 Study Design



CP = cholestatic pruritus; HS = healthy subject; MAD = multiple ascending dose; SAD = single ascending dose; SD = single dose; UP = uremic pruritus

[a] Subjects from the SD segment may screen to determine eligibility for participation in the MAD segment specific to their population.

Dose escalation will be determined by the Safety Review Team, which will include the Investigator, Sponsor Medical Monitor, clinical and PK staff from both the site and Sponsor, and other experts for guidance as needed. The Investigator and Sponsor Medical Monitor must both indicate approval for any planned dose escalation. Dose escalation will be based on available individual chemistry, hematology, urinalysis, standard 12-lead electrocardiogram (ECG), physical examination, vital sign, adverse event (AE), and PK data through the end of Visit 2. Each dose level is expected to have a minimum of 5 evaluable subjects who receive the assigned treatment and complete study procedures. Data from all subjects will be reviewed to ensure the results meet acceptable safety and target PK profiles. Although this is a dose escalation study, a lower dose may be administered in the next groups. Further, the same dose may be tested in 2 groups or an intermediate dose may be tested to gain more information regarding safety, tolerability, and/or PK.

7.1.1. Healthy Subjects

SAD-HS is anticipated to consist of 5 dose levels, with the flexibility to evaluate a sixth level. Each level will include 8 subjects. Overall, subjects will be allocated to receive EP547 or placebo as a single oral (PO) dose in a 3:1 ratio (EP547:placebo) within each dose level. The initial dose level for SAD-HS will be 25 mg, [redacted] Following confirmation by the Safety Review Team that escalation should proceed, each subsequent dose level tested in SAD-HS will be increased by no more than 3-fold from the preceding dose level. [redacted]

All dose levels in SAD-HS will be dosed according to a sentinel dosing design to ensure optimal safety. This means that initially, 2 subjects in each dose level will be allocated to receive EP547 or placebo. If the safety and tolerability results of the first 24 hours following dosing for the initial subjects are acceptable to the Safety Review Team, the other 6 subjects will be randomized in a 5:1 ratio (EP547:placebo) to receive EP547 or placebo.

The following treatments for SAD-HS are planned to be administered. However, fewer dose levels may be evaluated if the data from those groups can fully meet the objectives of the study.

Group 1: single PO dose of 25 mg EP547 (n = 6) or matching placebo (n = 2)

Group 2: single PO dose of EP547 that is no more than 3-fold greater than the dose in Group 1 (n = 6) or matching placebo (n = 2)

Group 3: single PO dose of EP547 that is no more than 3-fold greater than the dose in Group 2 (n = 6) or matching placebo (n = 2)

Group 4: single PO dose of EP547 that is no more than 3-fold greater than the dose in Group 3 (n = 6) or matching placebo (n = 2)

Group 5: single PO dose of EP547 that is no more than 3-fold greater than the dose in Group 4 [redacted] (n = 6) or matching placebo (n = 2)

If an additional dose level requires evaluation after conducting Group 5, Group 6 may be enrolled to evaluate a single PO dose of EP547 that is no more than 3-fold higher than the highest dose evaluated in the previous dose levels [redacted] (n = 6) or matching placebo (n = 2).

MAD-HS can begin after 3 dose levels of SAD-HS have been fully evaluated by the Safety Review Team. Subjects who participated in SAD-HS may not participate in MAD-HS. All dose levels in MAD-HS must fall within the range of doses tested in SAD-HS that were confirmed to be well tolerated (Section 7.3.1).

The initial dose level for MAD-HS will be no higher than the second dose tested in SAD-HS with predicted PK concentrations no higher than those observed in SAD-HS. Following confirmation by the Safety Review Team that escalation should proceed, each subsequent dose level tested in MAD-HS will be increased by no more than 3-fold from the preceding dose level. MAD-HS is anticipated to consist of 3 dose levels. Each level will include 8 subjects who will be randomized to receive EP547 or placebo as a daily PO dose over 7 days in a 3:1 ratio (EP547:placebo); there will be no sentinel dosing.

The following treatments for MAD-HS are planned to be administered. However, fewer dose levels may be evaluated if the data from those groups can fully meet the objectives of the study.

Group 1: daily PO dose of EP547 that is no higher than the second dose tested in SAD-HS with predicted PK concentrations no higher than those observed in SAD-HS (n = 6) or matching placebo (n = 2) over 7 days

Group 2: daily PO dose of EP547 that is no more than 3-fold greater than the dose in Group 1 (n = 6) or matching placebo (n = 2) over 7 days

Group 3: daily PO dose of EP547 that is no more than 3-fold greater than the dose in Group 2 (n = 6) or matching placebo (n = 2) over 7 days

7.1.2. Subjects with Cholestatic Pruritus

SD-CP may be conducted when the results from all dose levels of SAD-HS have been fully evaluated by the Safety Review Team. SD-CP is not placebo-controlled (ie, all subjects will receive EP547) and will be conducted in an unblinded manner. The dose level for SD-CP will be no higher than the third dose tested in SAD-HS. SD-CP will consist of 1 dose level. The dose level will include 6 subjects who will receive EP547 as a single PO dose.

MAD-CP can begin when the results from SD-CP have been fully evaluated by the Safety Review Team. Based on data obtained from SD-CP, the EP547 dose to be evaluated in MAD-CP must have predicted steady-state PK concentrations lower than that of the highest tolerated dose in MAD-HS. MAD-CP is anticipated to consist of 1 dose level. If an additional dose level requires evaluation after conducting the first dose level, a second dose level may be enrolled to evaluate a daily PO dose of EP547 that is no more than 3-fold greater than the dose in the previous group. Each dose level will include a minimum of 8 subjects who will be randomized to receive EP547 or placebo as a daily PO dose over 7 days in a 3:1 ratio (EP547:placebo); there will be no sentinel dosing. If additional subjects are available to participate in any MAD-CP dose level, up to 4 more subjects (for a total of 12) may be enrolled.

7.1.3. Subjects with Uremic Pruritus

SD-UP may be conducted when the results from all dose levels of SAD-HS have been fully evaluated by the Safety Review Team. SD-UP is not placebo-controlled (ie, all subjects will receive EP547) and will be conducted in an unblinded manner. The dose level for SD-UP will be no higher than the third dose tested in SAD-HS. SD-UP will consist of 1 dose level. The dose

level will include 6 subjects who will receive EP547 as a single PO dose the day after a hemodialysis session.

MAD-UP can begin when the results from SD-UP have been fully evaluated by the Safety Review Team. Based on data obtained from SD-UP, the EP547 dose to be evaluated in MAD-UP must have predicted steady-state PK concentrations lower than that of the highest tolerated dose in MAD-HS. MAD-UP is anticipated to consist of 1 dose level. If an additional dose level requires evaluation after conducting the first dose level, a second dose level may be enrolled to evaluate a daily PO dose of EP547 that is no more than 3-fold greater than the dose in the previous group. Each dose level will include a minimum of 8 subjects who will be randomized to receive EP547 or placebo as a daily PO dose over 7 days in a 3:1 ratio (EP547:placebo) with hemodialysis occurring 4 to 6 hours after dosing on Days 1, 4, and 6; there will be no sentinel dosing. If additional subjects are available to participate in any MAD-UP dose level, up to 4 more subjects (for a total of 12) may be enrolled.

7.1.4. Study Schedule

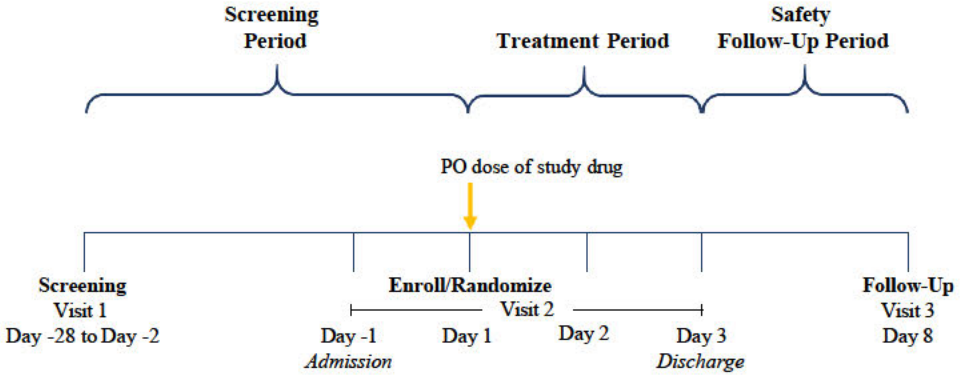
Although the number of dose levels to be evaluated in each single dose segment may differ, the overall study design amongst them is similar. The same is true for the multiple dose segments.

Subjects should fast for at least 8 hours before study days that require a blood sample for assessment of clinical chemistry, multiple blood samples for PK, and/or completion of questionnaires as described in Section 9.4.

7.1.4.1. Single Dose Segments

Screening:	Visit 1 (Screening) is to occur between Day -28 and Day -2.
Treatment Period:	There is 1 mandatory confinement period in the clinic (Visit 2), beginning from Day -1 (admission) to Day 3 until after the 48-hour postdose assessments are completed (discharge).
Safety Follow-Up:	Visit 3 (Follow-Up Visit) is to occur on Day 8 ± 1 (approximately 7 days after study drug administration).

Figure 2: Study Schedule for the Single Dose Segments



PO = oral
Shading represents the mandatory period when subjects will be confined to the study site.

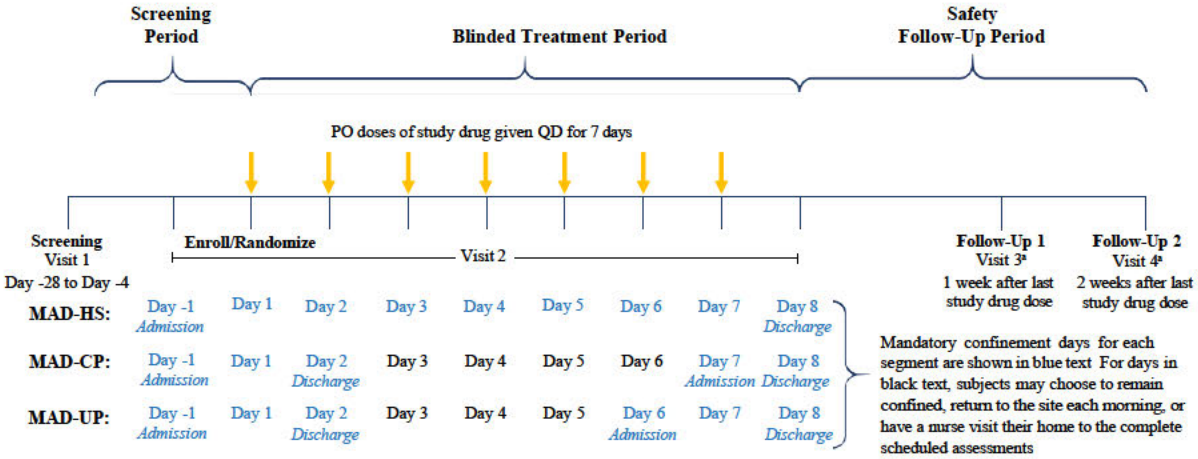
7.1.4.2. Multiple Dose Segments

Screening: Visit 1 (Screening) is to occur between Day -28 and Day -4.

Blinded Treatment Period: There is 1 confinement period in the clinic (Visit 2), beginning from Day -1 (admission) to Day 8 until after the 24-hour post-last dose assessments are completed (discharge). The full confinement period is mandatory for MAD-HS. For Day 3 through Day 6 in MAD-CP and Day 3 through Day 5 in MAD-UP, subjects may choose to remain confined, return to the site each morning, or have a nurse visit their home to complete scheduled assessments.

Safety Follow-Up: Visit 3 (Follow-Up Visit 1) and Visit 4 (Follow-Up Visit 2) are to occur approximately 1 and 2 weeks after the last dose of study drug, respectively. Subjects are to return to the site to complete scheduled assessments for Safety Follow-Up Visits. However, a nurse visit to their home may be permitted on a case-by-case basis with prior approval of the Sponsor.

Figure 3: Study Schedule for the Multiple-Dose Segments



CP = cholestatic pruritus; HS = healthy subject; MAD = multiple ascending dose; PO = oral; QD = once daily; UP = uremic pruritus

Shading represents the period when subjects may be confined to the study site.

[a] Subjects are to return to the site to complete scheduled assessments for Safety Follow-Up Visits. However, a nurse visit to their home may be permitted on a case-by-case basis with prior approval of the Sponsor.

7.2. Number of Subjects

A total of 80 to 132 subjects are expected to participate in the study, including 64 to 72 healthy subjects, 8 to 30 subjects with cholestatic pruritus, and 8 to 30 subjects with uremic pruritus (5 to 6 groups of 8 subjects each in SAD-HS; 3 groups of 8 subjects each in MAD-HS; 1 group of 6 subjects each in SD-CP and SD-UP; 1 to 2 groups of 8 to 12 subjects each in MAD-CP and MAD-UP; up to 6 subjects each from the SD-CP and SD-UP segments will participate in the MAD segment specific to their population if they meet the requirement for pruritus).

Subjects who discontinue before completing the treatment period or are non-evaluable will be replaced in order to meet evaluable subject requirements.

7.3. Dose Adjustment Criteria

Dosages of study drug should be maintained constant for each subject in a MAD segment. However, study drug dosing could be placed on hold as a result of safety findings. Safety criteria for determining if a dose level is well tolerated, discontinuing study drug due to an AE, stopping dose escalation, stopping dosing for all subjects, and PK criteria for selecting, adjusting, or stopping doses is described in Sections 7.3.1 through 7.3.5.

7.3.1. Safety Criteria for Determining if a Dose Level is Well Tolerated

The nature of any AEs, including the number and severity of AEs, and the suspected relationship of the AEs to study drug, will be used to determine if a dose level for a given segment is considered generally well tolerated in the population in which it is being evaluated.

7.3.2. Discontinuation of Study Drug Due to an Adverse Event

Subjects may be withdrawn from the study due to an AE at any time based on the clinical judgment of the Investigator in consideration with the subject's wishes. Subjects who terminate the treatment period early should complete the early study termination evaluations as soon as possible after the last dose of study drug, ideally within 2 days after the last dose. If termination occurs during the treatment period, the subject will have a follow-up visit approximately 1 week (±1 day) after the last dose of study drug. If termination of the treatment period occurs while participating in a MAD segment, the subject will also have a follow-up visit approximately 2 weeks (±2 days) after the last dose of study drug. After the final study visit, further standard of care treatment will be determined by the subject and treating physician. Subjects who discontinue before completing the treatment period or are non-evaluable may be replaced in order to meet evaluable subject requirements.

7.3.3. Safety Criteria for Stopping Dose Escalation

Dose escalation (or MAD dosing) for any segment will cease if 50% of EP547-treated subjects in the same dose level experience a treatment-related AE of severe intensity. Other signs of limited tolerability will also be considered, such as clustering of AEs within a System Organ Class that are largely moderate to severe in intensity. Additionally, all clinically significant abnormalities in chemistry, hematology, urinalysis, standard 12-lead ECG, physical examination, and vital sign results will be evaluated by the Safety Review Team before any dose escalation.

7.3.4. Safety Criteria for Stopping Dosing

Study drug dosing will be held for all subjects if any of the following criteria are met:

- A subject receiving EP547 experiences a serious adverse reaction (ie, a serious AE [SAE] considered at least possibly related to the study drug)
- At least 2 subjects receiving EP547 in the same dosing group experience a severe non-serious adverse reaction (ie, a severe, non-serious AE considered at least possibly related to the study drug)

Study drug dosing will only restart when all appropriate evaluations are performed to ensure subject safety and only if the Safety Review Team agrees that it is appropriate to restart. External

expert opinion may be sought to assist in evaluating the risk to subjects and determining if study drug dosing should be continued.

7.3.5. Pharmacokinetic Criteria for Selecting, Adjusting, or Stopping Doses

PK concentrations and/or PK parameters from each dose level in each population will be evaluated by the Safety Review Team before selection of doses in the subsequent segment. Any anticipated accumulation will be considered for PK predictions of doses in the MAD segments. There are no pre-defined PK criteria to adjust or stop dosing.

7.4. Criteria for Study Termination

The Sponsor may terminate the study at a study site at any time (eg, Good Clinical Practice [GCP] noncompliance or poorly performing sites, as determined by the number of subjects enrolled or the quality of the study data). If instructed by the Sponsor or designee, the Investigator must implement the termination in a timeframe to ensure subject safety and well-being.

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

8. SELECTION AND WITHDRAWAL OF SUBJECTS

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

8.1. Subject Inclusion Criteria

8.1.1. Healthy Subjects

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

1. Age 18 to 60 years, inclusive
2. If female, must be willing to not donate eggs from the time of informed consent until 30 days after the last dose of study drug and:
    a. Is surgically sterile; or
    b. Has been amenorrhoeic for ≥1 year and is over the age of 55 years; or
    c. Has a negative serum pregnancy test at Screening and agrees to use a barrier method (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, vasectomized partner, or abstinence) from the time of informed consent until 30 days after the last dose of study drug
    Abstinence is considered a highly effective method of birth control if the subject refrains from heterosexual intercourse from the time of informed consent until 30 days after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.
3. If male and is not surgically sterile for at least 3 months, must be willing to not donate sperm and must agree to use a barrier method of contraception (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, female surgical sterilization, male vasectomy, or abstinence) from Screening through 90 days after the last dose of study drug
4. Body mass index ≥19 to ≤35 kg/m^2
5. Medically healthy with no clinically significant medical history, physical examination, vital sign, standard 12-lead ECG, chemistry, hematology, urinalysis, or coagulation results at Screening as deemed by the Investigator
6. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study (including required confinement periods), and understand and provide written consent

8.1.2. Subjects with Cholestatic Pruritus

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

1. Age 18 to 80 years, inclusive
2. Has a cholestatic disorder as a result of one of the following conditions:
    a. Diagnosis of PBC that is consistent with American Association for the Study of Liver Diseases (AASLD) (Lindor 2019) and European Association for the Study of the Liver (EASL) Practice Guidelines (EASL 2017), defined as having ≥2 of the following 3 diagnostic factors:
        i. History of elevated alkaline phosphatase (ALP) levels for at least 6 months
        ii. Positive antimitochondrial antibody (AMA) titer or if AMA is negative or low titer (≤1:80), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (pyruvate dehydrogenase complex E2 component and 2-oxo-glutaric acid dehydrogenase complex)
        iii. Liver biopsy consistent with PBC (collected at any time before Screening)
    b. Diagnosis of PSC based on cholangiography at any point in time (EASL 2009, Chapman 2010)
    c. Confirmed diagnosis of chronic hepatitis B or C virus (HBV or HCV)
3. If female, must be willing to not donate eggs from the time of informed consent until 30 days after the last dose of study drug and:
    a. Is surgically sterile; or
    b. Has been amenorrhoeic for ≥1 year and is over the age of 55 years; or
    c. Has a negative serum pregnancy test at Screening and agrees to use a barrier method (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, vasectomized partner, or abstinence) from the time of informed consent until 30 days after the last dose of study drug
    Abstinence is considered a highly effective method of birth control if the subject refrains from heterosexual intercourse from the time of informed consent until 30 days after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.
4. If male and is not surgically sterile for at least 3 months, must be willing to not donate sperm and must agree to use a barrier method of contraception (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, female surgical sterilization, male vasectomy, or abstinence) from Screening through 90 days after the last dose of study drug
5. No clinically relevant medical history, physical examination, vital sign, standard 12-lead ECG, chemistry, hematology, urinalysis, or coagulation results at Screening beyond what is expected for subjects with a cholestatic disorder that would place the subject at undue risk as deemed by the Investigator

6. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study (including required confinement periods), and understand and provide written consent
7. For subjects participating in MAD-CP, has experienced self-reported daily or near-daily moderate to severe pruritus for >4 weeks before Screening
8. [redacted]
9. If currently taking medications to treat the cholestatic disorder, must be on a stable dose for >12 weeks before Screening and plans to maintain the regimen throughout the study
10. If currently taking medications known to impact pruritus, must be on a stable dose for >4 weeks before Screening and plans to maintain the regimen throughout the study

8.1.3. Subjects with Uremic Pruritus

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

1. Age 18 to 80 years, inclusive
2. Has ESRD and is receiving hemodialysis 3× per week of at least 4 hours in duration for ≥3 months before Screening; hemodialysis must be adequate (ie, ≥2 urea reduction ratio measurements ≥65% on different hemodialysis days from the month before Screening to Day -1)
3. If female, must be willing to not donate eggs from the time of informed consent until 30 days after the last dose of study drug and:
   a. Is surgically sterile; or
   b. Has been amenorrhoeic for ≥1 year and is over the age of 55 years; or
   c. Has a negative serum pregnancy test at Screening and agrees to use a barrier method (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, vasectomized partner, or abstinence) from the time of informed consent until 30 days after the last dose of study drug
   Abstinence is considered a highly effective method of birth control if the subject refrains from heterosexual intercourse from the time of informed consent until 30 days after the last dose of study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.
4. If male and is not surgically sterile for at least 3 months, must be willing to not donate sperm and must agree to use a barrier method of contraception (eg, condom) during intercourse and at least 1 other acceptable contraceptive measure (eg, hormonal contraceptives, intrauterine device, female surgical sterilization, male vasectomy, or abstinence) from Screening through 90 days after the last dose of study drug
5. No clinically relevant medical history, physical examination, vital sign, standard 12-lead ECG, chemistry, hematology, or coagulation results at Screening beyond what is

expected for subjects with ESRD that would place the subject at undue risk as deemed by the Investigator

6. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study (including required confinement periods), and understand and provide written consent
7. For subjects participating in MAD-UP, has experienced self-reported daily or near-daily moderate to severe pruritus for >4 weeks before Screening
8. [redacted]
9. If currently taking medications known to impact pruritus, must be on a stable dose for >4 weeks before Screening and plans to maintain the regimen throughout the study

8.2. Subject Exclusion Criteria

8.2.1. Healthy Subjects

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

1. Any prescription medications within 14 days of Screening
2. Positive result for human immunodeficiency virus (HIV) or presence of actively replicating viral hepatitis due to HBV or HCV infection at Screening
3. 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
4. Tobacco product or electronic cigarette use within 90 days of Day -1
5. Positive drug, alcohol, or cotinine screen results at Screening or Day -1
6. Significant history of abuse of drugs, solvents, or alcohol (>3 servings or units/day on average; 1 unit = 12 ounces [350 mL] of 5% alcohol beer, 5 ounces [150 mL] of 12% wine, or 1.5 ounces [45 mL] of 80 proof distilled spirits) in the past 2 years before Screening
7. Unable or unwilling to abstain from alcohol for 48 hours before Screening and from 48 hours before Day -1 until the end of the study
8. [redacted]
9. Participation in any clinical study with an investigational or approved drug/device within 30 days before Screening or is planning to participate in another clinical study while enrolled in this study
10. Allergy to any component of study drug
11. Previously participated in another dose level group in SAD-HS or MAD-HS

12. Donated or lost >200 mL of blood within 60 days before Day -1, donated plasma within 7 days before Day -1, or plans to donate blood or plasma during the study
13. Female who is pregnant, nursing, or intends to become pregnant during the study
14. Is directly affiliated with the study at the study 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 study site
15. 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.
16. Subject is, in the opinion of the Investigator, not suitable to participate in the study

8.2.2. Subjects with Cholestatic Pruritus

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

1. Has a concomitant disease or a history of any medical condition that, in the opinion of the Investigator, could pose undue risk to the subject, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to:
    a. Presence of decompensated cirrhosis within 12 months before Screening
    b. Presence of cirrhosis at Screening with Child-Pugh score >6, ascites or hepatic encephalopathy within 12 months of Screening, albumin of ≤2.8 g/dL (≤28 g/L), total bilirubin ≥3 mg/dL (≥51.3 µmol/L), or international normalized ratio (INR) ≥1.8
    c. Presence of drug-induced cholestasis
2. Recent, current, or planned use of any new medications or adjustments to current medications within 14 days of Screening until the end of the study
3. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× upper limit of normal (ULN) at Screening
4. Screening platelet count <100,000/µL
5. Screening total bilirubin ≥3 mg/dL (≥51.3 µmol/L) (total bilirubin ≥3 mg/dL [≥51.3 µmol/L] is acceptable if bilirubin is fractionated and direct bilirubin <50%)
6. Positive result for HIV at Screening
7. 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
8. Positive drug, alcohol, or cotinine screen results at Screening or Day -1
9. Significant history of abuse of drugs, solvents, or alcohol (>3 servings or units/day on average; 1 unit = 12 ounces [350 mL] of 5% alcohol beer, 5 ounces [150 mL] of 12% wine, or 1.5 ounces [45 mL] of 80 proof distilled spirits) in the past 2 years before Screening

10. Unable or unwilling to abstain from alcohol for 48 hours before Screening and from 48 hours before Day -1 until the end of the study
11. Participation in any clinical study with an investigational or approved drug/device within 30 days before Screening or is planning to participate in another clinical study while enrolled in this study (previous participation in SD-CP is allowed)
12. Allergy to any component of study drug
13. Previously participated in another dose level group in MAD-CP
14. Donated or lost >200 mL of blood within 60 days before Day -1, donated plasma within 7 days before Day -1, or plans to donate blood or plasma during the study
15. Female who is pregnant, nursing, or intends to become pregnant during the study
16. Is directly affiliated with the study at the study 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 study site
17. 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.
18. Subject is, in the opinion of the Investigator, not suitable to participate in the study
19. Scheduled to receive a liver transplant during the study (placement on a transplant waiting list is not exclusionary)
20. Is receiving ongoing UVB treatment or anticipates receiving such treatment during the study
21. For subjects participating in MAD-CP, pruritus is secondary to biliary obstruction
22. History or presence of hepatocellular carcinoma, hepatic abscess, or acute portal vein thrombosis

8.2.3. Subjects with Uremic Pruritus

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

1. Has a concomitant disease or a history of any medical condition that, in the opinion of the Investigator, could pose undue risk to the subject, impede completion of the study procedures, or would compromise the validity of the study measurements, including, but not limited to:
    a. Significant systolic or diastolic heart failure (eg, New York Heart Association Class IV congestive heart failure)
2. Recent, current, or planned use of any new medications or adjustments to current medications within 14 days of Screening until the end of the study unless modification to the hemodialysis regimen is needed or for subject safety
3. Positive result for HIV or presence of actively replicating viral hepatitis due to HBV or HCV infection at Screening

4. 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
5. Positive alcohol screen result at Screening or Day -1 or known use of drugs or tobacco at Screening
6. Significant history of abuse of drugs, solvents, or alcohol (>3 servings or units/day on average; 1 unit = 12 ounces [350 mL] of 5% alcohol beer, 5 ounces [150 mL] of 12% wine, or 1.5 ounces [45 mL] of 80 proof distilled spirits) in the past 2 years before Screening
7. Unable or unwilling to abstain from alcohol for 48 hours before Screening and from 48 hours before Day -1 until the end of the study
8. Participation in any clinical study with an investigational or approved drug/device within 30 days before Screening or is planning to participate in another clinical study while enrolled in this study (previous participation in SD-UP is allowed)
9. Allergy to any component of study drug
10. Previously participated in another dose level group in MAD-UP
11. Female who is pregnant, nursing, or intends to become pregnant during the study
12. Is directly affiliated with the study at the study 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 study site
13. 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.
14. Subject is, in the opinion of the Investigator, not suitable to participate in the study
15. Scheduled to receive a kidney transplant during the study (placement on a transplant waiting list is not exclusionary)
16. Is receiving ongoing UVB treatment or anticipates receiving such treatment during the study
17. Known noncompliance with hemodialysis treatment that, in the opinion of the Investigator, would impede completion or validity of the study
18. For subjects participating in MAD-UP, pruritus is attributed mainly to any disease unrelated to kidney disease, is only present during the hemodialysis sessions, or is attributed to a skin disorder that occurs in this population with associated itch (eg, acquired perforating dermatosis)

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:

- Abstain from alcohol during the 48 hours before Screening and from 48 hours before Day -1 until the end of the study.
- Abstain from eating food containing poppy seeds for 48 hours before Screening and from 48 hours before Day -1 until the end of the study.
- Avoid strenuous exercise from the 72 hours before Screening until the end of the study.
- Do not take any new prescribed medication, over-the-counter (OTC) medication, vitamin preparations or other food supplements, health supplements, or herbal remedies during the study (unless done so in consultation with the Medical Monitor).
  - An exception is made for acetaminophen (up to 1 gram per 24-hour period) as permitted by the Investigator for the treatment of headache or any other pain. Other medication to treat AEs may only be prescribed if deemed necessary by the Investigator.
- Maintain current dose and regimen of all prescribed medication, OTC medication, vitamin preparations or other food supplements, health supplements, and herbal remedies during the study (unless changed in consultation with the Medical Monitor).
- For subjects with cholestatic or uremic pruritus, do not undergo UVB treatment
- Do not use any drugs of abuse.
- Do not use any investigational drugs/devices.
- Do not donate blood or plasma.

8.4. Subject Withdrawal Criteria

Subjects will be free to withdraw consent and discontinue participation from the study at any time and without prejudice to further care per standard clinical practice. A subject's participation in the study may also be discontinued at any time at the discretion of the Investigator or Sponsor. Individual subjects may be excluded from the study if a medical records review indicates protocol deviations, or if other factors suggest that the subject will not be a suitable study subject.

If a subject is withdrawn from the study, the reason will be recorded on the electronic case report form (eCRF) page and the Sponsor will be notified promptly.

Subjects who terminate the treatment period early should complete the early study termination evaluations as soon as possible after the last dose of study drug, ideally within 2 days after the last dose. If termination occurs during the treatment period, the subject will have a follow-up visit approximately 1 week (±1 day) after the last dose of study drug. If termination of the treatment period occurs while participating in a MAD segment, the subject will also have a follow-up visit approximately 2 weeks (±2 days) after the last dose of study drug. After the final

study visit, further standard of care treatment will be determined by the subject and treating physician. Subjects who discontinue before completing the treatment period or are non-evaluable may be replaced in order to meet evaluable subject requirements.

9. TREATMENT OF SUBJECTS

9.1. Treatment Assignment

Treatment assignments for healthy subjects, subjects with cholestatic pruritus, and subjects with uremic pruritus are described in Sections 7.1.1, 7.1.2, and 7.1.3, respectively.

The Sponsor will allocate sequential randomization codes and kit numbers for each dose level from the randomization code and kit assignment list. Sites will request the allocated randomization and kit numbers from the Sponsor in advance of dosing by contacting [redacted].

9.2. Treatment Compliance

To ensure treatment compliance, the Investigator or authorized designee will administer all doses of study drug. Compliance will be further confirmed by bioanalytical assessment of EP547 in plasma.

The exact times of study drug administration and the number of capsules administered will be recorded in the eCRF.

9.3. Randomization and Blinding

9.3.1. Randomization

Subjects will be assigned a subject number after signing the Informed Consent Form (ICF). Subjects who meet all eligibility criteria will be randomized and assigned a randomization number just before dosing. Subjects in SAD-HS, MAD-HS, MAD-CP, and MAD-UP will be assigned to EP547 or placebo in a 3:1 ratio (EP547:placebo), with a block size of 4 for the MAD segments. The randomization code for each dose level will be generated by the CRO and managed by the Sponsor. Subjects in SD-CP and SD-UP will only receive EP547 and do not require randomization.

Subjects who withdraw for any reason without completing all screening evaluations successfully will be considered “screening failures”.

9.3.2. Blinding

Although SAD-HS and all of the MAD segments will be conducted in a blinded manner (ie, subjects, Investigator, study-site personnel, and CRO staff not involved in PK sample analysis or regulatory reporting will be blinded to treatment), the Sponsor, including the Sponsor Medical Monitor, will be unblinded to treatment assignment to assess safety on an ongoing basis. Communication between the blinded Investigator and unblinded Sponsor will be managed to ensure treatment assignment is not revealed. The SD-CP and SD-UP segments are not placebo-controlled (ie, all subjects will receive EP547) and will be conducted in an unblinded manner.

9.3.2.1. Emergency Unblinding

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 before unblinding as knowledge of the study drug could influence subject assessment.

If unblinding is required at the study site, code break envelope(s) will be available for all subjects. The sealed envelope(s) containing the treatment assignment(s) will be kept in a location that is locked with restricted access. The Investigator must contact the Sponsor and Medical Monitor to discuss the decision to unblind a subject's treatment. After approval from the Sponsor or Medical Monitor, or if attempts to reach the Sponsor and Medical Monitor are unsuccessful and immediate knowledge of the treatment assignment will impact the clinical management of the subject, the Investigator will be allowed to break the code to know whether a subject received EP547 or placebo. If opened, the name of the person who opened it, the date and time of opening, and the reason for opening must be written on the envelope. The Sponsor will be informed in case of unblinding at the earliest appropriate time.

9.3.2.2. Unblinding for Regulatory Reporting

Access to individual treatment assignments will be made available to the appropriate individual(s) at the CRO 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 days that require a blood sample for assessment of clinical chemistry, multiple blood samples for PK, [redacted]. Water is acceptable in the morning of site visits and each study day while confined to the study site to ensure the subject is hydrated for laboratory sample collection. On days with multiple blood samples for PK, study drug will be administered with approximately 240 mL of water, additional water will not be allowed from 1 hour predose to 1 hour postdose, and subjects will remain fasted until after the 4-hour PK blood sample is collected. If a subject with ESRD has a daily fluid restriction, study drug may be administered with a smaller volume of water at the Investigator's discretion.

[redacted]

Study procedures are listed for each visit in the following sections and summarized in the Schedule of Assessments (Appendix A for the single dose segments and Appendix B for the multiple dose segments). Further details regarding safety, PK, cardiodynamic, and PD assessments are located in Sections 11, 12, 13, and 14, respectively.

9.4.1. SAD Segments

9.4.1.1. Screening Period

9.4.1.1.1. Visit 1 (Day -28 to Day -2)

During the screening period, subjects are to arrive at the clinic after an overnight fast (at least 8 hours) and will undergo assessments at the site 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 -28 and Day -2:

- Completion of informed consent before performance of any study procedures or assessments
- Medical history
- Height
- Complete physical examination
- Vital signs
- Standard 12-lead ECG
- Body weight
- Laboratory assessments:
  - HIV, HBV, and HCV serology
  - Drug and cotinine screens (SAD-HS and SD-CP only)
  - Alcohol screen
  - Serum pregnancy test (females only)
  - Follicle-stimulating hormone (FSH) (females only)
  - Chemistry and hematology
  - Urinalysis (SAD-HS and SD-CP only)
  - Coagulation
- Assessment of baseline concomitant medications, including:
  - All medications taken within 14 days before Screening
  - Medications taken to treat a cholestatic disorder or ESRD within 12 weeks before Screening (SD-CP and SD-UP only)
  - Medications known to impact pruritus within 4 weeks before Screening (SD-CP and SD-UP only)
- Assessment of AEs
- Eligibility check

Screening results will be reviewed by the Investigator to determine the subject's eligibility. Subjects who are confirmed to be eligible will be asked to return to the site for Visit 2 (Day -1) to enroll in the study.

9.4.1.1.2. Visit 2 (Day -1) - Admission

Subjects who meet all eligibility requirements will be admitted for mandatory confinement at the clinic during Visit 2 (Day -1) and will undergo the following assessments:

- [redacted]
- Abbreviated physical examination
- Laboratory assessments:
  - Drug and cotinine screens (SAD-HS and SD-CP only)
  - Alcohol screen
  - Urine pregnancy test (SAD-HS and SD-CP females only)
- Assessment of concomitant medication usage
- Assessment of AEs
- Hemodialysis (SD-UP only)
- Eligibility check

Visit 2 (Day -1) results will be reviewed by the Investigator to confirm the subject's eligibility. Subjects who are confirmed to be eligible will continue to remain confined to the clinic until completion of Visit 2 (Day 3).

9.4.1.2. Treatment Period

9.4.1.2.1. Visit 2 (Day 1) - Predose

For subjects in SD-UP, Day 1 must be the day after a hemodialysis session. Subjects will continue to be confined at the clinic during Visit 2 (Day 1) and will undergo the following assessments before administration of study drug:

- Vital signs
- Standard 12-lead ECG
- Body weight
- Laboratory assessments:
  - Chemistry and hematology
  - Urinalysis (SAD-HS and SD-CP only)
  - [redacted]
- Assessment of concomitant medication usage
- Assessment of AEs
- Blood sample draw for PK assessment

- Continuous digital 12-lead ECG recording for Holter monitoring beginning approximately 1 hour before study drug administration (SAD-HS only)
- Urine collection for PK assessment from -6 to 0 hours predose (SAD-HS only)
- Allocation to EP547 or placebo in a 3:1 ratio (SAD-HS only)

Upon completion of the assessments listed above, study drug is to be administered orally as intact capsules (swallowed whole, not chewed or crushed), and taken with water. All dose levels in SAD-HS will be dosed according to a sentinel dosing design (Section 7.1.1). All subjects in SD-CP and SD-UP will receive EP547.

9.4.1.2.2. Visit 2 (Day 1) - Postdose

Subjects will continue to be confined at the clinic during Visit 2 (Day 1) and will undergo the following assessments after administration of study drug:

- Assessment of concomitant medication usage
- Assessment of AEs
- Urine collection for PK assessment from >0 to 6, >6 to 12, and >12 to 18 hours postdose (SAD-HS only)
- Blood sample draw for PK assessment at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours postdose
- Continue 24-hour continuous digital 12-lead ECG recording for Holter monitoring (SAD-HS only)
- Vital signs at 1, 2, 4, 9, and 12 hours postdose
- Standard 12-lead ECG at 3 hours postdose

9.4.1.2.3. Visit 2 (Day 2)

Subjects will continue to be confined at the clinic during Visit 2 (Day 2) and will undergo the following assessments:

- Laboratory assessments:
  - Chemistry and hematology
  - Urinalysis (SAD-HS and SD-CP only)
- Assessment of concomitant medication usage
- Assessment of AEs
- Blood sample draw for PK assessment at 18, 24, and 36 hours postdose
- End 24-hour continuous digital 12-lead ECG recording for Holter monitoring (SAD-HS only)
- Urine collection for PK assessment from >18 to 24, >24 to 30, and >30 to 36 hours postdose (SAD-HS only)

- Vital signs at 24 hours postdose

9.4.1.2.4. Visit 2 (Day 3) - Discharge

Subjects will continue to be confined at the clinic during Visit 2 (Day 3) until completion of the following assessments:

- Laboratory assessments:
  - Chemistry and hematology
  - Urinalysis (SAD-HS and SD-CP only)
- Assessment of concomitant medication usage
- Assessment of AEs
- Vital signs at 48 hours postdose
- Standard 12-lead ECG at 48 hours postdose
- Urine collection for PK assessment from >36 to 42 and >42 to 48 hours postdose (SAD-HS only)
- Blood sample draw for PK assessment at 48 hours postdose

Subjects may be discharged from the clinic after completion of all assessments listed above.

9.4.1.3. Safety Follow-Up Visit (Visit 3 [Day 8])

Subjects are to arrive at the clinic after an overnight fast (at least 8 hours) and will undergo the following assessments during the ±1-day visit window for Visit 3 (Day 8):

- Complete physical examination
- Vital signs
- Body weight
- Laboratory assessments:
  - Serum pregnancy test (females only)
  - Chemistry and hematology
  - Urinalysis (SAD-HS and SD-CP only)
- Assessment of concomitant medication usage
- Assessment of AEs
- Blood sample draw for PK assessment

9.4.1.4. Early Study Termination Visit

Subjects who discontinue from the study early should have the Early Study Termination Visit conducted as soon as possible after the dose of study drug, ideally within 2 days after the dose of

study drug. Subjects are to arrive at the clinic after an overnight fast (at least 8 hours) and will undergo the following assessments during the Early Study Termination Visit:

- Complete physical examination
- Vital signs
- Standard 12-lead ECG
- Body weight
- Laboratory assessments:
  - Serum pregnancy test (females only)
  - Chemistry and hematology
  - Urinalysis (SAD-HS and SD-CP only)
- Assessment of concomitant medication usage
- Assessment of AEs

9.4.2. MAD Segments

9.4.2.1. Screening Period

9.4.2.1.1. Visit 1 (Day -28 to Day -4)

During the screening period, subjects are to arrive at the clinic after an overnight fast (at least 8 hours) and will undergo assessments at the site 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 -28 and Day -4, unless specified otherwise:

- Completion of informed consent before performance of any study procedures or assessments
- Medical history
- Height
- Complete physical examination
- Vital signs
- Standard 12-lead ECG
- Body weight
- Laboratory assessments:
  - HIV, HBV, and HCV serology
  - Drug and cotinine screens (MAD-HS and MAD-CP only)

  - Alcohol screen
  - Serum pregnancy test (females only)
  - FSH (females only)
  - Chemistry and hematology
  - Urinalysis (MAD-HS and MAD-CP only)
  - Coagulation
  - [redacted]
- Assessment of baseline concomitant medications, including:
  - All medications taken within 14 days before Screening
  - Medications taken to treat a cholestatic disorder or ESRD within 12 weeks before Screening (MAD-CP and MAD-UP only)
  - Medications known to impact pruritus within 4 weeks before Screening (MAD-CP and MAD-UP only)
- Assessment of AEs
- [redacted]
- [redacted]
- [redacted]
- Eligibility check

Screening results will be reviewed by the Investigator to determine the subject's eligibility. Subjects who are confirmed to be eligible will be asked to return to the site for Visit 2 (Day -1) to enroll in the study.

9.4.2.1.2. Visit 2 (Day -1) – Admission

Subjects who meet all eligibility requirements will be admitted for confinement at the clinic during Visit 2 (Day -1) and will undergo the following assessments:

- [redacted]
- Abbreviated physical examination

- Laboratory assessments:
  - Drug and cotinine screens (MAD-HS and MAD-CP only)
  - Alcohol screen
  - Urine pregnancy test (MAD-HS and MAD-CP females only)
- Assessment of concomitant medication usage
- Assessment of AEs
- [redacted]
- Eligibility check

9.4.2.2. Treatment Period

9.4.2.2.1. Visit 2 (Day 1) - Predose

Subjects will continue to be confined at the clinic during Visit 2 (Day 1) and will undergo the following assessments before administration of study drug:

- [redacted]
- Vital signs
- Standard 12-lead ECG
- Body weight
- Laboratory assessments:
  - Chemistry and hematology
  - Urinalysis (MAD-HS and MAD-CP only)
  - [redacted]
- Assessment of concomitant medication usage
- Assessment of AEs
- Blood sample draw for PK assessment

- [redacted]
- Randomization to EP547 or placebo in a 3:1 ratio

Upon completion of the assessments listed above, study drug is to be administered orally as intact capsules (swallowed whole, not chewed or crushed), and taken with water.

9.4.2.2.2. Visit 2 (Day 1) - Postdose

Subjects will continue to be confined at the clinic during Visit 2 (Day 1) and will undergo the following assessments before administration of study drug:

- Assessment of concomitant medication usage
- Assessment of AEs
- [redacted]
- Blood sample draw for PK assessment at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours postdose
- Vital signs at 1, 2, 4, 9, and 12 hours postdose
- Skin biopsies for PK [redacted] at 2 hours postdose (last dose level for MAD-HS and all dose levels for MAD-CP and MAD-UP only)
- Laboratory assessment:
  - [redacted]
- Standard 12-lead ECG at 3 hours postdose
- Hemodialysis 4 to 6 hours postdose (MAD-UP only)

9.4.2.2.3. Visit 2 (Day 2)

Subjects will continue to be confined at the clinic during Visit 2 (Day 2) and will undergo the following assessments:

- Vital signs
- Laboratory assessments:
  - Chemistry and hematology
  - Urinalysis (MAD-HS and MAD-CP only)
  - [redacted]
- Assessment of concomitant medication usage
- Assessment of AEs
- [redacted]

- Blood sample draw for PK assessment:
  - At 18 hours postdose relative to the dose of study drug on Day 1
  - Predose (all MAD segments) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours postdose relative to the dose of study drug on Day 2 (MAD-UP only)
- Administer study drug orally as intact capsules (swallowed whole, not chewed or crushed) with water at approximately the same time of day as the dose administered on Day 1

Subjects in MAD-CP and MAD-UP may be discharged from the clinic after completion of all of the assessments listed above if they choose to return to the site each morning or have a nurse visit their home until the next mandatory confinement period (Day 6 to Day 8 for MAD-UP and Day 7 to Day 8 for MAD-CP) to complete scheduled assessments. Subjects in MAD-HS must remain confined to the study site through Day 8.

9.4.2.2.4. Visit 2 (Day 3)

Subjects in MAD-HS will continue to be confined at the clinic during Visit 2 (Day 3). Subjects in MAD-CP and MAD-UP may choose to remain confined, return to the site, or have a nurse visit their home for Visit 2 (Day 3). Subjects will undergo the following assessments for Visit 2 (Day 3):

- Vital signs
- Standard 12-lead ECG
- Assessment of concomitant medication usage
- Assessment of AEs
- [redacted]
- Blood sample draw for PK assessment:
  - At 18 hours postdose relative to the dose of study drug on Day 2 (MAD-UP only)
  - Predose relative to the dose of study drug on Day 3 (MAD-HS only)
- Administer study drug orally as intact capsules (swallowed whole, not chewed or crushed) with water at approximately the same time of day as the dose administered on Day 1
- [redacted]

9.4.2.2.5. Visit 2 (Day 4)

Subjects in MAD-HS will continue to be confined at the clinic during Visit 2 (Day 4). Subjects in MAD-CP and MAD-UP may choose to remain confined, return to the site, or have a nurse visit their home for Visit 2 (Day 4). Subjects will undergo the following assessments for Visit 2 (Day 4):

- [redacted]
- Vital signs
- Laboratory assessments:
  - Chemistry and hematology
  - Urinalysis (MAD-HS and MAD-CP only)
- Assessment of concomitant medication usage
- Assessment of AEs
- [redacted]
- Blood sample draw for PK assessment predose relative to the dose of study drug on Day 4
- Administer study drug orally as intact capsules (swallowed whole, not chewed or crushed) with water at approximately the same time of day as the dose administered on Day 1
- Hemodialysis 4 to 6 hours postdose (MAD-UP only)

9.4.2.2.6. Visit 2 (Day 5)

Subjects in MAD-HS will continue to be confined at the clinic during Visit 2 (Day 5). Subjects in MAD-CP and MAD-UP may choose to remain confined, return to the site, or have a nurse visit their home for Visit 2 (Day 5). Subjects will undergo the following assessments for Visit 2 (Day 5):

- [redacted]
- Vital signs
- Assessment of concomitant medication usage
- Assessment of AEs
- [redacted]
- Blood sample draw for PK assessment predose relative to the dose of study drug on Day 5 (MAD-HS only)
- Administer study drug orally as intact capsules (swallowed whole, not chewed or crushed) with water at approximately the same time of day as the dose administered on Day 1

9.4.2.2.7. Visit 2 (Day 6)

Subjects in MAD-UP will be admitted for confinement at the clinic and subjects in MAD-HS will continue to be confined at the clinic during Visit 2 (Day 6). Subjects in MAD-CP may choose to remain confined, return to the site, or have a nurse visit their home for Visit 2 (Day 6). Subjects will undergo the following assessments for Visit 2 (Day 6):

- [redacted]
- Vital signs
- Assessment of concomitant medication usage
- Assessment of AEs
- [redacted]
- Blood sample draw for PK assessment:
  - Predose relative to the dose of study drug on Day 6 (MAD-HS and MAD-UP only)
  - At 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours postdose relative to the dose of study drug on Day 6 (MAP-UP only)
- Administer study drug orally as intact capsules (swallowed whole, not chewed or crushed) with water at approximately the same time of day as the dose administered on Day 1
- Hemodialysis 4 to 6 hours postdose (MAD-UP only)

9.4.2.2.8. Visit 2 (Day 7)

Subjects in MAD-CP will be admitted for confinement at the clinic and subjects in MAD-HS and MAD-UP will continue to be confined at the clinic during Visit 2 (Day 7). Subjects will undergo the following assessments for Visit 2 (Day 7):

- [redacted]
- Vital signs
- [redacted]
- Assessment of concomitant medication usage
- Assessment of AEs
- [redacted]

- Blood sample draw for PK assessment:
  - At 18 hours postdose relative to the dose of study drug on Day 6 (MAD-UP only)
  - Predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours postdose relative to the dose of study drug on Day 7
- Administer study drug orally as intact capsules (swallowed whole, not chewed or crushed) with water at approximately the same time of day as the dose administered on Day 1
- [redacted]

9.4.2.2.9. Visit 2 (Day 8) - Discharge

Subjects will continue to be confined at the clinic during Visit 2 (Day 8) until completion of the following assessments:

- [redacted]
- Laboratory assessment:
  - Chemistry and hematology
  - Urinalysis (MAD-HS and MAD-CP only)
  - [redacted]
- Assessment of concomitant medication usage
- Assessment of AEs
- Vital signs at 24 hours postdose relative to the dose of study drug on Day 7
- Standard 12-lead ECG at 24 hours postdose relative to the dose of study drug on Day 7
- Body weight
- Blood sample draw for PK assessment:
  - At 24 hours postdose relative to the dose of study drug on Day 7

Subjects may be discharged from the clinic after completion of all assessments listed above.

9.4.2.3. Safety Follow-Up Period

9.4.2.3.1. Visit 3 (Day 14)

Subjects are to return to the site to complete scheduled assessments for Visit 3 (Day 14). However, a nurse visit to their home may be permitted on a case-by-case basis with prior

approval of the Sponsor. Subjects will undergo the following assessments after an overnight fast (at least 8 hours) during the ±1-day visit window for Visit 3 (Day 14):

- [redacted]
- Abbreviated physical examination
- Vital signs
- Laboratory assessments:
  - Chemistry and hematology
  - Urinalysis (MAD-HS and MAD-CP only)
  - [redacted]
  - Serum pregnancy test (females only)
- Assessment of concomitant medication usage
- Assessment of AEs
- Blood sample draw for PK assessment

9.4.2.3.2. Visit 4 (Day 21)

Subjects are to return to the site to complete scheduled assessments for Visit 4 (Day 21). However, a nurse visit to their home may be permitted on a case-by-case basis with prior approval of the Sponsor. Subjects will undergo the following assessments after an overnight fast (at least 8 hours) during the ±2-day visit window for Visit 4 (Day 21):

- [redacted]
- Complete physical examination
- Vital signs
- Laboratory assessments:
  - Chemistry and hematology
  - Urinalysis (MAD-HS and MAD-CP only)
  - [redacted]
  - Serum pregnancy test (females only)
- Assessment of concomitant medication usage
- Assessment of AEs

- Blood sample draw for PK assessment

9.4.2.4. Early Study Termination Visit

Subjects who discontinue from the study early should have the Early Study 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. Subjects are to arrive at the clinic after an overnight fast (at least 8 hours) and will undergo the following assessments during the Early Study Termination Visit:

- [redacted]
- Complete physical examination
- Vital signs
- Standard 12-lead ECG
- Body weight
- Laboratory assessments:
  - Serum pregnancy test (females only)
  - Chemistry and hematology
  - Urinalysis (MAD-HS and MAD-CP only)
- Assessment of concomitant medication usage
- Assessment of AEs

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drugs

EP547 lockable capsules will be prepared by the central vendor to contain the desired amount of drug substance to meet the needs of the given dose level. Each lockable placebo capsule will contain placebo such as microcrystalline cellulose and will be manufactured in a way to ensure the study blind. Each dose may be made up of multiple capsules of the same or different capsule strengths.

10.2. Study Drug Packaging and Labeling

Just-in-time manufacturing will be used to supply the study drug, EP547 or placebo capsules, at the specified dose level selected for each segment. Each study drug kit will be labeled with a unique kit number and will be supplied to study sites in a blinded manner. Study drug shipments will be sent to sites with code break envelope(s) containing the treatment assignment(s) that can be utilized by the site for emergency unblinding.

10.3. Study Drug Storage

The study drug capsules may be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F), with excursions to 10°C (50°F).

10.4. Study Drug Administration

Study drug is to be administered orally as intact capsules (swallowed whole, not chewed or crushed), and taken with water. During the MAD segments, doses are to be administered daily at approximately the same time of day over 7 days. There are no fasting or fed requirements for study drug administration (only for study procedures as described in Section 9.4). Subjects who routinely take a bile acid sequestrant (eg, cholestyramine, colestipol, or colesevelam) will be instructed to hold their morning dose until 2 hours after study drug administration. If their bile acid sequestrant baseline dosing regimen does not allow for a 2-hour hold, dosing of these medications must be held for a minimum of 1 hour after study drug administration. Alternatively, the bile acid sequestrant may be taken at least 4 hours prior to study drug administration.

10.5. Additional Dosing Instructions for Subjects with Uremic Pruritus

For subjects in SD-UP, Day 1 (study drug administration) must be the day after a hemodialysis session.

For subjects in MAD-UP, study drug will be administered 4 to 6 hours before the hemodialysis session on Days 1, 4, and 6 and at approximately the same time of day on Days 2, 3, 5, and 7 (days without a hemodialysis session).

10.6. Study Drug Dispensing and Accountability

All study drug is to be administered at the study site. The site staff will be responsible for documenting and maintaining study drug dispensation and accountability records.

10.7. Study Drug Handling and Disposal

Study drug will be sent to the study site under appropriate storage conditions. Upon receipt of study drug, study 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.

All study drug will be provided for use only in this study and is not to be used for any other purpose. The study staff will maintain a full record of study drug accountability as described in Section 10.6.

Upon completion of the study, used and unused study drug and study drug containers are to be returned to the Sponsor (or designee) or, if prior Sponsor approval is obtained, disposed of in accordance with applicable site procedures. Study 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.

10.8. 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 study-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, body weight, physical examinations, standard 12-lead ECGs, and laboratory evaluations of safety will be performed as indicated in the Schedule of Assessments (Appendix A for the single dose segments and Appendix B for the multiple dose segments).

Although SAD-HS and all of the MAD segments will be conducted in a blinded manner (ie, subjects, Investigator, study-site personnel, and CRO staff not involved in PK sample analysis or regulatory reporting will be blinded to treatment), the Sponsor, including the Sponsor Medical Monitor, will be unblinded to treatment assignment to assess safety on an ongoing basis. The SD-CP and SD-UP segments are not placebo-controlled (ie, all subjects will receive EP547) and will be conducted in an unblinded manner.

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 treatment-emergent AEs (TEAEs). 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, in the opinion of the Investigator, constitute an AE. 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

The Investigator will assess the severity of an AE using the 3-point scale below:

- **Mild** - Awareness of a sign or symptom that is easily tolerated
- **Moderate** - Discomfort enough to cause interference with usual activity
- **Severe** - Incapacitating or causes inability to work or undertake usual activity

11.1.3. Determining Causality of Adverse Events

Causality refers to the relationship of the event to the study drug (EP547 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 ICF until the end of study participation. AEs will be assessed for likelihood of causal relationship to the study drug (EP547 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 11.4).

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 pre-existing 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;
- 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. The SAER Form must be submitted to the Sponsor or designee within 24 hours of the Investigator's first awareness of the event. Follow-up information to all SAEs should be submitted to the Sponsor, or designee, in the same timeframe as initial reports.

All SAE reports must be **reported within 24 hours of the Investigator's knowledge of the event** to [redacted]. Any supporting documentation (eg, medical records) sent to Novotech with the SAER Form must have subject identifying information (eg, subject names, subject addresses, and medical records number) redacted by the site.

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 their IRBs/IECs.

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 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 Novotech 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 Novotech 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. 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.

11.3. Concomitant Medications

The addition of concomitant medications is not permitted during the study, except for acetaminophen (up to 1 gram per 24-hour period) as permitted by the Investigator for the treatment of headache or any other pain. Other medication to treat AEs may only be prescribed if deemed necessary by the Investigator. For subjects with cholestatic or uremic pruritus, dosages of any concomitant therapies are to remain stable for the duration of this study unless adjustments are needed for subject safety.

Any change in regimen for any concomitant medication other than acetaminophen must be reported to the Sponsor in a timely manner and done in consultation with the Medical Monitor if subject safety is not immediately compromised.

All medications taken within 14 days before Screening and details of concomitant medications from Screening through the end of study participation should be recorded in the subject's source documents and in the eCRF. In addition, medications taken to treat a cholestatic disorder or ESRD within 12 weeks before Screening or medications known to impact pruritus within 4 weeks before Screening should also be recorded.

11.4. Medical History

The Investigator will collect and review the subject's medical 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.

11.5. Vital Signs

Vital signs, including supine systolic and diastolic blood pressure, pulse rate, oxygen saturation, body temperature, and respiratory rate, will be measured after at least 5 minutes of rest.

For the single dose segments, vital signs will be measured at Screening; predose and at 1, 2, 4, 9, and 12 hours postdose on Day 1; 24 hours postdose on Day 2; 48 hours postdose on Day 3; on Day 8; and Early Study Termination, if applicable. The time margin for vital signs is 15 minutes for 1 and 2 hours postdose and 15 minutes for 4, 9, and 12 hours postdose.

For the multiple dose segments, vital signs will be measured at Screening; predose and at 1, 2, 4, 9, and 12 hours postdose on Day 1; predose on Days 2 to 7; 24 hours after the last dose on Day 8; on Days 14 and 21; and at Early Study Termination, if applicable. The time margin for vital signs is 15 minutes for 1 and 2 hours postdose and 20 minutes for 4, 9, and 12 hours postdose.

11.6. Body Weight

Body weight should be measured with no shoes on and using a calibrated scale throughout the study.

11.7. Physical Examinations

Complete 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, including standard Child-Pugh scoring assessments to determine whether ascites or hepatic encephalopathy are present. Abbreviated physical examinations will include HEENT, cardiovascular, chest/lung, abdomen, and extremities.

11.8. Standard 12-Lead Electrocardiograms

12-lead ECGs are to be performed with subjects in a supine position after at least 5 minutes of rest. For the single dose segments, the standard 12-lead ECG is to be performed during Screening; predose and at 3 hours postdose on Day 1; 48 hours postdose on Day 3; and Early Study Termination, if applicable. For the multiple dose segments, the standard 12-lead ECG is to be performed at Screening; predose and at 3 hours postdose on Day 1; predose on Day 3; 24 hours after the last dose on Day 8; and Early Study Termination, if applicable. The time margin for 12-lead ECGs is 20 minutes for 3 hours postdose.

11.9. Laboratory Evaluations of Safety

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

- Chemistry: sodium, albumin, ALP, bicarbonate, calcium, bile acids, corrected calcium, chloride, total and direct bilirubin, AST, ALT, BUN, urea, creatinine, magnesium, phosphorus, potassium, creatine phosphokinase (CPK), total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), lactate dehydrogenase (LDH), gamma-glutamyltransferase (GGT), and total protein
- Hematology: hemoglobin, hematocrit, white blood cell (WBC) count (total and differential), red blood cell count, platelet count, and platelet volume
- Urinalysis (dipstick) (SAD-HS, SD-CP, MAD-HS, and MAD-CP only): 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
- Coagulation: activated partial thromboplastin time (aPTT), INR, and prothrombin time (PT)
- Pregnancy testing: urine testing on Day -1 for all female SAD-HS, SD-CP, MAD-HS, and MAD-CP subjects and serum testing for all female subjects for all other instances

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. See the laboratory manual for additional details.

11.10. Other Laboratory Evaluations

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

- Serology: HIV, HBV, HCV
- Non-childbearing confirmation: FSH (females only)
- Drug screen (SAD-HS, SD-CP, MAD-HS, and MAD-CP only): Cannabinoids, cocaine, opiates, amphetamines, barbiturates, and benzodiazepines
- Cotinine screen (SAD-HS, SD-CP, MAD-HS, and MAD-CP only)
- Alcohol screen

The drug and cotinine screens on Day -1 and the alcohol screen at Screening and Day -1 will be conducted locally; all other planned laboratory evaluations will be conducted at a central laboratory. See the laboratory manual for additional details.

11.11. Subject Safety Guidelines

11.11.1. Potential Side Effects

Results from nonclinical studies of EP547 demonstrate a nonclinical profile suitable for advancement into human clinical studies. Refer to the Investigator's Brochure for additional EP547 information regarding nonclinical study results.

11.11.2. Overdose

No specific information is available on the treatment of overdose of EP547. Additionally, there is no specific antidote to EP547. In a case of overdose, appropriate supportive measures should be employed.

12. PHARMACOKINETICS ASSESSMENT

Blood, urine, and skin samples for PK will be utilized to analyze EP547 concentrations; the metabolite profile may also be analyzed from these samples.

12.1. Blood Sampling for Pharmacokinetics

Blood sampling for PK of EP547 will be collected as follows:

- **SAD-HS, SD-CP, and SD-UP:** predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours postdose on Day 1; 18, 24, and 36 hours postdose on Day 2; 48 hours postdose on Day 3; and at follow-up on Day 8.
- **MAD-HS:** predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 18 hours postdose relative to the dose of study drug on Day 1; predose on Day 2 through Day 6; predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 24 hours postdose relative to the last dose of study drug on Day 7; and at follow-up on Day 14 and Day 21.
- **MAD-CP:** predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 18 hours postdose relative to the dose of study drug on Day 1; predose on Day 2; predose on Day 4; predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 24 hours postdose relative to the last dose of study drug on Day 7; and at follow-up on Day 14 and Day 21.
- **MAD-UP:** predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 18 hours postdose relative to the dose of study drug on Days 1, 2, and 6; predose on Day 4; predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, and 24 hours postdose relative to the last dose of study drug on Day 7; and at follow-up on Day 14 and Day 21.

The MAD dosing and PK blood sampling schedule is summarized in Appendix C. The assessment window for blood sample collection timepoints for the single and multiple dose segments is also included in Appendix C.

12.2. Urine Collection for Pharmacokinetics (SAD-HS Only)

Urine sampling for PK of EP547 will be collected at predose (-6 to 0 hours) and from >0 to 6, >6 to 12, and >12 to 18 hours postdose on Day 1; >18 to 24, >24 to 30, and >30 to 36 hours postdose on Day 2; and >36 to 42 and >42 to 48 hours postdose on Day 3.

12.3. Skin Biopsy for Pharmacokinetics (Last Dose Level for MAD-HS and All Dose Levels for MAD-CP and MAD-UP Only)

Given that EP547 is hypothesized to be an inverse agonist (inhibitor) of MRGPRX4 in the skin to reduce itch, three 3-mm biopsies of the skin from the back will be performed under local anesthesia on Day 1 at 2 hours postdose with an assessment window of +30 minutes. One biopsy will be used for PK to evaluate drug concentrations at the site of action and the other 2 biopsies will be used for PD assessment as described in Section 14.5 to further elucidate the mechanism of action of EP547.

13. CARDIODYNAMIC ASSESSMENT

13.1. Holter Monitoring for 12-Lead ECG Acquisition and Subsequent Cardiodynamic Analysis (SAD-HS Only)

Clinical evaluation of QT/QTc interval prolongation risk and proarrhythmic potential will be conducted for EP547, which is recommended by the US FDA for all new non-antiarrhythmic drugs having systemic bioavailability (FDA 2005a). Continuous digital 12-lead ECGs will be recorded from approximately 1 hour predose on Day 1 to 24 hours postdose on Day 2 under constant supervision for subjects in SAD-HS only. Subjects will rest quietly in the supine position for at least 10 minutes before each extraction timepoint and for 5 minutes during each extraction with the understanding that a full undisturbed supine period may not be possible given other assessments at competing timepoints. Twelve-lead ECG extraction timepoints will be at -30, -20, and -10 minutes predose on Day 1; at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours postdose on Day 1; and at 18 and 24 hours postdose on Day 2. Twelve-lead ECGs will be extracted from the continuous recording from a 5-minute window preceding the ECG timepoints and scheduled to end 1 to 2 minutes before the scheduled PK draw to conduct early QT assessment based on concentration-QT analysis. Subjects are to continue fasting through 4 hours postdose as food can impact the results.

[redacted]

14.10. Height

Height will be measured using a stadiometer with no shoes.

15. STATISTICS

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. Populations for Analysis

The following analysis populations will be considered:

- **Enrolled Population:** This population will comprise all subjects who sign the ICF to participate in the study, complete the screening visit procedures, and meet all eligibility criteria for enrollment.
- **Safety Population:** This population will comprise all subjects who receive at least 1 dose of study drug.
- **PK Population:** This population will comprise all subjects who receive at least 1 dose of EP547 and provide adequate blood samples for bioanalysis.
- **PD Population:** This population will comprise all subjects belonging to the Safety Population without major protocol deviations.

15.2. Outcome Measures

15.2.1. Primary Safety Outcome Measures

Primary safety outcome measures include:

- AEs
- Clinical laboratory assessments
- Vital signs and body weight
- Standard 12-lead ECGs
- Physical examinations

15.2.2. Secondary Pharmacokinetic and Cardiodynamic Outcome Measures

Secondary PK and cardiodynamic outcome measures include:

- Plasma EP547 and metabolites (as applicable) concentrations
- Plasma PK parameters estimated using noncompartmental analysis (NCA), as appropriate[2]:
  - SAD segments: C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{∞}, AUC_t, $\%AUC_{extra,}$ CL/F, and V_z/F
  - MAD segments: C_{max}, C_{trough}, t_{max}, k_{el}, $t_{1/2}$, AUC_{τ} (as appropriate), AUC_t, CL/F, V_z/F, and R_{ss}

[2] The PK parameters definitions are in Section 4.

- Urine PK parameters estimated using NCA, as appropriate:
  - SAD-HS segment: A_e, F_e, CLr
- Skin EP547 and metabolites (as applicable) concentrations
- Holter monitoring for 12-lead ECG acquisition and subsequent cardiodynamic analysis

[redacted]

15.3. Sample Size Considerations

No formal sample size calculation has been made. The sample size has been selected to provide adequate information on safety, tolerability, PK, and PD following single and multiple doses of EP547.

15.4. Safety Analysis

The Safety Population will be used for the summaries of the safety data according to the treatment received.

The safety and tolerability of EP547 will be assessed by comparing the frequency and severity of AEs as well as treatment discontinuations due to AEs. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class and preferred term. The World Health Organization (WHO) DRUG Dictionary will be used to categorize verbatim descriptions of non-study medications into the Anatomic Therapeutic Chemistry (ATC) classification system. Changes in vital signs, body weight, physical examinations, standard 12-lead ECGs, and laboratory evaluations will be compared across dose levels, when applicable, and to placebo.

Cardiodynamic analysis of the data from Holter monitoring will be conducted separately.

15.5. Pharmacokinetic Analysis

Depending on the segment, different PK parameters for plasma EP547 concentrations and metabolites (as applicable) will be calculated. The actual sampling times will be used in the PK parameter calculations. The PK parameters to be determined or calculated using NCA from the

plasma concentration data for EP547 include, but are not limited to, the parameters as listed below:

- SAD segments: C_{max}, t_{max}, k_{el}, $t_{1/2}$, AUC_{∞}, AUC_t, $\%AUC_{extra}$, CL/F, and V_z/F
- MAD segments: C_{max}, C_{trough}, t_{max}, k_{el}, $t_{1/2}$, AUC_{τ} (as appropriate), AUC_t, CL/F, V_z/F, and R_{ss}

To assess dose proportionality, a power model will be applied to the PK parameters, C_{trough}, C_{max}, AUC_t, AUC_{∞}, and AUC_{τ} (as appropriate). For the MAD segment parameter AUC_t, visit day will be added as a fixed effect in the mixed model. The details of the analysis will be described in the SAP.

The following PK parameters for urine EP547 concentrations and metabolites (as applicable) will be calculated using NCA for the SAD-HS segment: A_e, F_e, CLr.

Skin EP547 and metabolites (as applicable) concentrations will be summarized.

For PK analyses, only the EP547 treatment groups will be statistically analyzed. Plasma, urine, and skin concentrations of EP547 will be listed and summarized by nominal timepoint (as applicable) and treatment group. The PK parameters will be listed and summarized by treatment.

[redacted]

15.7. Subgroup Analyses

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

15.8. Multiple Comparison/Multiplicity

This is the first study to evaluate EP547. Statistical methodologies adjusting for multiple comparisons do not apply because comparisons to placebo in this Phase 1 study are qualitative rather than quantitative.

15.9. Planned Interim Analysis

An interim analysis may be conducted during the study at a time the Sponsor deems appropriate. The interim analysis would be administrative in nature to address business needs.

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, for the interim analysis. The SAP will be amended if emerging data from the completed interim analysis leads to substantial change in the study protocol that has significant impact on the statistical analyses.

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

Based on the final eCRF, a database will be designed and built to meet US FDA: 21 Code of Federal Regulations (CFR) 11 requirements. A Data Management Plan will be written specifying the procedures that will be used for data cleaning, medical coding, SAE reconciliation, QC, laboratory data, and data cleaning that will occur for the study. A Data Validation Plan 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 Conference on 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 study staff will agree upon the timing of these visits.

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 initials, date of birth, 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 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, and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects.

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 Investigator will make the eCRFs 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, and 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 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.

Subjects will be provided a separate consent form before providing blood samples for genetic analysis and must be willing and able to provide consent as described above.

16.9. 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 approval. The only exception is when the Investigator considers a subject's safety to be compromised if immediate action is not taken.

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

Examples of important deviations include:

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

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

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.

17.3. Change in Study 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 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.

18. LIST OF REFERENCES

Bassari R, Koea JB. Jaundice associated pruritis: a review of pathophysiology and treatment. World J Gastroenterol. 2015;21(5):1404-13.

Bergasa NV. Pruritus of Cholestasis. In: Carstens E, Akiyama T, editors. Itch: Mechanisms and Treatment. Frontiers in Neuroscience. Boca Raton (FL)2014.

Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010;51(2):660-78.

EASL. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol. 2009;51(2):237-67.

EASL. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67(1):145-72.

FDA. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. FDA Maryland; 2005a. p. 1-27.

FDA. Guidance for industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. FDA Maryland; 2005b. p. 1-16.

[redacted]

Hu X, Sang Y, Yang M, et al. Prevalence of chronic kidney disease-associated pruritus among adult dialysis patients: A meta-analysis of cross-sectional studies. Medicine (Baltimore). 2018;97(21):e10633.

[redacted]

Lindor KD, Bowlus CL, Boyer J, et al. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology. 2019;69(1):394-419.

Meixiong J, Vasavda C, Green D, et al. Identification of a bilirubin receptor that may mediate a component of cholestatic itch. Elife. 2019a;8:1-25.

Meixiong J, Vasavda C, Snyder SH, et al. MRGPRX4 is a G protein-coupled receptor activated by bile acids that may contribute to cholestatic pruritus. Proc Natl Acad Sci USA. 2019b;116(21):10525-30.

Mettang T. Uremic Itch Management. Curr Probl Dermatol. 2016;50:133-41.

Mittal A. Cholestatic Itch Management. Curr Probl Dermatol. 2016;50:142-8.

Ozen N, Cinar FI, Askin D, et al. Uremic pruritus and associated factors in hemodialysis patients: A multi-center study. Kidney Res Clin Pract. 2018;37(2):138-47.

[redacted]

Rayner HC, Larkina M, Wang M, et al. International Comparisons of Prevalence, Awareness, and Treatment of Pruritus in People on Hemodialysis. Clin J Am Soc Nephrol. 2017;12(12):2000-7.

Shirazian S, Aina O, Park Y, et al. Chronic kidney disease-associated pruritus: impact on quality of life and current management challenges. Int J Nephrol Renovasc Dis. 2017;10:11-26.

Simonsen E, Komenda P, Lerner B, et al. Treatment of Uremic Pruritus: A Systematic Review. Am J Kidney Dis. 2017;70(5):638-55.

[redacted]

APPENDIX A. SCHEDULE OF ASSESSMENTS FOR THE SINGLE DOSE SEGMENTS

Visit	Screening[a]	Treatment Period				Safety Follow-Up	Early Study Term[b]	Notes
	Visit 1	Visit 2				Visit 3		
Study Day (Visit Window)	**-28 to -2**	**-1**	**1 (pre-dose)**	**1 (post-dose)**	**2**	**3**	**8 (±1)**	
Mandatory Confinement		X	X	X	X	X			
Admission		X							
Discharge						X			
General Assessments									
Informed consent	X								
Medical history	X								
Height	X								Measured using a stadiometer with no shoes.
FSH (females only)	X								
HIV, HBV, HCV serology	X								
Drug and cotinine screens (SAD-HS and SD-CP only)	X	X							Day -1 will be conducted locally.
Alcohol screen	X	X							Will be conducted locally.
Eligibility check	X	X							
Randomization			X						All dose levels in SAD-HS will be dosed according to a sentinel dosing design (Section 7.1.1). All subjects in SD-CP and SD-UP will receive EP547.
Study drug administration			X						Administered orally as intact capsules with water. For SD-UP, Day 1 (study drug administration) must be the day after a hemodialysis session.
Hemodialysis (SD-UP only)		X							Refer to note above.
Safety Assessments									
Pregnancy testing	X	X					X	X	Urine pregnancy test on Day -1 for all female SAD-HS and SD-CP subjects and serum pregnancy test for all female subjects for Screening, Day 8, and Early Study Term, if applicable.

Visit	Screening[a]	Treatment Period				Safety Follow-Up	Early Study Term[b]	Notes
	Visit 1	Visit 2				Visit 3		
Study Day (Visit Window)	**-28 to -2**	**-1**	**1 (pre-dose)**	**1 (post-dose)**	**2**	**3**	**8 (±1)**	
Physical examination	C	A					C	C	Will be either complete (C) or abbreviated (A) (Section 11.7).
Standard 12-lead ECG	X		X	X		X		X	To be performed in a supine position after ≥5 min of rest during Screening; predose and at 3 h postdose on Day 1; 48 h postdose on Day 3; and Early Study Term, if applicable.
Vital signs	X		X	X	X	X	X	X	Includes supine systolic and diastolic blood pressure, pulse rate, oxygen saturation, body temperature, and respiratory rate, measured after ≥5 min of rest at Screening; predose and at 1, 2, 4, 9, and 12 h postdose on Day 1; 24 h postdose on Day 2; 48 h postdose on Day 3; on Day 8; and Early Study Term, if applicable.
Body weight	X		X				X	X	Should be measured with no shoes on and using a calibrated scale throughout the study.
Chemistry and hematology	X		X		X	X	X	X	Drawn after an overnight fast (≥8 h) and predose as applicable. Refer to Section 11.9 for chemistry, hematology, and urinalysis (dipstick) assessments.
Urinalysis (SAD-HS and SD-CP only)	X		X		X	X	X	X	Refer to Section 11.9 for chemistry, hematology, and urinalysis (dipstick) assessments.
Coagulation	X								Refer to Section 11.9 for coagulation assessments.
Concomitant medications	X	X	X	X	X	X	X	X	Record all of the following: • Medications taken within 14 days before Screening (all subjects) • Medications taken to treat a cholestatic disorder or ESRD within 12 weeks before Screening (SD-CP and SD-UP only) • Medications known to impact pruritus within 4 weeks before Screening (SD-CP and SD-UP only)
AE assessment	X	X	X	X	X	X	X	X	To be documented from the signing of the Informed Consent Form until the end of study participation.

Visit	Screening[a]	Treatment Period				Safety Follow-Up	Early Study Term[b]	Notes
	Visit 1	Visit 2				Visit 3		
Study Day (Visit Window)	**-28 to -2**	**-1**	**1 (pre-dose)**	**1 (post-dose)**	**2**	**3**	**8 (±1)**		
Pharmacokinetic Assessments									
Blood sampling for PK			X	X	X	X	X		Drawn at predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 h postdose on Day 1; 18, 24, and 36 h postdose on Day 2; 48 h postdose on Day 3; and on Day 8.
Urine sampling for PK (SAD-HS only)			X	X	X	X			Collected at predose (-6 to 0 h) and from >0 to 6, >6 to 12, and >12 to 18 h postdose on Day 1; >18 to 24, >24 to 30, and >30 to 36 h postdose on Day 2; and >36 to 42 and >42 to 48 h postdose on Day 3.
Cardiodynamic Assessments (SAD-HS Only)									
Holter monitoring (SAD-HS only)			X	X	X				Continuous digital 12-lead ECGs will be recorded from approximately 1 h predose on Day 1 to 24 h postdose on Day 2 (Section 13.1).
[redacted]									
[redacted]		[redacted]							[redacted]
[redacted]			[redacted]						[redacted]

AE = adverse event; CP = cholestatic pruritus; ECG = electrocardiogram; ESRD = end-stage renal disease; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HS = healthy subject; PK = pharmacokinetic; SAD = single ascending dose; SD = single dose; Term = termination; UP = uremic pruritus; [redacted]

Subjects should fast for at least 8 hours before study days that require a blood sample for assessment of clinical chemistry, multiple blood samples for PK, and/or completion of questionnaires. Water is acceptable in the morning of site visits and each study day while confined to the study site to ensure the subject is hydrated for laboratory sample collection. On Day 1, study drug will be administered with approximately 240 mL of water, additional water will not be allowed from 1 hour predose to 1 hour postdose, and subjects will remain fasted until after the 4-hour PK blood sample is collected. If a subject with ESRD has a daily fluid restriction, study drug may be administered with a smaller volume of water at the Investigator's discretion.

[a] Screening: May be conducted over more than 1 day but must be completed between Day -28 and Day -2.

[b] Early Study 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.

APPENDIX B. SCHEDULE OF ASSESSMENTS FOR THE MULTIPLE DOSE SEGMENTS

Visit		Screening[a]	Treatment Period										Safety Follow-Up[b]		Early Study Term[c]	Notes
		Visit 1	Visit 2										Visit 3	Visit 4		
Study Day (Visit Window)		-28 to -4	-1	1 (pre-dose	1 (post-dose)	2	3	4	5	6	7	8	14 (±1)	21 (±2)		
MAD-HS	Mandatory Confinement		X	X	X	X	X	X	X	X	X	X				
	Admission		X													
	Discharge											X				
MAD-CP	Mandatory Confinement		X	X	X	X					X	X				For Days 3-6, subjects may choose to remain confined, return to the site each morning, or have a nurse visit their home to the complete scheduled assessments.
	Admission		X								X					
	Discharge					X						X				
MAD-UP	Mandatory Confinement		X	X	X	X				X	X	X				For Days 3-5, subjects may choose to remain confined, return to the site each morning, or have a nurse visit their home to the complete scheduled assessments.
	Admission		X							X						
	Discharge					X						X				
General Assessments																
Informed consent		X														
Medical history		X														
Height		X														Measured using a stadiometer with no shoes.
FSH (females only)		X														
HIV, HBV, HCV serology		X														
Drug and cotinine screens (MAD-HS and MAD-CP only)		X	X													Day -1 will be conducted locally.

Visit	Screening[a]	Treatment Period									Safety Follow-Up[b]		Early Study Term[c]	Notes
	Visit 1	Visit 2									Visit 3	Visit 4		
Study Day (Visit Window)	**-28 to -4**	**-1**	**1 (pre-dose**	**1 (post-dose)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**14 (±1)**	**21 (±2)**		
Alcohol screen	X	X													Will be conducted locally.
Eligibility check	X	X													
Randomization			X												Subjects in each dosing group will be randomized in a 3:1 ratio (EP547:placebo).
Study drug administration			X		X	X	X	X	X	X					Administer study drug QD for 7 days as intact capsules with water. For MAD-UP, administer study drug 4 to 6 h before the hemodialysis session on Days 1, 4, and 6 and at approximately the same time of day on Days 2, 3, 5, and 7 (days without a hemodialysis session).
Hemodialysis (MAD-UP only)				X			X		X						Refer to note above.
Safety Assessments															
Pregnancy testing	X	X										X	X	X	Urine pregnancy test on Day -1 for all female MAD-HS and MAD-CP subjects and serum pregnancy test for all female subjects for Screening, Days 14 and 21, and Early Study Term, if applicable.
Physical examination	C	A										A	C	C	Will be either complete (C) or abbreviated (A) (Section 11.7).
Standard 12-lead ECG	X		X	X		X					X			X	To be performed in a supine position after ≥5 min of rest during Screening; predose and at 3 h postdose on Day 1; predose on Day 3; 24 h after the last dose on Day 8; and Early Study Term, if applicable.
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	Includes supine systolic and diastolic blood pressure, pulse rate, oxygen saturation, body temperature, and respiratory rate, measured after ≥5 min of rest at Screening; predose and at 1, 2, 4, 9, and 12 h postdose on Day 1; predose on Days 2-7; 24 h after the last dose on Day 8; on Days 14 and 21; and at Early Study Term, if applicable.

Visit	Screening[a]	Treatment Period									Safety Follow-Up[b]		Early Study Term[c]	Notes
	Visit 1	Visit 2									Visit 3	Visit 4		
Study Day (Visit Window)	**-28 to -4**	**-1**	**1 (pre-dose**	**1 (post-dose)**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**14 (±1)**	**21 (±2)**		
Body weight	X		X								X			X	Should be measured with no shoes on and using a calibrated scale throughout the study.
Chemistry and hematology	X		X		X		X				X	X	X	X	Drawn after an overnight fast (≥8 h) and predose as applicable. Refer to Section 11.9 for chemistry, hematology, and urinalysis (dipstick) assessments.
Urinalysis (MAD-HS and MAD-CP only)	X		X		X		X				X	X	X	X	Refer to Section 11.9 for chemistry, hematology, and urinalysis (dipstick) assessments.
Coagulation	X														Refer to Section 11.9 for coagulation assessments.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Record all of the following: • Medications taken within 14 days before Screening (all subjects) • Medications taken to treat a cholestatic disorder or ESRD within 12 weeks before Screening (MAD-CP and MAD-UP only) • Medications known to impact pruritus within 4 weeks before Screening (MAD-CP and MAD-UP only)
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	To be documented from the signing of the Informed Consent Form until the end of study participation.
Pharmacokinetic Assessments															
Blood sampling for PK			X	X	X	X	X	X	X	X	X	X	X		Refer to Appendix C for the MAD Dosing and PK Sampling Schedule.
Skin biopsy				X											Collected 2 h postdose under local anesthesia for the last dose level for MAD-HS and all dose levels for MAD-CP and MAD-UP.
[redacted]															
[redacted]			[redacted]	[redacted]						[redacted]				[redacted]	

Visit	Screening[a]	Treatment Period									Safety Follow-Up[b]		Early Study Term[c]	Notes
	Visit 1	Visit 2									Visit 3	Visit 4		
Study Day (Visit Window)	-28 to -4	-1	1 (pre-dose)	1 (post-dose)	2	3	4	5	6	7	8	14 (±1)	21 (±2)		
[redacted]															

AE = adverse event; CP = cholestatic pruritus; ECG = electrocardiogram; ESRD = end-stage renal disease; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HS = healthy subject; MAD = multiple ascending dose; [redacted]

[redacted]; PK = pharmacokinetic; QD = once daily; Term = termination; UP = uremic pruritus; [redacted]

Subjects should fast for at least 8 hours before study days that require a blood sample for assessment of clinical chemistry, multiple blood samples for PK, and/or completion of questionnaires. Water is acceptable in the morning of site visits and each study day while confined to the study site to ensure the subject is hydrated for laboratory sample collection. On days with multiple blood samples for PK, study drug will be administered with approximately 240 mL of water, additional water will not be allowed from 1 hour predose to 1 hour postdose, and subjects will remain fasted until after the 4-hour PK blood sample is collected. If a subject with ESRD has a daily fluid restriction, study drug may be administered with a smaller volume of water at the Investigator's discretion.

[a] Screening: May be conducted over more than 1 day but must be completed between Day -28 and Day -4.

[b] Subjects are to return to the site to complete scheduled assessments for Safety Follow-Up Visits. However, a nurse visit to their home may be permitted on a case-by-case basis with prior approval of the Sponsor.

[c] Early Study 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.

APPENDIX C. DOSING AND PK BLOOD SAMPLING SCHEDULE FOR THE MAD SEGMENTS

		Blood Sample Collection Timepoints (h postdose)			Assessment Window (min)[a]
Study Day	Dosing	MAD-HS	MAD-CP	MAD-UP	
Day 1		Predose	Predose	Predose	< 30 min before dose
	Give 1st dose at t=0				
		0.25	0.25	0.25	±2
		0.5	0.5	0.5	±5
		1	1	1	±10
		1.5	1.5	1.5	±10
		2	2	2	±10
		2.5	2.5	2.5	±10
		3	3	3	±10
		4	4	4	±10
		6	6	6	±10
		9	9	9	±10
		12	12	12	±15
Day 2		18	18	18	±15
		Predose	Predose	Predose	< 30 min before dose
	Give 2nd dose at t=0				
				0.25	±2
				0.5	±5
				1	±10
				1.5	±10
				2	±10
				2.5	±10
				3	±10
				4	±10
				6	±10
				9	±10
				12	±15
Day 3				18	±15
		Predose			< 30 min before dose
	Give 3rd dose at t=0				
Day 4		Predose	Predose	Predose	< 30 min before dose
	Give 4th dose at t=0				
Day 5		Predose			< 30 min before dose
	Give 5th dose at t=0				
Day 6		Predose		Predose	< 30 min before dose
	Give 6th dose at t=0				
				0.25	±2
				0.5	±5
				1	±10
				1.5	±10
				2	±10
				2.5	±10
				3	±10
				4	±10
				6	±10
				9	±10
				12	±15

Study Day	Dosing	Blood Sample Collection Timepoints (h postdose)			Assessment Window (min)[a]
		MAD-HS	MAD-CP	MAD-UP	
Day 7		Predose	Predose	18 Predose	±15 < 30 min before dose
	Give 7th dose at t=0				
		0.25	0.25	0.25	±2
		0.5	0.5	0.5	±5
		1	1	1	±10
		1.5	1.5	1.5	±10
		2	2	2	±10
		2.5	2.5	2.5	±10
		3	3	3	±10
		4	4	4	±10
		6	6	6	±10
		9	9	9	±10
		12	12	12	±15
Day 8		24	24	24	±15
Day 14		Anytime	Anytime	Anytime	Not applicable
Day 21		Anytime	Anytime	Anytime	Not applicable

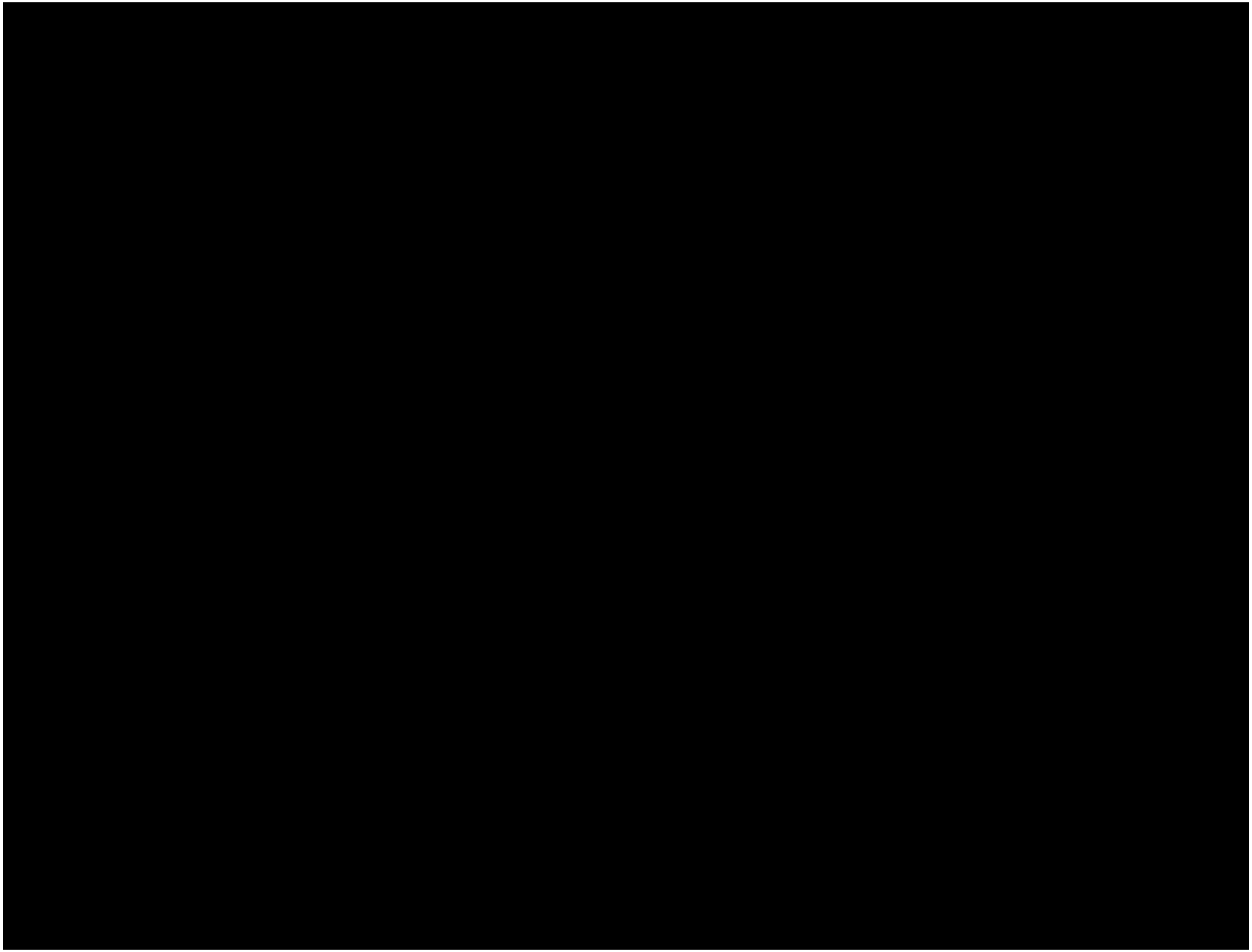
CP = cholestatic pruritus; HS = healthy subject; MAD = multiple ascending dose; PK = pharmacokinetic; t = time; UC = uremic pruritus.

On days with multiple blood samples for PK, study drug will be administered with approximately 240 mL of water, additional water will not be allowed from 1 hour predose to 1 hour postdose, and subjects will remain fasted until after the 4-hour PK blood sample is collected. If a subject with ESRD has a daily fluid restriction, study drug may be administered with a smaller volume of water at the Investigator's discretion.

[a] The assessment window for blood sample collection timepoints for the first dose is the same for the single and multiple dose segments.

[redacted]

[redacted]



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APPENDIX I. SUMMARY OF CHANGES BY AMENDMENT

Summary of Changes for Amendment 2.0 Dated 19 February 2021

[redacted]

Revised text in Amendment 2.0 is indicated in bold font, and text deleted from the Amendment 1.0 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	Amendment 1.0	Amendment 2.0	Reason for Change
Approval Page	[redacted]	[redacted]	The approval page was amended to reflect a change in biostatistical responsibilities.
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	8. For subjects participating in [redacted]	[redacted]	[redacted]

Section	Amendment 1.0	Amendment 2.0	Reason for Change
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Section	Amendment 1.0	Amendment 2.0	Reason for Change
[redacted]	[redacted]	[redacted]	[redacted]

Summary of Changes for Amendment 1.0 Dated 14 December 2020

Protocol EP-547-101 was amended to:

Eligibility Criteria:

- Revise the duration of stable dosing for medications known to impact pruritus from 12 weeks to 4 weeks before Screening to allow more subjects with pruritus to participate without confounding baseline efficacy measurements or impacting subject safety.
- Increase the window for collecting urea reduction ratio measurements for determining eligibility for subjects with end-stage renal disease (ESRD) to be consistent with standard of care.

Safety Assessments:

- Clarify the safety criteria for stopping dosing to be more consistent with Section 8.2.9 (Stopping Rules) of the following European Medicines Agency Publication: Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. The change was previously put into effect via a Protocol Clarification Letter dated 08 September 2020.
- Remove all urine-based assessments (ie, urinalysis, drug and cotinine screens, and Day -1 pregnancy test) for subjects with ESRD given their potential for minimal or no residual kidney function.
- Add a body weight measurement to the final day of the treatment period for the multiple ascending dose (MAD) segment to allow for assessment of safety.
- Allow body weight to be measured with more than one calibrated scale during the study to provide more flexibility.
- Change the alcohol screen from being conducted centrally to be conducted locally for Screening to simplify assessment conduct.
- Revise the start of predose recordings of the continuous digital 12-lead electrocardiograms (ECGs) from 1 hour predose to approximately 1 hour predose to allow for greater flexibility.
- Add albumin to the list of urinalysis analytes for completeness.

[redacted]

[redacted]

Study Drug Dosing and Storage and Assignment of Treatment and Subject and Randomization Numbers:

- Provide guidance for dosing a bile acid sequestrant with respect to study drug to minimize their potential impairment on exposure of EP547.
- Allow subjects with ESRD who have a daily fluid restriction to be given a smaller volume of water than the 240-mL volume specified in the protocol at the Investigator's discretion when study drug is administered so that they may participate in the study.
- Revise the study drug storage conditions to include excursions to 10°C (50°F), which is supported by data from a recently completed drug stability study.
- Change the process for assigning treatment to overcome logistical challenges associated with waiting until the subjects check in on Day -1.
- Clarify when subject and randomization numbers will be assigned.

Revised text in Amendment 1.0 is indicated in bold font, and text deleted from the Original version is crossed out in the table below. Italicized text is used to describe change. Minor/editorial changes are not listed individually in the summary table.

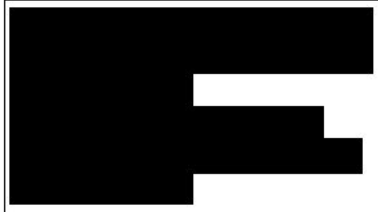
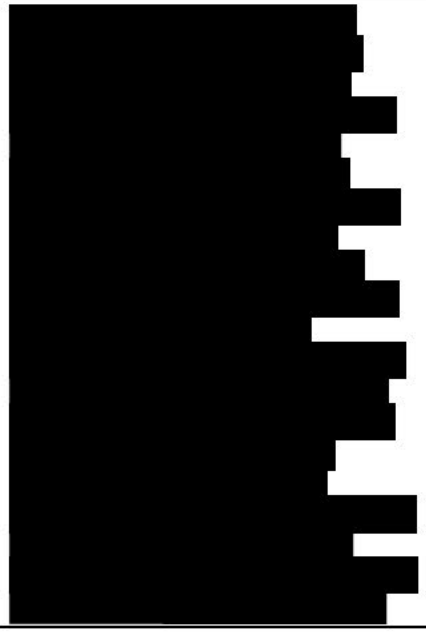
Section	Original Version	Amendment 1.0	Reason for Change
[redacted]	[redacted]	[redacted]	[redacted]

Section	Original Version	Amendment 1.0	Reason for Change
Global	*The protocol included the following assessments:* • *Urinalysis at Screening and Days 1, 2, 3, and 8, and early termination for all single dose segments* • *Urinalysis at Screening and Days 1, 2, 4, 8, 14, 21, and early termination for all multiple dose segments* • *Drug and cotinine screens at Screening and Day -1 for all segments* • *Urine pregnancy testing for female subjects at Day -1 for all segments*	*Removed urinalysis, drug and cotinine screens, and urine pregnancy testing for subjects with ESRD from the protocol*	Removed all urine-based assessments for subjects with ESRD given that these subjects will likely have minimal or no residual kidney function.
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted] devices are to be placed.
Global	*Alcohol screen at Screening was to be conducted centrally*	*Alcohol screen at Screening will be conducted locally*	The change in location of where the alcohol screen will be assessed was made to simplify assessment conduct.

Section	Original Version	Amendment 1.0	Reason for Change
Synopsis (Inclusion Criteria) 8.1.2 (Subjects with Cholestatic Pruritus)	• 9. If currently taking medications to treat the cholestatic disorder ~~or any pruritus associated with it~~, must be on a stable dose for >12 weeks before Screening and plans to maintain the regimen throughout the study	9. If currently taking medications to treat the cholestatic disorder, must be on a stable dose for >12 weeks before Screening and plans to maintain the regimen throughout the study 10. **If currently taking medications known to impact pruritus, must be on a stable dose for >4 weeks before Screening and plans to maintain the regimen throughout the study**	The revised duration will allow more subjects with a cholestatic disorder taking medications for pruritus to participate without confounding baseline efficacy measurements or impacting subject safety.
Synopsis (Inclusion Criteria) 8.1.3 (Subjects with Uremic Pruritus)	2. Has end-stage renal disease (ESRD) and is receiving hemodialysis 3× per week of at least 4 hours in duration for ≥3 months before Screening; hemodialysis must be adequate (ie, ≥2 urea reduction ratio measurements ≥65% on different hemodialysis days ~~during~~ the month before Screening)	2. Has end-stage renal disease (ESRD) and is receiving hemodialysis 3× per week of at least 4 hours in duration for ≥3 months before Screening; hemodialysis must be adequate (ie, ≥2 urea reduction ratio measurements ≥65% on different hemodialysis days **from** the month before Screening **to Day -1**)	The window for collecting urea reduction ratio measurements for determining eligibility for subjects with ESRD was increased to be consistent with standard of care.
Synopsis (Inclusion Criteria) 8.1.3 (Subjects with Uremic Pruritus)	9. If currently taking medications ~~to treat any~~ pruritus ~~associated with ESRD~~, must be on a stable dose for >~~12~~ weeks before Screening and plans to maintain the regimen throughout the study	9. If currently taking medications **known to impact** pruritus, must be on a stable dose for >**4** weeks before Screening and plans to maintain the regimen throughout the study	The revised duration will allow more subjects with ESRD taking medications for pruritus to participate without confounding efficacy baseline measurements or impacting safety.
Synopsis (Exclusion Criteria) 8.2.3 (Subjects with Uremic Pruritus)	5. Positive ~~drug,~~ alcohol~~, or cotinine~~ screen result~~s~~ at Screening or Day -1	5. Positive alcohol screen result at Screening or Day -1 **or known use of drugs or tobacco at Screening**	Known use of drugs or tobacco use at Screening was added since the drug and cotinine assessments for subjects with ESRD were removed.
Synopsis (Study Drug Storage) 10.3 (Study Drug Storage)	The study drug capsules may be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F).	The study drug capsules may be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F)**, with excursions to 10°C (50°F)**.	Study drug storage conditions were revised to incorporate findings from a recently completed drug stability study.

Section	Original Version	Amendment 1.0	Reason for Change
Synopsis (Study Drug Administration) 10.4 (Study Drug Administration)	*New text*	**Subjects who routinely take a bile acid sequestrant (eg, cholestyramine, colestipol, or colesevelam) will be instructed to hold their morning dose until 2 hours after study drug administration. If their bile acid sequestrant baseline dosing regimen does not allow for a 2-hour hold, dosing of these medications must be held for a minimum of 1 hour after study drug administration. Alternatively, the bile acid sequestrant may be taken at least 4 hours prior to study drug administration.**	Bile acid sequestrants bind bile acids and disrupt their enterohepatic circulation by preventing their reabsorption from the gut. If EP547 undergoes significant enterohepatic circulation, bile acid sequestrants will also bind EP547 and disrupt its absorption into the bloodstream.
Synopsis (Fasting Requirements) 9.4 (Study Visits) Appendix A (Schedule of Assessments for the Single Dose Segments *[Footnotes]*) Appendix B (Schedule of Assessments for the Multiple Dose Segments *[Footnotes]*) Appendix C (Dosing and PK Blood Sampling Schedule for the MAD Segments *[Footnotes]*)	*New text*	**If a subject with ESRD has a daily fluid restriction, study drug may be administered with a smaller volume of water at the Investigator's discretion.**	Relaxing the water volume requirement will allow subjects with ESRD who have a daily fluid restriction the opportunity to participate in the study.

Section	Original Version	Amendment 1.0	Reason for Change
Synopsis (Safety Criteria for Stopping Dosing) 7.3.4 (Safety Criteria for Stopping Dosing)	Study drug dosing will be held for all subjects if any of the following criteria are met: • A~~t least 1~~ subject receiving EP547 experiences a serious AE ~~(~~SAE~~)~~ ~~that results in drug~~ related ~~death or is a drug-related event that is immediately life-threatening~~ • At least 2 subjects receiving EP547 experience a ~~drug~~ related ~~SAE in the same System Organ Class~~	Study drug dosing will be held for all subjects if any of the following criteria are met: • A subject receiving EP547 experiences a serious **adverse reaction (ie, a serious** AE **[**SAE**] considered at least possibly** related **to the study drug)** • At least 2 subjects receiving EP547 **in the same dosing group** experience a **severe non-serious adverse reaction (ie, a severe, non-serious AE considered at least possibly** related **to the study drug)**	The safety criteria for stopping dosing were clarified to be more consistent with Section 8.2.9 (Stopping Rules) of the following European Medicines Agency Publication: Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.
Synopsis (Blood Sampling for Pharmacokinetics) 12.1 (Blood Sampling for Pharmacokinetics)	*New text*	**The assessment window for blood sample collection timepoints for the single and multiple dose segments is also included in Appendix C.**	Text was added to reflect the addition of blood sample collection timepoints for the single dose segments to Appendix C.
Synopsis (Skin Biopsy for Pharmacokinetics [Last Dose Level for MAD-HS and All Dose Levels for MAD-CP and MAD-UP Only]) 12.3 (Skin Biopsy for Pharmacokinetics [Last Dose Level for MAD-HS and All Dose Levels for MAD-CP and MAD-UP Only])	Given that EP547 is hypothesized to be an inverse agonist (inhibitor) of mas-related G protein-coupled receptor X4 (MRGPRX4) in the skin to reduce itch, three 3-mm biopsies of the skin from the back will be performed under local anesthesia on Day 1 at 2 hours postdose.	Given that EP547 is hypothesized to be an inverse agonist (inhibitor) of mas-related G protein-coupled receptor X4 (MRGPRX4) in the skin to reduce itch, three 3-mm biopsies of the skin from the back will be performed under local anesthesia on Day 1 at 2 hours postdose **with an assessment window of +30 minutes**.	An assessment window for biopsy collection was included for clarity.

Section	Original Version	Amendment 1.0	Reason for Change
Synopsis (Holter Monitoring for 12-Lead ECG Acquisition and Subsequent Cardiodynamic Analysis [SAD-HS Only]) 13.1 (Holter Monitoring for 12-Lead ECG Acquisition and Subsequent Cardiodynamic Analysis [SAD-HS Only])	Continuous digital 12-lead ECGs will be recorded from 1 hour predose on Day 1 to 24 hours postdose on Day 2 under constant supervision for subjects in SAD-HS only.	Continuous digital 12-lead ECGs will be recorded from **approximately** 1 hour predose on Day 1 to 24 hours postdose on Day 2 under constant supervision for subjects in SAD-HS only.	The start of predose recordings of the continuous digital 12-lead ECGs was revised from 1 hour predose to approximately 1 hour predose to allow for greater flexibility.
			

Section	Original Version	Amendment 1.0	Reason for Change
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
9.1 (Treatment Assignment)	~~Sites will request kit assignments for eligible subjects after they have checked in for admission on Day -1 via email by contacting~~ [redacted] ~~The Sponsor will assign kit numbers to each subject following the randomization code and kit assignment list.~~	**The Sponsor will allocate sequential randomization codes and kit numbers for each dose level from the randomization code and kit assignment list. Sites will request the allocated randomization and kit numbers from the Sponsor in advance of dosing by contacting** [redacted]	The process for assigning treatment was changed to overcome logistical challenges associated with waiting until the subjects check in on Day -1.

Section	Original Version	Amendment 1.0	Reason for Change
9.3.1 (Randomization)	Subjects who meet all eligibility criteria will be assigned a ~~subject~~ number just before dosing.	**Subjects will be assigned a subject number after signing the Informed Consent Form (ICF).** Subjects who meet all eligibility criteria will be **randomized and** assigned a **randomization** number just before dosing.	The text was revised to clarify when subject and randomization numbers will be assigned.
9.4.1.1.1 (Visit 1 [Day -28 to Day -2])	• Assessment of baseline concomitant medications, including: – All medications taken within 14 days before Screening – Medications taken to treat a cholestatic disorder or ESRD ~~or any~~ pruritus ~~associated with these conditions~~ within ~~12~~ weeks before Screening (SD-CP and SD-UP only)	• Assessment of baseline concomitant medications, including: – All medications taken within 14 days before Screening – Medications taken to treat a cholestatic disorder or ESRD **within 12 weeks before Screening (SD-CP and SD-UP only)** – **Medications known to impact** pruritus within **4** weeks before Screening (SD-CP and SD-UP only)	The revised duration will allow more subjects with a cholestatic disorder or ESRD taking medications for pruritus to participate without confounding baseline efficacy measurements or impacting safety.
9.4.1.2.1 (Visit 2 [Day 1] – Predose)	• Continuous digital 12-lead ECG recording for Holter monitoring beginning 1 hour before study drug administration (SAD-HS only)	• Continuous digital 12-lead ECG recording for Holter monitoring beginning **approximately** 1 hour before study drug administration (SAD-HS only)	The start of predose recordings of the continuous digital 12-lead ECGs was revised from 1 hour predose to approximately 1 hour predose to allow for greater flexibility.

Section	Original Version	Amendment 1.0	Reason for Change
9.4.2.1.1 (Visit 1 (Day -28 to Day -2)	• Assessment of baseline concomitant medications, including: – All medications taken within 14 days before Screening – Medications taken to treat a cholestatic disorder or ESRD ~~or any~~ pruritus ~~associated with these conditions~~ within ~~12~~ weeks before Screening (MAD-CP and MAD-UP only)	• Assessment of baseline concomitant medications, including: – All medications taken within 14 days before Screening – Medications taken to treat a cholestatic disorder or ESRD **within 12 weeks before Screening (MAP-CP and MAD-UP only)** – **Medications known to impact** pruritus within **4** weeks before Screening (MAD-CP and MAD-UP only)	The revised duration will allow more subjects with a cholestatic disorder or ESRD taking medications for pruritus to participate without confounding baseline efficacy measurements or impacting safety.
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Section	Original Version	Amendment 1.0	Reason for Change
9.4.2.2.9 (Visit 2 [Day 8] – Discharge)	*New assessment*	• **Body weight**	Body weight was added to the final day of the treatment period to allow for assessment of safety.
11.3 (Concomitant Medications)	In addition, medications taken to treat a cholestatic disorder or ESRD or ~~any~~ pruritus ~~associated with these conditions~~ within ~~12~~ weeks before Screening should also be recorded.	In addition, medications taken to treat a cholestatic disorder or ESRD **within 12 weeks before Screening** or **medications known to impact** pruritus within **4** weeks before Screening should also be recorded.	The revised duration will allow more subjects with a cholestatic disorder or ESRD taking medications for pruritus to participate without confounding baseline efficacy measurements or impact safety.
11.6 (Body Weight) Appendix A (Schedule of Assessments for the Single Dose Segments *[Body Weight Row]*) Appendix B (Schedule of Assessments for the Multiple Dose Segments *[Body Weight Row]*)	Body weight should be measured with no shoes on and using ~~the same~~ scale throughout the study.	Body weight should be measured with no shoes on and using **a calibrated** scale throughout the study.	The ability to use more than one calibrated scale during the study was added to provide more flexibility.
11.9 (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 (dipstick) **(SAD-HS, SD-CP, MAD-HS, and MAD-CP only)**: 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	Albumin was added to the list of urinalysis analytes for completeness.
11.9 (Laboratory Evaluations of Safety) 11.10 (Other Laboratory Evaluations)	*New text*	**See the laboratory manual for additional details.**	Reference to the laboratory manual was added to direct sites to details not provided in the protocol.

Section	Original Version	Amendment 1.0	Reason for Change
[redacted]	[redacted]	[redacted]	[redacted]
Appendix A (Schedule of Assessments for the Single Dose Segments *[Concomitant Medications]*)	Record all ~~me~~dications taken within 14 days before Screening (all subjects) ~~and me~~dications taken to treat a cholestatic disorder or ESRD or ~~any~~ pruritus ~~associated with these conditions~~ within ~~12~~ weeks before Screening (SD-CP and SD-UP only)~~.~~	Record all **of the following:** • **M**edications taken within 14 days before Screening (all subjects) • **M**edications taken to treat a cholestatic disorder or ESRD **within 12 weeks before Screening (SD-CP and SD-UP only)** • **Medications known to impact** pruritus within **4** weeks before Screening (SD-CP and SD-UP only)	The revised duration will allow more subjects with a cholestatic disorder or ESRD taking medications for pruritus to participate without confounding baseline efficacy measurements or impact safety.
Appendix A (Schedule of Assessments for the Single Dose Segments *[Holter Monitoring Row]*)	Continuous digital 12-lead ECGs will be recorded from 1 h predose on Day 1 to 24 h postdose on Day 2 (Section 13.1).	Continuous digital 12-lead ECGs will be recorded from **approximately** 1 h predose on Day 1 to 24 h postdose on Day 2 (Section 13.1).	The start of predose recordings of the continuous digital 12-lead ECGs was revised from 1 hour predose to approximately 1 hour predose to allow for greater flexibility.
Appendix B (Schedule of Assessments for the Multiple Dose Segments *[Body Weight Row]*)	*Body weight was not included for the Day 8 (Visit 2) assessments.*	*Body weight was added to the Day 8 (Visit 2) assessments.*	Body weight was added to the final day of the treatment period to allow for assessment of safety.
Appendix B (Schedule of Assessments for the Multiple Dose Segments *[Concomitant Medications Row]*)	Record all ~~me~~dications taken within 14 days before Screening (all subjects) ~~and me~~dications taken to treat a cholestatic disorder or ESRD or ~~any~~ pruritus ~~associated with these conditions~~ within ~~12~~ weeks before Screening (MAD-CP and MAD-UP only)~~.~~	Record all **of the following:** • **M**edications taken within 14 days before Screening (all subjects) • **M**edications taken to treat a cholestatic disorder or ESRD **within 12 weeks before Screening (MAD-CP and MAD-UP only)** • **Medications known to impact** pruritus within **4** weeks before Screening (MAD-CP and MAD-UP only)	The revised duration will allow more subjects with a cholestatic disorder or ESRD taking medications for pruritus to participate without confounding baseline efficacy measurements or impact safety.

Section	Original Version	Amendment 1.0	Reason for Change
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
APPENDIX C (Dosing and PK Blood Sampling Schedule for the MAD Segments)	*No footnote*	[a] The assessment window for blood sample collection timepoints for the first dose is the same for the single and multiple dose segments.	Added the assessment window for the single dose segment blood sample collection timepoints for completeness.
[redacted]	[redacted]	[redacted]	[redacted]

Section	Original Version	Amendment 1.0	Reason for Change
	[redacted]	[redacted]	

1. TITLE PAGE

Randomized, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of EP547 in Healthy Subjects and Subjects with Cholestatic or Uremic Pruritus

Protocol Number:	EP-547-101
Protocol Version Number:	Addendum 1.0 to Amendment 2.0
Issue Date:	19 March 2021
Drug Development Phase:	Phase 1
Sponsor:	Escient Pharmaceuticals, Inc. 10578 Science Center Drive, Suite 250 San Diego, CA 92121 USA [redacted] [redacted] Chief Executive Officer Escient Pharmaceuticals, Inc. [redacted]

Randomized, Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of EP547 in Healthy Subjects and Subjects with Cholestatic or Uremic Pruritus

Protocol Number:	EP-547-101
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Issue Date:	19 March 2021

Sponsor Statement

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

[redacted]

[redacted]
Chief Executive Officer
Escient Pharmaceuticals, Inc.

[redacted]

Date

[redacted]
Vice President, Head of Clinical Development
Escient Pharmaceuticals, Inc.

[redacted]

Date

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

Investigator's Agreement

I have read this protocol addendum for EP-547-101 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 addendum.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

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

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3. 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
AE	adverse event
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t
CI	confidence interval
C_{max}	maximum (peak) plasma concentration
CP	cholestatic pruritus
FDA	Food and Drug Administration
FE	food effect
FSH	follicle-stimulating hormone
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HS	healthy subject
ICF	Informed Consent Form
MAD	multiple ascending dose
PK	pharmacokinetic(s)
PO	oral
SAD	single ascending dose
SD	single dose
$t_{1/2}$	terminal half-life
t_{max}	time to achieve maximum (peak) plasma concentration
UP	uremic pruritus

4. PURPOSE

This addendum is a pilot evaluation of the effect of food on the pharmacokinetics (PK) of a single dose of EP547 in healthy subjects at a single site.

5. BACKGROUND AND RATIONALE

Protocol EP-547-101 is a first-in-human, Phase 1, randomized, single and multiple ascending dose (SAD and MAD) study with EP547 in healthy subjects and subjects with cholestatic or uremic pruritus. Each population includes a SAD or single dose (SD) segment followed by a MAD segment for a total of 6 segments (SAD-HS and MAD-HS in healthy subjects [HS]; SD-CP and MAD-CP in subjects with cholestatic pruritus [CP]; and SD-UP and MAD-UP in subjects with uremic pruritus [UP]).

To date, clinical conduct for SAD-HS and MAD-HS is complete; evaluations in subjects with cholestatic or uremic pruritus are ongoing. EP547 has been tested in 48 healthy subjects with 18 treated in the multiple dose regimen. Dosing levels evaluated in healthy subjects included 25 mg to 675 mg single doses and 25, 75, and 225 mg multiple dose regimens. All doses tested to date were well tolerated with no safety signals identified.

For this addendum, a food effect segment in healthy subjects (FE-HS) at a single site will be evaluated. Data from this substudy will provide data to inform appropriate dosing instructions for future studies.

6. OBJECTIVE

The objective of this substudy is:

- To assess the single-dose PK of EP547 following oral administration under fed and fasted conditions in healthy subjects

7. INVESTIGATIONAL PLAN

7.1. Substudy Design

Twelve healthy subjects will participate in this 2-period, unblinded, randomized, crossover food effect substudy to evaluate the PK of a single dose of EP547 administered orally (PO) in a fasted or fed condition. Subjects who participated in SAD-HS or MAD-HS may not participate in FE-HS. Subjects will be randomized in a 1:1 ratio to either Sequence 1 (Fasted for FE Period 1, Fed for FE Period 2) or Sequence 2 (Fed for FE Period 1, Fasted for FE Period 2). The dose level to be tested in FE-HS will be 75 mg, which was selected based on safety and tolerability data and EP547 PK characteristics from SAD-HS and MAD-HS, and from data generated by nonclinical studies.

Doses between the 2 FE Periods must be separated by a minimum of 10 days to allow for washout of study drug. Study drug for each FE Period will be administered with approximately 240 mL of water; additional water will not be allowed from 1 hour predose to 1 hour postdose.

Fasted Regimen:

EP547 will be administered after an overnight fast for a minimum of 8 hours. Subjects will remain fasted until after the 4-hour PK blood sample is collected.

Fed Regimen:

Subjects will fast overnight for a minimum of 8 hours. Approximately 30 minutes before administration of study drug, subjects will be provided a high fat/high calorie breakfast and will be instructed to consume the entire meal in 30 minutes or less. Subjects must consume at least 90% of their meal to be eligible for dosing. The start and stop time and percentage of the breakfast consumed will be recorded. Per guidance from the Food and Drug Administration (FDA), the high fat/high calorie meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively (FDA 2002). No other food or drink (other than water as specified above) will be permitted until after the 4-hour PK blood sample is collected.

Both Regimens:

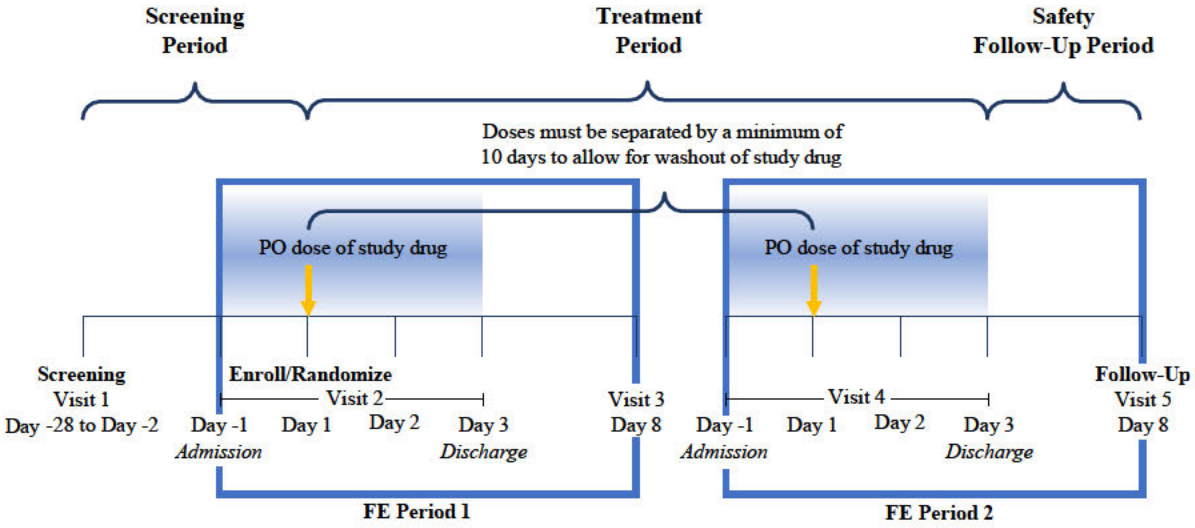
Each meal and/or snack served at the clinic will be standardized, similar in caloric content and composition (except for the high-fat/high calorie breakfast served as part of the fed regimen), and consumed at approximately the same time in each FE Period during confinement.

7.2. Study Schedule

Subjects should fast for at least 8 hours before study days that require a blood sample for assessment of clinical chemistry or multiple blood samples for PK as described in Section 9.4 of Protocol EP-547-101, Amendment 2.0.

Screening:	Visit 1 (Screening) is to occur between Day -28 and Day -2.
FE Periods:	For each FE Period, there is 1 mandatory confinement period in the clinic, beginning from Day -1 (admission) to Day 3 until after the 48-hour postdose assessments are completed (discharge). Subjects are to return to the clinic on Day 8 to complete additional assessments.
Treatment Period:	The Treatment Period includes a portion of both FE periods and is to begin on Day 1 of Visit 2 and end on Day 3 of Visit 4.
Safety Follow-Up:	Visit 5 (Day 8) is also the Safety Follow-Up Visit and is to occur 7 days after the last administration of study drug. If termination occurs during the Treatment Period, the subject will have a Safety Follow-Up Visit approximately 7 days (±1 day) after the last dose of study drug and is to undergo the procedures for Visit 5 (Day 8).

Figure 1: Study Schedule



FE = food effect; PO = oral.
Shading represents the mandatory period when subjects will be confined to the study site.
Visit 5 (Day 8) is also the Safety Follow-Up Visit and is to occur 7 days after the last administration of study drug. If termination occurs during the Treatment Period, the subject will have a Safety Follow-Up Visit approximately 7 days (±1 day) after the last dose of study drug and is to undergo the procedures for Visit 5 (Day 8).

7.3. Number of Subjects

A total of 12 heathy subjects are expected to participate in the substudy.

Subjects who discontinue before completing the Treatment Period or have insufficient PK data may be replaced at the Sponsor's discretion.

8. STUDY POPULATION

Subjects who meet all inclusion criteria and none of the exclusion criteria for healthy subjects as specified in Section 8.1.1 and Section 8.2.1 of Protocol EP-547-101, Amendment 2.0, respectively, are eligible to participate in the substudy.

9. RANDOMIZATION AND BLINDING

9.1.1. Randomization

Subjects will be assigned a subject number after signing the Informed Consent Form (ICF). Subjects who meet all eligibility criteria will be randomized and assigned a randomization number just before dosing. Subjects in FE-HS will be randomized in a 1:1 ratio to either Sequence 1 (Fasted for FE Period 1, Fed for FE Period 2) or Sequence 2 (Fed for FE Period 1, Fasted for FE Period 2).

The randomization code for FE-HS will be generated by the Contract Research Organization and managed by the Sponsor.

Subjects who withdraw for any reason without completing all screening evaluations successfully will be considered "screening failures".

9.1.2. Blinding

The FE-HS segment is open-labeled and will be conducted in an unblinded manner.

9.2. Study Visits

Study procedures are listed for each visit in the following sections and summarized in the Schedule of Assessments (Appendix A). Further details regarding the listed safety, PK, and pharmacodynamic assessments are located in Sections 11, 12, and 14, of Protocol EP-547-101, Amendment 2.0, respectively.

9.2.1. Screening Period

9.2.1.1. Visit 1 (Day -28 to Day -2)

During the Screening Period, subjects are to arrive at the clinic after an overnight fast (at least 8 hours) and will undergo assessments at the site 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 -28 and Day -2:

- Completion of informed consent before performance of any study procedures or assessments
- Medical history
- Height
- Complete physical examination
- Vital signs
- Standard 12-lead ECG
- Body weight
- Laboratory assessments:
  - Human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) serology
  - Drug and cotinine screens
  - Alcohol screen
  - Serum pregnancy test (females only)
  - Follicle-stimulating hormone (FSH) (females only)
  - Chemistry and hematology

  - Urinalysis
  - Coagulation
- Assessment of baseline concomitant medications, including all medications taken within 14 days before Screening
- Assessment of adverse events (AEs)
- Eligibility check

Screening results will be reviewed by the Investigator to determine the subject's eligibility. Subjects who are confirmed to be eligible will be asked to return to the site for Visit 2 (Day -1) to enroll in the study.

9.2.1.2. Visit 2 (Day -1) and Visit 4 (Day -1) - Admission

Subjects will be admitted for mandatory confinement at the clinic during Day -1 of each FE Period and will undergo the following assessments:

- Abbreviated physical examination
- Laboratory assessments:
  - Drug and cotinine screens
  - Alcohol screen
  - Urine pregnancy test
- Assessment of concomitant medication usage
- Assessment of AEs
- Eligibility check (Visit 2 only)

Visit 2 (Day -1) results will be reviewed by the Investigator to confirm the subject's eligibility. For both FE Periods, eligible subjects will continue to remain confined to the clinic until completion of Day 3 assessments of the respective period.

9.2.2. Treatment Period

9.2.2.1. Visit 2 (Day 1) and Visit 4 (Day 1) - Predose

Subjects will continue to be confined at the clinic during Day 1 of each FE Period and will undergo the following assessments before administration of study drug:

- Vital signs
- Standard 12-lead ECG
- Body weight (Visit 2 only)
- Laboratory assessments:
  - Chemistry and hematology
  - Urinalysis

  - [redacted]
- Assessment of concomitant medication usage
- Assessment of AEs
- Blood sample draw for PK assessment
- Randomization to Sequence 1 or Sequence 2 in a 1:1 ratio
- Remain fasted or consume a high fat/high calorie breakfast approximately 30 minutes predose as determined by randomized treatment sequence.

Upon completion of the assessments listed above, study drug is to be administered orally as intact capsules (swallowed whole, not chewed or crushed), and taken with water.

9.2.2.2. Visit 2 (Day 1) and Visit 4 (Day 1) - Postdose

Subjects will continue to be confined at the clinic during Day 1 of each FE Period and will undergo the following assessments after administration of study drug:

- Assessment of concomitant medication usage
- Assessment of AEs
- Blood sample draw for PK assessment at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours postdose
- Vital signs at 1, 2, 4, 9, and 12 hours postdose
- Standard 12-lead ECG at 3 hours postdose

9.2.2.3. Visit 2 (Day 2) and Visit 4 (Day 2)

Subjects will continue to be confined at the clinic during Day 2 of each FE Period and will undergo the following assessments:

- Laboratory assessments:
  - Chemistry and hematology
  - Urinalysis
  - [redacted]
- Assessment of concomitant medication usage
- Assessment of AEs
- Blood sample draw for PK assessment at 18, 24, and 36 hours postdose
- Vital signs at 24 hours postdose

9.2.2.4. Visit 2 (Day 3) and Visit 4 (Day 3) - Discharge

Subjects will continue to be confined at the clinic during Day 3 of each FE Period until completion of the following assessments:

- Laboratory assessments:
  - Chemistry and hematology
  - Urinalysis
- Assessment of concomitant medication usage
- Assessment of AEs
- Vital signs at 48 hours postdose
- Standard 12-lead ECG at 48 hours postdose
- Blood sample draw for PK assessment at 48 hours postdose

Subjects may be discharged from the clinic after completion of all assessments listed above.

9.2.2.5. Visit 3 (Day 8) and Visit 5 (Day 8)

Subjects are to arrive at the clinic after an overnight fast (at least 8 hours) and will undergo assessments on Day 8 of each FE Period:

- Complete physical examination (Visit 5 only)
- Vital signs
- Body weight (Visit 5 only)
- Laboratory assessments:
  - Serum pregnancy test (females only)
  - Chemistry and hematology
  - Urinalysis
- Assessment of concomitant medication usage
- Assessment of AEs
- Blood sample draw for PK assessment

9.2.3. Safety Follow-Up Visit (Visit 5 [Day 8])

In addition to being the last visit in FE Period 2, Visit 5 [Day 8] is also the Safety Follow-Up Visit. If termination occurs during the Treatment Period, the subject will have a Safety Follow-Up Visit approximately 7 days (±1 day) after the last dose of study drug and is to undergo the procedures for Visit 5 (Day 8) as described in Section 9.2.2.5.

9.2.4. Early Study Termination Visit

Subjects who discontinue from the study early should have the Early Study Termination Visit conducted as soon as possible after the dose of study drug, ideally within 2 days after the dose of

study drug. Subjects are to arrive at the clinic after an overnight fast (at least 8 hours) and will undergo the following assessments during the Early Study Termination Visit:

- Complete physical examination
- Vital signs
- Standard 12-lead ECG
- Body weight
- Laboratory assessments:
  - Serum pregnancy test (females only)
  - Chemistry and hematology
  - Urinalysis
- Assessment of concomitant medication usage
- Assessment of AEs

10. PHARMACOKINETICS ASSESSMENT

Blood sampling for PK of EP547 will be collected as follows for each FE Period:

- **FE-HS:** predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 hours postdose on Day 1; 18, 24, and 36 hours postdose on Day 2; 48 hours postdose on Day 3; and on Day 8.

The assessment window for blood sample collection timepoints for the FE-HS segment is the same as the single dose segments and the first dose in the multiple dose segments, which is included in Appendix C of Protocol EP-547-101, Amendment 2.0.

11. STATISTICS

The effect of food on the PK of EP547 (area under the concentration-time curve from time 0 to infinity, area under the concentration-time curve calculated to the last observable concentration at time t, maximum [peak] plasma concentration, terminal half-life, and time to achieve maximum [peak] plasma concentration [AUC_{∞}, $AUC_{0\text{-}t}$, C_{max}, $t_{1/2}$, and t_{max}]) will be examined. An analysis of variance model will be fitted separately to each of the log transformed PK parameters with period and treatment (fed or fasted) as fixed effects and subject as a random effect. Point estimates for the differences in means (EP547 fed – EP547 fasted) and corresponding 90% confidence intervals (CIs) will be constructed from the least-squares means, using the residual variance. These will then be back-transformed to provide point estimates and corresponding 90% CIs for the ratio of geometric means fed:fasted.

The sample size of 12 subjects was selected as the minimum needed to adequately estimate the effect of food on the PK of EP547.

12. REFERENCES

FDA. Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies. FDA Maryland; 2002. p. 1-9.

APPENDIX A. SCHEDULE OF ASSESSMENTS FOR THE FOOD EFFECT SUBSTUDY

Visit	**Screening Visit 1**[a]	**FE Period 1 / FE Period 2**[b]						**Early Study Term**[c]	**Notes**
		Visit 2 / Visit 4					**Visit 3 / Visit 5**[d]		
Study Day (Visit Window)	**-28 to -2**	**-1**	**1 (pre-dose)**	**1 (post-dose)**	**2**	**3**	**8**		
Mandatory Confinement		X	X	X	X	X			
Admission		X							
Discharge						X			
General Assessments									
Informed consent	X								
Medical history	X								
Height	X								Measured using a stadiometer with no shoes.
FSH (females only)	X								
HIV, HBV, HCV serology	X								
Drug and cotinine screens	X	X							Day -1 will be conducted locally.
Alcohol screen	X	X							Will be conducted locally.
Eligibility check	X	X[e]							
Randomization			X[e]						Subjects will be randomized in a 1:1 ratio to either Sequence 1 (Fasted for FE Period 1 followed by Fed for FE Period 2) or Sequence 2 (Fed for FE Period 1 followed by Fasted for FE Period 2).
Study drug administration			X						Administered orally as intact capsules with water.
Fed regimen			X						To be assessed during Visit 2 or Visit 4 as determined by treatment sequence. High fat/high calorie breakfast will be provided approximately 30 min prior to dosing.
Fasted regimen			X						To be assessed during Visit 2 or Visit 4 as determined by treatment sequence. Subjects will remain fasted until after the 4-hour PK blood sample is collected.

Visit	Screening Visit 1[a]	FE Period 1 / FE Period 2[b]						Early Study Term[c]	Notes
		Visit 2 / Visit 4					Visit 3 / Visit 5[d]		
Study Day (Visit Window)	**-28 to -2**	**-1**	**1 (pre-dose)**	**1 (post-dose)**	**2**	**3**	**8**		
Safety Assessments									
Pregnancy testing	X	X					X	X	For all female subjects. Urine pregnancy test on Day -1 and serum pregnancy test for all other indicated visits.
Physical examination	C	A					C[f]	C	Will be either complete (C) or abbreviated (A) (Section 11.7 of Protocol EP-547-101, Amendment 2.0).
Standard 12-lead ECG	X		X	X		X		X	To be performed in a supine position after ≥5 min of rest during Screening; predose and at 3 h postdose on Day 1; 48 h postdose on Day 3; and Early Study Term, if applicable.
Vital signs	X		X	X	X	X	X	X	Includes supine systolic and diastolic blood pressure, pulse rate, oxygen saturation, body temperature, and respiratory rate, measured after ≥5 min of rest at Screening; predose and at 1, 2, 4, 9, and 12 h postdose on Day 1; 24 h postdose on Day 2; 48 h postdose on Day 3; on Day 8; and Early Study Term, if applicable.
Body weight	X		X[e]				X[f]	X	Should be measured with no shoes on and using a calibrated scale throughout the study.
Chemistry and hematology	X		X		X	X	X	X	Drawn after an overnight fast (≥8 h) and predose as applicable. Refer to Section 11.9 of Protocol EP-547-101, Amendment 2.0, for chemistry and hematology assessments.
Urinalysis	X		X		X	X	X	X	Refer to Section 11.9 of Protocol EP-547-101, Amendment 2.0, for urinalysis (dipstick) assessments.
Coagulation	X								Refer to Section 11.9 of Protocol EP-547-101, Amendment 2.0, for coagulation assessments.
Concomitant medications	X	X	X	X	X	X	X	X	Record all medications taken within 14 days before Screening (all subjects)
AE assessment	X	X	X	X	X	X	X	X	To be documented from the signing of the Informed Consent Form until the end of study participation.

Visit	Screening Visit 1[a]	FE Period 1 / FE Period 2[b]						Early Study Term[c]	Notes
		Visit 2 / Visit 4					Visit 3 / Visit 5[d]		
Study Day (Visit Window)	**-28 to -2**	**-1**	**1 (pre-dose)**	**1 (post-dose)**	**2**	**3**	**8**		
Pharmacokinetic Assessments									
Blood sampling for PK			X	X	X	X	X		Drawn at predose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 h postdose on Day 1; 18, 24, and 36 h postdose on Day 2; 48 h postdose on Day 3; and on Day 8.
[redacted]									
[redacted]			[redacted]		[redacted]				[redacted]

AE = adverse event; ECG = electrocardiogram; FE = food effect; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PK = pharmacokinetic; Term = termination.

Subjects should fast for at least 8 hours before study days that require a blood sample for assessment of clinical chemistry or multiple blood samples for PK. Water is acceptable in the morning of site visits and each study day while confined to the study site to ensure the subject is hydrated for laboratory sample collection. On Day 1, study drug will be administered with approximately 240 mL of water; additional water will not be allowed from 1 hour predose to 1 hour postdose.

[a] Screening: May be conducted over more than 1 day but must be completed between Day -28 and Day -2.

[b] Doses between the 2 FE Periods must be separated by a minimum of 10 days to allow for washout of study drug.

[c] Early Study 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.

[d] Visit 5 (Day 8) is also the Safety Follow-Up Visit and is to occur 7 days after the last administration of study drug. If termination occurs during the Treatment Period, the subject will have a Safety Follow-Up Visit approximately 7 days (±1 day) after the last dose of study drug and is to undergo the procedures for Visit 5 (Day 8).

[e] To be conducted for Visit 2 only.

[f] To be conducted for Visit 5 only.