Official Title: Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP547 in Subjects with Cholestatic Pruritus Due to Primary Biliary Cholangitis or Primary Sclerosing Cholangitis

NCT Number: NCT05525520

Document Date: EP-547-201 Protocol, Amendment 3.0 (02 October 2023)

1. TITLE PAGE

Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP547 in Subjects with Cholestatic Pruritus Due to Primary Biliary Cholangitis or Primary Sclerosing Cholangitis

Study Acronym:	PACIFIC Study
Protocol Number:	EP-547-201
EudraCT Number:	2021-002526-25
IND Number:	154162
Protocol Version Number:	Amendment 3.0
Issue Date:	02 October 2023
Drug Development Phase:	Phase 2
Sponsor:	Escient Pharmaceuticals, Inc. 10578 Science Center Drive, Suite 250 San Diego, CA 92121 USA Phone/Fax: +1 (858) 617-8220

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Escient Pharmaceuticals, Inc.
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Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP547 in Subjects with Cholestatic Pruritus Due to Primary Biliary Cholangitis or Primary Sclerosing Cholangitis

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Sponsor Statement

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

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 02-Oct-2023 | 12:43 PDT
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02-Oct-2023 | 12:43 PDT

[redacted], MD
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Escient Pharmaceuticals, Inc.

Date

DocuSigned by:
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Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 02-Oct-2023 | 10:08 PDT
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02-Oct-2023 | 10:08 PDT

[redacted] PhD
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Signing Reason: I approve this document
Signing Time: 02-Oct-2023 | 11:12 PDT
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02-Oct-2023 | 11:12 PDT

[redacted], MS
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Escient Pharmaceuticals, Inc.

Date

Investigator's Agreement

I have read the protocol for EP-547-201 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL HISTORY

Document	Amendment Type	Date
Amendment 3.0	Global	02 October 2023
Amendment 2.3	Country-specific (Belgium)	17 March 2023
Amendment 2.2	Country-specific (Spain)	03 March 2023
Amendment 2.1	Country-specific (France)	15 December 2022
Amendment 2.0	Global	20 April 2022
Amendment 1.0	Global	17 November 2021
Original Protocol	Not applicable	15 June 2021

Procedures in Case of Emergency

Table 1: Emergency Contact Information

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

CRO = Contract Research Organization.

2. SYNOPSIS

Name of Sponsor/Company: Escient Pharmaceuticals, Inc.	
Name of Investigational Product: EP547 Tablet	
Study Number: EP-547-201	**Phase of Development:** Phase 2
Title of Study: Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effects of EP547 in Subjects with Cholestatic Pruritus Due to Primary Biliary Cholangitis or Primary Sclerosing Cholangitis	
Study Centers: Multi-center study to be conducted globally	

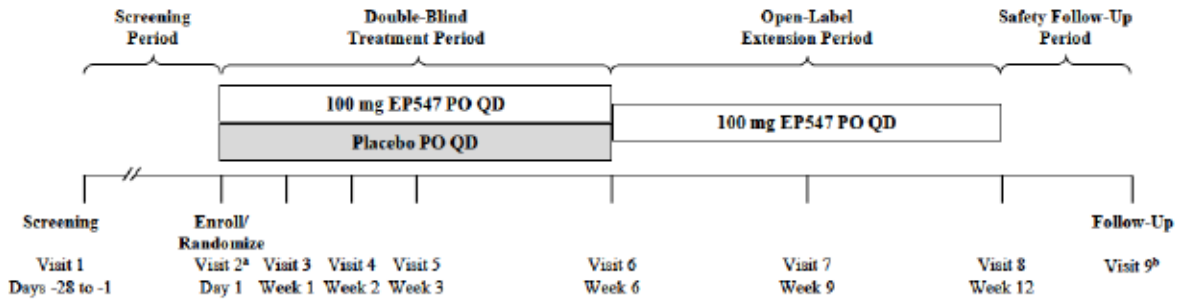
Objectives:
<u>Primary</u>
• To assess the efficacy of EP547 compared to placebo on pruritus as assessed by the Worst Itch Numeric Rating Scale (WI-NRS)
<u>Secondary</u>
• To assess the efficacy of EP547 compared to placebo on the following:
  o Pruritus-related quality of life using the 5-D Itch Scale
  o Pruritus severity using the Patient Global Impression of Severity (PGI-S)
  o Overall pruritus response to therapy using the Patient Global Impression of Change (PGI-C)
• To assess the safety and tolerability of EP547
• To assess the pharmacokinetics (PK) of EP547
[redacted]	

Methodology:

EP-547-201 is a randomized, double-blind, placebo-controlled study to evaluate the effects of EP547 on pruritus over 6 weeks in subjects with cholestatic pruritus due to primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC). Where allowed per regulatory/local requirements, subjects will be able to attend study visits at a physical study site as well as remotely (hybrid model) or at a virtual site where all visits will be conducted remotely (decentralized model). For both the hybrid and decentralized models, a home health nurse visit at the subject's home or work and a telemedicine visit with the study site staff (eg, smartphone or computer) will be arranged to conduct procedures for each remote study visit.

The study includes a Screening Period of up to 4 weeks to assess subject eligibility; a 6-week Double-Blind Treatment Period; a 6-week Open-Label Extension Period; and a 2-week Safety Follow-Up Period after administration of the last dose of study drug (EP547 or placebo). Approximately 58 subjects will be randomized to receive either 100 mg doses of EP547 or placebo orally (PO) once daily (QD) in a 1:1 ratio. In the Open-Label Extension Period, all subjects will receive 100 mg doses of EP547.

EP-547-201 Study Design



PO = oral, QD = once daily.

[a] For the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. When enrollment/randomization and first dose of study drug are on separate days, the first dose of study drug is considered Day 1.

[b] Any subject who completes the Open-Label Extension Period or discontinues study drug (EP547 or placebo) early will complete a follow-up visit approximately 2 weeks (±3 days) after the last dose of study drug.

Screening Period

The Screening Period will consist of 1 study visit (Visit 1). During this period, subjects will undergo assessments to determine study eligibility. Visit 1 (Day-28 to Day -1) may be conducted over more than 1 day but must be completed between Day -28 and Day -1.

Double-Blind Treatment Period

The Double-Blind Treatment Period will consist of 5 study visits (Visits 2, 3, 4, 5, and 6 [Day 1 and Weeks 1, 2, 3, and 6]). During this period, all subjects who meet eligibility requirements will be enrolled into the study and randomized to receive double-blind, PO, QD doses of EP547 or placebo for 6 weeks beginning on Visit 2 (Day 1). Subjects will be randomized to receive either 100 mg doses of EP547 or placebo in a 1:1 ratio. Randomization will be conducted centrally via an Interactive Web Response System (IWRS) and stratified based on type of cholestatic disease (PBC, PSC). Visit 2 (Day 1) will not have a visit window; however, for the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. When enrollment/randomization and first dose of study drug are on

separate days, the first dose of study drug is considered Day 1. All other visits in the Double-Blind Treatment Period will have a visit window of ±3 days.

Open-Label Extension Period

The Open-Label Extension Period will consist of 2 study visits (Visit 7 [Week 9] and Visit 8 [Week 12]). During this period, all subjects who complete the Double-Blind Treatment Period and are still receiving study drug will receive open-label 100 mg doses of EP547. Visit 7 and Visit 8 will have a visit window of ±3 days.

Safety Follow-Up Period

Any subject who completes the Open-Label Extension Period or discontinues study drug (EP547 or placebo) early will complete a follow-up visit (Visit 9) approximately 2 weeks (±3 days) after the last dose of study drug.

Number of Subjects (Planned):

Approximately 58 subjects with cholestatic pruritus due to PBC or PSC will be randomized in the study.

Diagnosis and Main Criteria for Inclusion:

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

Inclusion Criteria

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

1. Age 18 to 80 years, inclusive
2. Has experienced self-reported daily or near-daily moderate to severe pruritus before Screening
3. Has a mean daily WI-NRS score indicative of moderate to severe pruritus (score ≥4) during Screening (Day -7 through Day -1); data from at least 4 of the 7 days are required to be considered an acceptable profile
4. If currently taking medications to treat the cholestatic disorder (including obeticholic acid [OCA]), must be on a stable dose for >12 weeks before Screening and plans to maintain the regimen throughout the study
5. If currently taking a fibrate, must be on a stable dose for >12 weeks before Screening and plans to maintain the regimen throughout the study
6. Either is not treated with or has been on a stable regimen with any medications to treat pruritus for >4 weeks before Screening and plans to maintain the regimen throughout the study
7. If female, must have a negative serum pregnancy test at Screening and be willing to not donate eggs from Screening until the last dose of study drug and:
    a. Is surgically sterile; or
    b. Has been amenorrhoeic for ≥1 year without an alternative medical cause; or

c. If of childbearing potential[1], must agree to use at least 1 form of an acceptable method of contraception from Screening until the last dose of study drug. Acceptable birth control methods include:
   - Barrier methods of contraception (eg, male condom, female condom, cervical cap or diaphragm, and contraceptive sponge)
   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
   - Progestogen only hormonal contraception
   - Intrauterine device
   - Intrauterine hormone releasing system
   - Bilateral tubal occlusion
   - Vasectomized partner
   - Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study drug), the reliability of which needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject

8. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study, and understand and provide written consent
9. For subjects with concomitant inflammatory bowel disease (IBD):
   a. Colonoscopy (if subject has a colon) or other appropriate endoscopic procedure within 18 months of Day 1 confirming no dysplasia or colorectal cancer
   b. Subjects with Crohn's disease (CD) must be in remission as defined by a Crohn's Disease Activity Index (CDAI) <150 at Screening
   c. Subjects with ulcerative colitis (UC) must have a Partial Mayo Scoring Index score ≤3 with no individual sub-score exceeding 1 point at Screening

Subjects with PBC must also meet the following inclusion criteria to be eligible for study participation:

10. Documented history of PBC that is consistent with the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines (Lindor 2019), defined as having ≥2 of the following 3 factors upon diagnosis:
    a. History of elevated alkaline phosphatase (ALP) levels
    b. Historic positive antimitochondrial antibody (AMA) or AMA-M2 by immunofluorescence, enzyme linked immunosorbent assay (ELISA), or immunoblot or if AMA is negative, positive for PBC-specific antibodies (anti-GP210 and/or anti-SP100)
    c. Liver histology at any point in time consistent with PBC
11. If currently taking ursodeoxycholic acid (UDCA), must be on a stable dose of not more than 20 mg/kg/day for ≥12 weeks. If not currently taking UDCA, must not be treated with UDCA within 12 weeks before Screening or plan to be treated with UDCA during the study

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

Subjects with PSC must also meet all the following inclusion criteria to be eligible for study participation:

12. Documented history of PSC based on either cholangiography (ie, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, or percutaneous transhepatic cholangiogram) or if small duct PSC, confirmed by typical histologic evidence of PSC for ≥1 year (EASL 2009, Chapman 2010)
13. If currently taking UDCA, must be on a stable dose of not more than 23 mg/kg/day for ≥12 weeks. If not currently taking UDCA, must not be treated with UDCA within 12 weeks before Screening or plan to be treated with UDCA during the study

Exclusion Criteria

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

1. Pruritus is attributed mainly to any disease unrelated to PBC or PSC
2. Prior liver transplant or presently listed for transplantation
3. Is receiving ongoing ultraviolet B (UVB) treatment or plasmapheresis or anticipates receiving such treatments during the study
4. Evidence of compensated or decompensated cirrhosis based on ANY of the following:
    a. Historical liver biopsy demonstrating cirrhosis
    b. Liver stiffness as assessed by a FibroScan® score of ≥16.9 kPa for subjects with PBC or ≥14.4 kPa for subjects with PSC within 6 months of Screening
    c. History or presence of portal hypertension with complications, including known gastric or esophageal varices, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, history of variceal bleeds, or related therapeutic or prophylactic interventions (eg, non-selective beta blockers being used to prevent complications of portal hypertension [propranolol, nadolol, or carvedilol], insertion of variceal bands, transjugular intrahepatic portosystemic shunt, or direct intrahepatic portocaval shunt)
5. History of malignancy of any organ system, including but not limited to hepatocellular carcinoma, cholangiocarcinoma, and gall bladder carcinoma, treated or untreated, within the past 5 years (localized squamous cell or basal cell carcinoma of the skin that have been excised or resolved is not exclusionary)
6. Alternate causes of liver diseases such as hepatic sarcoidosis, alcoholic liver disease, histology confirmed autoimmune hepatitis, overlap hepatitis, or nonalcoholic steatohepatitis (NASH), or uncontrolled viral hepatitis as defined in Section 12.9
7. Presence of documented secondary sclerosing cholangitis (eg, ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis) on prior clinical investigations
8. Immunoglobulin G4 (IgG4) >4× upper limit of normal (ULN) at Screening or evidence of systemic IgG4-related disease
9. Current evidence of clinically significant high-grade strictures or presence of biliary stent at Screening
10. History of recurrent bacterial cholangitis or recent episode within 3 months before Screening
11. Endoscopic interventions with therapeutic intent such as biliary duct dilation within 3 months before Screening or planned during the study
12. History of significant small bowel resection or short bowel syndrome

13. Presence of 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
14. Clinically relevant medical history, physical examination, vital sign, standard 12-lead electrocardiogram (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
15. Has any of the following laboratory results at Screening:
    a. Total bilirubin >2.0 mg/dL; total bilirubin >2.0 mg/dL is acceptable for subjects with medically documented Gilbert's syndrome if direct bilirubin is <0.3 mg/dL
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× ULN
    c. ALP >10× ULN
    d. International normalized ratio (INR) >1.3
    e. Platelet count <150,000/µL
    f. Urine albumin to creatinine ratio ≥30 mg/g
16. Estimated glomerular filtration rate <60 mL/min/1.73 m^2 as determined by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening
17. History of human immunodeficiency virus (HIV) or positive for HIV infection at Screening
18. Significant history of abuse of drugs, solvents, or moderate alcohol consumption (≥1 serving or unit/day on average for women and ≥2 servings or units/day on average for men; 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
19. Has received a prohibited medication within 2 weeks or 5 half-lives of Day 1, whichever is longer, as described in Section 8.4.1
20. 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 with an investigational or approved drug/device while enrolled in this study
21. History of known or suspected hypersensitivity to any component of the study drug
22. Female who is pregnant, nursing, or intends to become pregnant during the study
23. 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
24. 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.
25. Subject is, in the opinion of the Investigator, not suitable to participate in the study

Study Drug Materials and Management:

Study Drugs

For the Double-Blind Treatment Period, tablets containing 25 mg or 75 mg of EP547 or placebo will be supplied in a way to ensure the study blind. For the Open-Label Extension Period, tablets containing 25 mg or 75 mg of EP547 will be supplied. Subjects receiving EP547 will take one 25-mg and one 75-mg EP547 tablet per dose (for a total dose of 100 mg) and subjects receiving placebo will take 2 placebo tablets per dose.

Study Drug Packaging and Labeling

For the Double-Blind Treatment Period, study drug kits each containing 2 tablets per dose and packaged into blister card/wallets will be labeled with a unique number and will be supplied to study sites in a blinded manner.

Study drug kits for the Open-Label Extension Period will be packaged and labeled similarly as those for the Double-Blind Treatment Period but will be supplied to the sites in an unblinded manner.

Study Drug Storage

The study drug tablets should be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F), with excursions allowed between 15°C to 30°C (59°F to 86°F).

Study Drug Administration

Each study drug dose, containing 2 tablets, is to be administered orally as intact tablets (swallowed whole, not chewed or crushed), and taken with water. Doses are to be administered daily at approximately the same time of day after a fast of at least 8 hours.

Study Drug Dispensing and Accountability

Subjects will complete dosing records, which will be reviewed at each study visit by study site staff.

Subjects should be instructed to retain the study drug kit (including blister cards/wallets), even if empty, and to return it and any remaining study drug to the study site at their next visit or to a direct-to-patient courier service. The study site staff should perform study drug accountability and, if applicable, follow-up with the subject to retrieve any remaining study drug that has not been returned.

Key Study Procedures and Efficacy, Pharmacodynamic, Safety, and PK Evaluations:

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

Key Study Procedures

Fasting Requirements

Subjects should fast for at least 8 hours before each dose of study drug and before study visits that require a blood sample for assessment of chemistry, PK (predose), or completion of questionnaires. Water is acceptable in the morning of study visits to ensure the subject is hydrated for laboratory sample collection.

Discontinuation of Study Drug

Subjects who terminate treatment with study drug early, regardless of the reason, will 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 of study drug.

Whenever possible, subjects should remain in the study and complete the remaining study visits and assessments even when study drug has been discontinued. Subjects who discontinue study drug for any reason and continue with the study visits as planned through the Week 12 visit (participating only in efficacy and safety, but not PK measures) will participate in the Safety Follow-Up Visit if the last dose of study drug was administered less than 2 weeks before the Week 12 visit to ensure that at least 2 weeks of follow-up data are collected for all randomized subjects.

If a subject discontinues study drug and chooses not to complete all of the remaining study visits, the subject will have a Follow-Up Visit approximately 2 weeks (±3 days) after the last dose of study drug if at least 2 weeks of follow-up data have not already been collected. If a subject fails to attend the follow-up visit and has not withdrawn consent, all reasonable efforts will be made to contact the subject to ensure that he/she is in satisfactory health. All contacts and contact attempts must be documented in the subject's medical record.

Efficacy and Pharmacodynamic Assessments

Efficacy evaluations, including patient-reported assessments of pruritus (WI-NRS), pruritus-related quality of life (5-D Itch Scale), pruritus severity (PGI-S), overall response to therapy (PGI-C), sleep disturbance (PROMIS Short Form – Sleep Disturbance), fatigue (D-FIS), and overall quality of life (EQ-5D-3L) will be assessed.

PD assessments, including blood and/or urine sampling for genotyping (optional), pruritus-related biomarkers (bile acids and heme metabolites), kidney-related biomarkers, and future analysis will also be assessed.

All efficacy and PD assessments will be performed as indicated in the Schedule of Assessments (Appendix A).

Questionnaires

At Visit 1 (Screening) before completing the daily WI-NRS for Day -14, subjects will receive training on how to respond to questionnaires. Sites will review the responses from each subject at least twice a week to ensure proper compliance.

Worst Itch Numeric Rating Scale (WI-NRS):

Subjects will be asked to rate the severity of their worst level of itching in the past 24 hours in the morning, and at the same time of day, using the WI-NRS. The WI-NRS is an 11-point scale ranging from 0 (No Itching) to 10 (Worst Itching Imaginable) (Phan 2012) and requires approximately 1 minute to complete. Higher scores indicate greater itch severity. Itching severity scores collected via the WI-NRS have been categorized in the literature as mild (<4), moderate (≥4 to <7), or severe (≥7) (Fishbane 2020, Hirschfield 2020, Levy 2020, Stander 2020). An example of the WI-NRS is included in Appendix B.

Subjects will be instructed to complete the WI-NRS daily, in the morning, and at the same time of day, beginning at Day -14 to the Follow-Up Visit. For days that coincide with a study visit (for Visit 2 and beyond), the WI-NRS is to be completed before the visit.

The WI-NRS scores from Day -7 through Day -1 will be averaged together to confirm compliance and determine subject eligibility for continued participation regarding pruritus sensation. The average WI-NRS score using the daily values from the week before the first dose of study drug (Visit 2 [Day 1]) will serve as the baseline score. The 7 daily WI-NRS scores prior to Visit 6 (Week 6) will be averaged together for primary endpoint analyses. Data from at least 4 of the 7 days for each week are required to be considered an acceptable profile.

5-D Itch Scale:

The 5-D Itch Scale was developed as a brief but multidimensional questionnaire designed for pruritus that measures changes over time (Elman 2010). The 5 dimensions are degree, duration, direction, disability, and distribution. It requires approximately 1 to 2 minutes to complete, and scores can range between 5 (no pruritus) and 25 (most severe pruritus). The scores of each of the 5 domains are achieved separately and then summed together to obtain a total 5-D score. An example of the 5-D Itch Scale is included in Appendix C.

Patient Global Impression of Severity (PGI-S):

The PGI-S was validated in women with stress urinary incontinence, but may be used to rate the severity of other specific conditions (Yalcin 2003). For this questionnaire, the specific condition to be rated is pruritus. Subjects will be asked to rate the severity of their pruritus in the past 7 days using a 4-point scale from None to Severe. The PGI-S requires less than 1 minute to complete. An example of the PGI-S is included in Appendix D.

Patient Global Impression of Change (PGI-C):

Subjects will be asked to rate their impression of overall change in pruritus in the past 7 days compared to before they started taking study drug using the PGI-C. The PGI-C is a 7-point scale ranging from Much Improved to Much Worse and requires approximately 1 minute to complete (Guy 1976). Higher scores indicate less improvement in pruritus. An example of the PGI-C is included in Appendix E.

Patient-Reported Outcomes Information System (PROMIS) Short Form – Sleep Disturbance:

The PROMIS Short Form – Sleep Disturbance is an 8-item instrument that assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep, including perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep (HealthMeasures 2021). Subjects will be asked to answer each item using a 5-point scale. The scale takes approximately 1 to 2 minutes to complete. An example of the PROMIS Short Form – Sleep Disturbance is included in Appendix F.

Fatigue Impact Scale for Daily Administration (D-FIS):

The D-FIS, which was adapted from the original Fatigue Impact Scale (Schiehser 2013), is a validated, self-report scale that measures the impact of fatigue on ability to function over the past day by having participants rate 8 items on a scale from 0 (No Problem) to 4 (Extreme Problem). Scores range from 0 to 32 with a higher score reflecting a higher impact of fatigue (Fisk 2002). The scale takes approximately 2 to 3 minutes to complete. An example of the D-FIS is included in Appendix G.

3-Level EuroQol-5D (EQ-5D-3L):

The EQ-5D-3L is a widely used quality of life instrument developed in Europe that includes 1 question for each of the following 5 quality of life dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman 2011). The EQ-5D-3L also includes a visual analog scale, by which respondents can report their perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status). The questionnaire takes approximately 1 to 2 minutes to complete. An example of the EQ-5D-3L is included in Appendix H.

Blood and Urine Sampling for Pharmacodynamic Assessments

Blood samples for genotyping (optional) and pruritus-related biomarkers (bile acids and heme metabolites) and blood and urine samples for future analysis will be assessed. Samples for genotyping and future analysis may be stored for up to 10 years after completion of the study.

Blood and Urine Sampling for Analysis of Kidney-Related Biomarkers

Blood will be collected for analysis of kidney-related biomarkers such as cystatin-C and neutrophil gelatinase-associated lipocalin.

Urine will be collected for analysis of kidney-related biomarkers such as clusterin, cystatin-C, kidney injury molecule-1, N-acetyl-β-D-glucosaminidase, neutrophil gelatinase-associated lipocalin, and osteopontin.

Safety Assessments

Safety evaluations, including adverse events (AEs), concomitant medications, medical history, vital signs, physical examinations, standard 12-lead ECGs, laboratory evaluations of safety, and disease-specific assessments (Partial Mayo Score for subjects with UC and CDAI for subjects with CD) will be performed as indicated in the Schedule of Assessments (Appendix A).

Adverse Event Collection

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

Adverse Events of Special Interest

[redacted] The applicability of the finding in monkeys to humans is unknown. Notably, no adverse changes in serum chemistry markers (eg, creatinine and blood urea nitrogen [BUN]) were observed with daily doses of EP547 as high as 225 mg for 1 week in healthy volunteers in the Phase 1 study. Any clinically meaningful new, worsening from baseline, or abnormal laboratory findings or symptoms suggestive of acute kidney injury (AKI) (eg, 'blood urea increased' or 'protein urine present' AEs as identified by the Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ] 'Acute renal failure') will be considered AEs of special interest (AESI) and should be reported on the serious AE (SAE)/AESI/Grade 3+ Report Form.

Monitoring and Management of Potential Drug-Induced Liver Injury

Subjects will be assessed for potential drug-induced- liver injury (DILI) during both the Double-Blind Treatment Period and Open-Label Extension Period according to the consensus guidelines for clinical trials in adults with chronic cholestatic liver disease (Palmer 2020). Monitoring, interrupting, and stopping rules based on multiples of ULN, threshold values, baseline values, and/or nadir values of ALT, AST, ALP, and total bilirubin and liver-related symptoms are described in the algorithms for treatment-emergent hepatocellular and cholestatic DILI signals presented below.

Elevated ALP values should be confirmed to be of hepatic origin with gamma-glutamyltransferase (GGT). Examples of liver-related symptoms include severe fatigue, nausea, new onset of or worsening of pruritus, right upper quadrant pain, immunologic reaction (eg, rash, >5% eosinophilia), and hepatic decompensation. If the algorithm calls for repeat blood tests, the tests are to be performed within 2 to 5 calendar days after receipt of laboratory values by the site for hepatocellular DILI signals and within 7 to 10 calendar days after receipt of laboratory values by the site for cholestatic DILI signals. ALT, AST, ALP, and total bilirubin, at a minimum, will be assessed as part of the repeat blood tests.

Monitoring for Hepatocellular Injury

The algorithm for monitoring and interrupting study drug for treatment-emergent hepatocellular DILI signals in subjects with a normal ALT baseline value is provided in the table below.

Algorithm for Monitoring and Interrupting Study Drug for Treatment-Emergent Hepatocellular DILI Signals in Subjects with a Normal ALT Baseline Value

Treatment-Emergent ALT	Bilirubin	Liver-Related Symptoms	Action
ALT ≥5× ULN	Normal Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	Repeat blood tests and monitor for symptoms.
ALT ≥8× ULN	Normal or elevated	None or present	Interrupt study drug and repeat blood tests. Study drug can be restarted if another etiology (not hepatocellular injury) is identified and abnormalities return to baseline levels.
ALT ≥3× ULN	Total bilirubin ≥2× baseline Gilbert's syndrome or hemolysis: direct bilirubin >2× baseline if baseline >0.5 mg/dL	None or present	
ALT ≥5× ULN	Normal or elevated	Present	

ALT = alanine aminotransferase; DILI = drug induced liver injury; ULN = upper limit of normal.

The algorithm for monitoring and interrupting study drug for treatment-emergent hepatocellular DILI signals in subjects with an elevated ALT baseline value is provided in the table below.

Algorithm for Monitoring and Interrupting Study Drug for Treatment-Emergent Hepatocellular DILI Signals in Subjects with an Elevated ALT Baseline Value

Treatment-Emergent ALT	Bilirubin	Liver-Related Symptoms	Action
ALT ≥3× baseline	Normal Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	Repeat blood tests and monitor for symptoms.
ALT ≥5× baseline	Normal or elevated	None or present	Interrupt study drug and repeat blood tests. Study drug can be restarted if another etiology (not hepatocellular injury) is identified and abnormalities return to baseline levels.
ALT ≥2× baseline	Total bilirubin ≥2× baseline Gilbert's syndrome or hemolysis: direct bilirubin >2× baseline if baseline >0.5 mg/dL	None or present	
ALT ≥2× baseline	Normal or elevated	Present	

ALT = alanine aminotransferase; DILI = drug induced liver injury.

Monitoring for Cholestatic Injury

The algorithm for monitoring and interrupting study drug for treatment-emergent cholestatic DILI signals is provided in the table below.

Algorithm for Monitoring and Interrupting Study Drug for Treatment-Emergent Cholestatic DILI Signals

Treatment-Emergent ALP	Bilirubin	Liver-Related Symptoms	Action
ALP ≥2× baseline without alternative explanation	Normal Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	Repeat blood tests and monitor for symptoms.
	Total bilirubin ≥2× baseline Gilbert's syndrome or hemolysis: direct bilirubin >2× baseline if baseline >0.5 mg/dL	None or present	Interrupt study drug and repeat blood tests. Study drug can be restarted if another etiology (not cholestatic injury) is identified and abnormalities return to baseline levels.
	Normal or elevated	Present	
ALP ≥3× baseline without alternative explanation	Normal or elevated	None or present	

ALP = alkaline phosphatase; DILI = drug induced liver injury.

In addition to the algorithms above, the Investigator may use clinical judgement to increase monitoring for DILI or interrupt or discontinue study drug as warranted for reasons of subject safety. An episode of DILI leading to hepatic decompensation in a study subject will result in permanent study drug discontinuation.

If a subject cannot return to the study site for a scheduled or unscheduled visit, or an immediate assessment is required, the use of a local laboratory is acceptable at the discretion of the Investigator. All local laboratory values obtained as part of DILI monitoring as well as their normal ranges are to be collected and entered into the clinical database.

Observation for Acute Kidney Injury

[redacted]. Therefore, the Investigator should monitor for acute deterioration of kidney function based on laboratory parameters or clinical symptoms.

In subjects with the following serum creatinine levels, adapted from the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury (KDIGO 2012), interruption of study drug and repeating blood tests should be considered, preferably within 3 to 7 days:

- Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) from baseline: consider interrupting study drug, repeat blood test within 3 to 7 days
- Increase in serum creatinine to ≥1.5 × baseline (which is known or presumed to have occurred within the prior 7 days): interrupt study drug, repeat blood test within 3 to 5 days

These KDIGO guidelines typically apply to hospital settings, where baseline values within given timeframes (ie, the preceding 48 hours to 7 days) are available. However, in interventional studies such

as the current study, values this recent will not likely be available in most cases. In such instances, the Investigator can refer to the baseline value (prior to starting study drug) and evaluate the change. In cases of AKI where an etiology is identified, the reported AE term should reflect the etiology for the impairment of renal function (eg, AKI due to hypovolemia).

Additionally, all abnormal complete blood count, serum creatinine, BUN, and urine albumin to creatinine ratio values during the Double-Blind Treatment Period and Open-Label Treatment Period are to be followed as deemed clinically necessary by the Investigator.

Pharmacokinetic Assessments

Blood sampling for PK of EP547 will be collected predose and [redacted] postdose at Visits 2 and 5 (Day 1 and Week 3) and predose at Visits 3, 4, and 6 (Weeks 1, 2, and 6) to analyze EP547 concentrations; the metabolite profile may also be analyzed from these samples.

Endpoints:

The primary efficacy endpoint is the change from baseline in WI-NRS at Week 6.

The secondary efficacy endpoints are:

- Change from baseline in 5-D Itch Scale
- The proportion of subjects with improvement in pruritus as defined by PGI-C
- The proportion of subjects with improvement in pruritus severity from baseline as defined by change in PGI-S
- The proportion of subjects with a reduction in WI-NRS ≥2 from baseline
- The proportion of subjects with a reduction in WI-NRS ≥3 from baseline
- The proportion of subjects with a reduction in WI-NRS ≥4 from baseline
- The proportion of subjects with WI-NRS <4

[redacted]

Statistical Methods:

The primary efficacy endpoint, as measured as the weekly mean of the daily WI-NRS score, will be analyzed using a mixed effects model for repeated measures (MMRM) based on the data from all visits up to Visit 6 (Week 6). The model will include treatment, type of cholestatic disease (PBC, PSC), week, and treatment by week interaction as fixed effects, and baseline WI-NRS score as a covariate. The treatment effect will be the contrast between EP547 and placebo least-squares (LS) means. Testing of hypothesis is 2-sided at a 5% type I error level.

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

The efficacy and PD endpoints above will be further evaluated during the Open-Label Extension Period. Summaries of change over time will evaluate both change from baseline (Visit 2 [Day 1]) and change from the initiation of the Open-Label Extension Period (Visit 6 [Week 6]).

Safety data will be summarized separately for the Double-Blind Treatment Period and Open-Label Extension Period by randomized Double-Blind treatment received.

An interim analysis may be conducted to support business decisions. The primary analysis will be conducted after the last subject randomized has completed the Double-Blind Treatment Period to determine whether the primary efficacy endpoint of change from baseline in WI-NRS at Week 6 is statistically significant. The final analysis will be conducted when all randomized subjects have completed the Open-Label Extension Period or are discontinued from the study, and the final database is locked.

Sample Size Considerations:

Assuming a standard deviation of 2.5 points, a sample size of 26 subjects per treatment group provides approximately [redacted]% power to detect a difference of [redacted] points between EP547 and placebo with respect to the change in weekly mean of the daily WI-NRS score based on a 2-sided, 2-sample comparison of means at the 5% significance level. With an anticipated early withdrawal rate of approximately 10%, the planned enrollment of 29 subjects per treatment group will ensure that at least 26 subjects complete the 6 weeks of double-blind treatment.

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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
4PB	4-phenylbutyrate
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
AESI	adverse events of special interest
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	antimitochondrial antibody
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemistry
BCRP	breast cancer resistance protein
BUN	blood urea nitrogen
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CFR	Code of Federal Regulations
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
D-FIS	Fatigue Impact Scale for Daily Administration
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DRT	Data Review Team

Abbreviation or Specialist Term	Explanation
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
EQ-5D-3L	3-Level EuroQol-5D
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-c	high-density lipoprotein cholesterol
HEENT	head, eyes, ears, nose, throat
hERG	human ether-à-go-go-related gene
HEV	hepatitis E virus
HIV	human immunodeficiency virus
IBD	inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
KDIGO	Kidney Disease: Improving Global Outcomes
LDH	lactate dehydrogenase
LDL-c	low-density lipoprotein cholesterol
LS	least-squares
MAR	missing at random

Abbreviation or Specialist Term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model for repeated measures
MRGPR	mas-related G protein-coupled receptor
NASH	nonalcoholic steatohepatitis
NK	natural killer
OAT1	organic anion transporter 1
OAT3	organic anion transporter 3
OCA	obeticholic acid
PBC	primary biliary cholangitis
PD	pharmacodynamic
PFIC1	progressive familial intrahepatic cholestasis type 1
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetics
PO	oral
PP	Per Protocol
PQC	product quality complaint
PRO	patient-reported outcomes
PROMIS	Patient-Reported Outcomes Information System
PSC	primary sclerosing cholangitis
PT	prothrombin time
QC	quality control
QD	once daily
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	Standardized MedDRA Query
T4	thyroxine
TE	transient elastography
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone

Abbreviation or Specialist Term	Explanation
UC	ulcerative colitis
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
UVB	ultraviolet B
WBC	white blood cell
WHO	World Health Organization
WI-NRS	Worst Itch Numeric Rating Scale

5. INTRODUCTION

5.1. Cholestatic 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).

Patients with cholestatic pruritus have difficulty coping with the intense itching and develop associated stress. Pruritus has a clinically meaningful negative effect on patients' quality of life, sleep, fatigue, 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 pruritus is not fully understood and the itch-causing pruritogen(s) and their cognate receptor(s) have remained largely elusive. Cholestatic pruritus 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 highly effective, the responsible pruritogens are hypothesized to originate from the liver and bile. Numerous candidate pruritogens are present in bile and upregulated in cholestatic patients, including opioids, lysophosphatidic acid, bilirubin, and bile acids. Therapies targeting these mechanisms, such as opioid antagonists, rifampicin, ileal bile acid transporter inhibitors, and bile acid-binding resins like cholestyramine, are frontline therapy for cholestatic pruritus (Bassari 2015, Mittal 2016); however, efficacy is variable and patients are poorly managed with these medications (Bassari 2015, Mittal 2016).

Although a variety of interventions have been explored, the need for improved treatment of cholestatic pruritus remains high. Therefore, development of additional safe and effective, mechanistically based therapeutic options for this condition 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 multi-ligand receptors that reside chiefly in barrier tissues such as sensory neurons and closely associated local immune cells. They act as a first-line innate surveillance system for early detection of a variety of endogenous and exogenous potentially offensive stimuli.

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 (data on file), and their skin accumulation in association with pruritic cholestatic diseases implicates MRGPRX4 in this disease state. Several experiments have been conducted and published in support of this, including observations that acute injection of bile acids results in pruritus in both mice and humans, and bile acid-modulating therapy is effective in controlling patient pruritus (Meixiong 2019a, Meixiong 2019b, Yu 2019). Similarly, bilirubin has been demonstrated to play a role in pruritus, 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).

It has been reported that 4-phenylbutyrate (4PB), a drug approved in Japan to treat ornithine transcarbamylase deficiency, relieved intractable itch in patients with progressive familial intrahepatic cholestasis type 1 (PFIC1) (Hasegawa 2014). This is a rare, inherited liver disease caused by mutations in ATP8B1, a transmembrane protein that mediates the translocation of phospholipids, and is characterized by severe cholestasis and sustained intractable itch. While 4PB therapy had no beneficial effect on liver function in the patients with PFIC1, doses of 350 to 500 mg/kg/day showed significant reduction of intractable itch. 4PB is also an antagonist of MRGPRX4 that can block activation by bile acids, bilirubin, and other MRGPRX4 agonists (data on file). Thus, MRGPRX4 antagonism by 4PB is potentially the underlying mechanism of its antipruritic effect in patients with PFIC1 and may therefore constitute preliminary clinical proof of concept for MRGPRX4 inhibition in cholestatic pruritus.

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

5.3. EP547 and Study Rationale

EP547 is a potent small-molecule inverse agonist of MRGPRX4 under development as an orally administered therapy for cholestatic pruritus.

Clinical safety and pharmacokinetics (PK) of EP547 are based on the results from Study EP-547-101, a first-in-human randomized, Phase 1 clinical study of oral single and multiple daily doses of EP547 in healthy subjects, in subjects with cholestatic disorders with pruritus, and in hemodialysis subjects with uremic pruritus. [redacted]. EP547 has been tested in 66 individuals, with 24 treated with a multiple dose regimen (ie, daily doses of EP547 over 7 days) as follows by population:

- **Healthy subjects:** 30 subjects received single doses of 25 mg to 675 mg and 18 subjects received 25, 75, or 225 mg as a multiple dose regimen. An additional 5 subjects received single 75-mg doses under fed and fasted conditions.
- **Subjects with a cholestatic disorder:** 5 subjects received a 75-mg single dose and 2 subjects received a 30 mg multiple dose regimen.
- **Subjects with uremic pruritus:** 6 subjects received a 75-mg single dose; 4 of these subjects also received a 20 mg multiple dose regimen.

EP547 PK was highly predictable, showed strong dose linearity, and supports once daily (QD) dosing. All doses tested to date across the 3 populations were well tolerated with no safety signals. The absence of safety signals, in conjunction with favorable PK profiles, support further investigation of EP547 in subjects with cholestatic pruritus in this Phase 2 clinical study.

Study EP-547-201 is designed to evaluate the effects of EP547 on reducing the sensation of pruritus over 6 weeks in approximately 58 subjects diagnosed with cholestatic pruritus due to PBC or PSC. Because prompt antipruritic action is expected given the mechanism of action of EP547 via its direct effect on the MRGPRX4 receptor, a relatively short duration of treatment to

establish proof of concept is possible. A meaningful seasonality aspect of pruritus is usually not seen in patients with moderate to severe pruritus by the clinicians consulted in designing this study, and is also unlikely to confound results considering the relatively short duration of the study.

Other than a single published investigation of the prevalence and natural history of pruritus among clinical study subjects with PBC (Talwalkar 2003), evaluations of the natural history of pruritus are rare in PBC, and essentially nonexistent in PSC. Characterization of pruritus through administration of various symptom-specific questionnaires in this study will yield important insights into the natural history of pruritus in these populations that may inform the design of future clinical studies and the development of investigational compounds for the treatment of these diseases.

Lastly, given the rarity of cholestatic pruritus, the most efficient path to establishing proof of concept for efficacy and further characterizing safety and tolerability is to evaluate a single EP547 dose administered QD in a placebo-controlled manner. Results from Study EP-547-201 will guide further development and study design for a subsequent dose finding evaluation.

5.4. EP547 Dose Rationale

The 100 mg EP547 dose level to be evaluated in Study EP-547-201 was selected based on a variety of factors to maximize efficacy without adversely impacting safety.

The 100 mg EP547 dose level is well below the highest multiple dose regimen of 225 mg that was preliminarily shown to be safe and well tolerated in healthy subjects from Study EP-547-101. There were no safety or tolerability issues observed in the cholestatic pruritus population in the 75-mg single and 30-mg multiple dose evaluations. Dose selection was further supported by results from PK simulations generated from a custom model that incorporated healthy subject PK, drug-specific metabolism, and anatomical/physiological changes in the liver for patients with Child Pugh A and B. These simulations showed that liver impairment is not expected to alter the PK for a 100 mg dose. PK data in subjects with cholestatic liver disease in Study EP-547-101 are consistent with the simulated predictions and directly demonstrate that PK is similar to that of healthy subjects.

[redacted]

The 100 mg EP547 dose is anticipated to be within the therapeutic dosing range of EP547 and therefore should enable demonstration of clinical proof of concept. Although preclinical models to replicate the human phenotype of bile acid and heme metabolite-induced itch are not available for assessment of efficacy, as rodents (and other nonclinical species) do not express the MRGPRX4 receptor, a therapeutic range has been estimated. Such determinations were made using pharmacologic data from 4PB, a small molecule antagonist of MRGPRX4 that relieved intractable itch in patients with PFIC1 (Hasegawa 2014). [redacted]

[redacted]

5.5. Summary of Benefits and Risks

5.5.1. Benefit Summary

This study is investigating a potential benefit of EP547 to relieve or lessen cholestatic itch, which may also be associated with an improvement in fatigue, quality of sleep, and overall quality of life. EP547 is not intended to improve a subject's cholestatic liver disease.

5.5.2. Risk Summary and Mitigation Strategy

Safety results from the Phase 1 Study EP-547-101 did not reveal any adverse safety trends, and all doses tested were well tolerated.

Nonclinical safety pharmacology studies indicate no undesirable pharmacodynamic (PD) effects on respiratory, cardiovascular, and central nervous system (CNS) physiological functions when EP547 is administered at doses within and above the predicted therapeutic range. [redacted]. Notably, no adverse changes in serum chemistry markers (eg, creatinine and blood urea nitrogen [BUN]) were observed with daily doses of EP547 as high as 225 mg for 1 week in healthy volunteers in the Phase 1 study. Nonetheless, out of precaution, subjects participating in this study are required to have an estimated glomerular filtration rate ≥60 mL/min/1.73 m^2 as determined by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening, and medications with known nephrotoxic potential are prohibited from use during the study (Section 8.4.1). Additionally, any clinically meaningful new, worsening from baseline, or abnormal laboratory findings or symptoms suggestive of acute kidney injury

(AKI) (eg, 'blood urea increased' or 'protein urine present' adverse events [AEs] as identified by the Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ] 'Acute renal failure') will be considered AEs of special interest (AESI, Section 12.1.5). Subjects will be closely monitored for observations of AKI, and study drug may be interrupted for subjects who experience elevations in serum creatinine levels according to the algorithm described in Section 12.13.4.

5.5.3. Overall Benefit:Risk Conclusion

Overall, the safety measures to be employed and the clinical experience to date with EP547 suggest minimal risk to subjects participating in Study EP-547-201. Although a variety of interventions for cholestatic pruritus have been explored, there is currently no medication approved for this indication in adults, and the need for improved treatments remains high. Therefore, development of additional safe and effective, mechanistically based therapeutic options for this condition is essential. If determined to be effective in this study, EP547 may ultimately have the potential to offer substantial relief for patients suffering from cholestatic pruritus, including those enrolled in this study. Considering all available safety information and measures taken to minimize risk to subjects, the overall benefit-risk profile of EP547 is deemed to be acceptable for the conduct of Study EP-547-201.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

- To assess the efficacy of EP547 compared to placebo on pruritus as assessed by the Worst Itch Numeric Rating Scale (WI-NRS)

6.2. Secondary Objectives

- To assess the efficacy of EP547 compared to placebo on the following:
  - Pruritus-related quality of life using the 5-D Itch Scale
  - Pruritus severity using the Patient Global Impression of Severity (PGI-S)
  - Overall pruritus response to therapy using the Patient Global Impression of Change (PGI-C)
- To assess the safety and tolerability of EP547
- To assess the PK of EP547

6.3. Exploratory Objectives

[redacted]

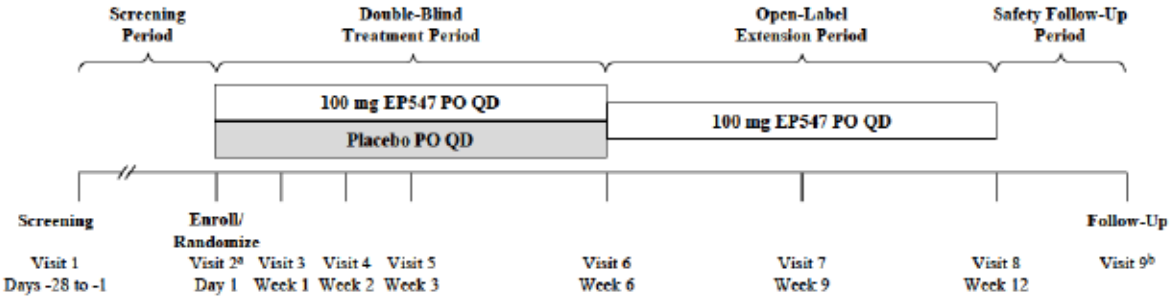
7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

EP-547-201 is a randomized, double-blind, placebo-controlled study to evaluate the effects of EP547 on pruritus over 6 weeks in subjects with cholestatic pruritus due to PBC or PSC. Where allowed per regulatory/local requirements, subjects will be able to attend study visits at a physical study site as well as remotely (hybrid model) or at a virtual site where all visits will be conducted remotely (decentralized model). For both the hybrid and decentralized models, a home health nurse visit at the subject's home or work and a telemedicine visit with the study site staff (eg, smartphone or computer) will be arranged to conduct procedures for each remote study visit.

As shown in Figure 1, the study includes a Screening Period of up to 4 weeks to assess subject eligibility; a 6-week Double-Blind Treatment Period; a 6-week Open-Label Extension Period; and a 2-week Safety Follow-Up Period after administration of the last dose of study drug (EP547 or placebo). Approximately 58 subjects will be randomized to receive either 100 mg doses of EP547 or placebo orally (PO) QD in a 1:1 ratio. In the Open-Label Extension Period, all subjects will receive 100 mg doses of EP547.

Figure 1: EP-547-201 Study Design



PO = oral, QD = once daily.

[a] For the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. When enrollment/randomization and first dose of study drug are on separate days, the first dose of study drug is considered Day 1.

[b] Any subject who completes the Open-Label Extension Period or discontinues study drug (EP547 or placebo) early will complete a follow-up visit approximately 2 weeks (±3 days) after the last dose of study drug.

7.1.1. Screening Period

The Screening Period will consist of 1 study visit (Visit 1). During this period, subjects will undergo assessments to determine study eligibility. Visit 1 (Day-28 to Day -1) may be conducted over more than 1 day but must be completed between Day -28 and Day -1.

7.1.2. Double-Blind Treatment Period

The Double-Blind Treatment Period will consist of 5 study visits (Visits 2, 3, 4, 5, and 6 [Day 1 and Weeks 1, 2, 3, and 6]). During this period, all subjects who meet eligibility requirements will be enrolled into the study and randomized to receive double-blind, PO, QD doses of EP547 or placebo for 6 weeks beginning on Visit 2 (Day 1). Subjects will be randomized to receive either 100 mg doses of EP547 or placebo in a 1:1 ratio. Randomization will be conducted centrally via an Interactive Web Response System (IWRS) and stratified based on type of cholestatic disease (PBC, PSC). Visit 2 (Day 1) will not have a visit window; however, for the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. When enrollment/randomization and first dose of study drug are on separate days, the first dose of study drug is considered Day 1. All other visits in the Double-Blind Treatment Period will have a visit window of ±3 days.

7.1.3. Open-Label Extension Period

The Open-Label Extension Period will consist of 2 study visits (Visit 7 [Week 9] and Visit 8 [Week 12]). During this period, all subjects who complete the Double-Blind Treatment Period and are still receiving study drug will receive open-label 100 mg doses of EP547. Visit 7 and Visit 8 will have a visit window of ±3 days.

7.1.4. Safety Follow-Up Period

Any subject who completes the Open-Label Extension Period or discontinues study drug (EP547 or placebo) early will complete a follow-up visit (Visit 9) approximately 2 weeks (±3 days) after the last dose of study drug.

7.2. End of Study

A subject is considered to have completed the study if he/she has completed all phases of the study, including the last study visit (ie, the Follow-Up Visit [Visit 9]).

The end of the study is defined as the date of the last study visit of the last subject in the study globally.

7.3. Number of Subjects

Approximately 58 subjects with cholestatic pruritus due to PBC or PSC will be randomized in the study.

7.4. Dose Adjustment Criteria

Dosages for study drug should be maintained constant during the study. However, dosing of study drug may be interrupted or discontinued due to safety findings. Refer to Section 8.5 for guidance on mandatory discontinuation of study drug due to severe and related AEs.

7.5. Criteria for Study Termination

The Sponsor may terminate the study at a study site at any time (eg, Good Clinical Practice [GCP] noncompliance or poor study data quality). If instructed by the Sponsor or designee, the

Investigator must implement the termination in a timeframe to ensure subject safety and well-being. Refer to Section 8.5.2 (Discontinuation from the Study) for instructions for subjects whose participation from the study is discontinued.

The Investigator and/or Sponsor (or designee) must notify the 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 at Visit 1 may have that assessment repeated once at the discretion of the Investigator within the screening window and be enrolled if a repeat assessment is within the indicated range as specified below for participating in the study.

8.1. Subject Inclusion Criteria

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

1. Age 18 to 80 years, inclusive
2. Has experienced self-reported daily or near-daily moderate to severe pruritus before Screening
3. Has a mean daily WI-NRS score indicative of moderate to severe pruritus (score ≥4) during Screening (Day -7 through Day -1); data from at least 4 of the 7 days are required to be considered an acceptable profile
4. If currently taking medications to treat the cholestatic disorder (including obeticholic acid [OCA]), must be on a stable dose for >12 weeks before Screening and plans to maintain the regimen throughout the study
5. If currently taking a fibrate, must be on a stable dose for >12 weeks before Screening and plans to maintain the regimen throughout the study
6. Either is not treated with or has been on a stable regimen with any medications to treat pruritus for >4 weeks before Screening and plans to maintain the regimen throughout the study
7. If female, must have a negative serum pregnancy test at Screening and be willing to not donate eggs from Screening until after the last dose of study drug and:
    a. Is surgically sterile; or
    b. Has been amenorrhoeic for ≥1 year without an alternative medical cause; or
    c. If of childbearing potential[2], must agree to use at least 1 form of an acceptable method of contraception from Screening until the last dose of study drug. Acceptable birth control methods include:

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

- Barrier methods of contraception (eg, male condom, female condom, cervical cap or diaphragm, and contraceptive sponge)
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Progestogen only hormonal contraception
- Intrauterine device
- Intrauterine hormone releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study drug), the reliability of which needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject

8. Must be able to communicate well with the Investigator, understand and comply with the requirements of the study, and understand and provide written consent
9. For subjects with concomitant inflammatory bowel disease (IBD):
    a. Colonoscopy (if subject has a colon) or other appropriate endoscopic procedure within 18 months of Day 1 confirming no dysplasia or colorectal cancer
    b. Subjects with Crohn's disease (CD) must be in remission as defined by a Crohn's Disease Activity Index (CDAI) <150 at Screening
    c. Subjects with ulcerative colitis (UC) must have a Partial Mayo Scoring Index score ≤3 with no individual sub-score exceeding 1 point at Screening

Subjects with PBC must also meet the following inclusion criteria to be eligible for study participation:

10. Documented history of PBC that is consistent with the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines (Lindor 2019), defined as having ≥2 of the following 3 factors upon diagnosis:
    a. History of elevated alkaline phosphatase (ALP) levels
    b. Historic positive antimitochondrial antibody (AMA) or AMA-M2 by immunofluorescence, enzyme linked immunosorbent assay (ELISA), or immunoblot or if AMA is negative, positive for PBC-specific antibodies (anti-GP210 and/or anti-SP100)
    c. Liver histology at any point in time consistent with PBC
11. If currently taking ursodeoxycholic acid (UDCA), must be on a stable dose of not more than 20 mg/kg/day for ≥12 weeks. If not currently taking UDCA, must not be treated with UDCA within 12 weeks before Screening or plan to be treated with UDCA during the study

Subjects with PSC must also meet all the following inclusion criteria to be eligible for study participation:

12. Documented history of PSC based on either cholangiography (ie, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, or percutaneous transhepatic cholangiogram) or if small duct PSC, confirmed by typical histologic evidence of PSC for ≥1 year (EASL 2009, Chapman 2010)
13. If currently taking UDCA, must be on a stable dose of not more than 23 mg/kg/day for ≥12 weeks. If not currently taking UDCA, must not be treated with UDCA within 12 weeks before Screening or plan to be treated with UDCA during the study

8.2. Subject Exclusion Criteria

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

1. Pruritus is attributed mainly to any disease unrelated to PBC or PSC
2. Prior liver transplant or presently listed for transplantation
3. Is receiving ongoing ultraviolet B (UVB) treatment or plasmapheresis or anticipates receiving such treatments during the study
4. Evidence of compensated or decompensated cirrhosis based on ANY of the following:
    a. Historical liver biopsy demonstrating cirrhosis
    b. Liver stiffness as assessed by a FibroScan® score of ≥16.9 kPa for subjects with PBC or ≥14.4 kPa for subjects with PSC within 6 months of Screening
    c. History or presence of portal hypertension with complications, including known gastric or esophageal varices, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, history of variceal bleeds, or related therapeutic or prophylactic interventions (eg, non-selective beta blockers being used to prevent complications of portal hypertension [propranolol, nadolol, or carvedilol], insertion of variceal bands, transjugular intrahepatic portosystemic shunt, or direct intrahepatic portocaval shunt)
5. History of malignancy of any organ system, including but not limited to hepatocellular carcinoma, cholangiocarcinoma, and gall bladder carcinoma, treated or untreated, within the past 5 years (localized squamous cell or basal cell carcinoma of the skin that have been excised or resolved is not exclusionary)
6. Alternate causes of liver diseases such as hepatic sarcoidosis, alcoholic liver disease, histology confirmed autoimmune hepatitis, overlap hepatitis, or nonalcoholic steatohepatitis (NASH), or uncontrolled viral hepatitis as defined in Section 12.9
7. Presence of documented secondary sclerosing cholangitis (eg, ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis) on prior clinical investigations

8. Immunoglobulin G4 (IgG4) >4× upper limit of normal (ULN) at Screening or evidence of systemic IgG4-related disease
9. Current evidence of clinically significant high-grade strictures or presence of biliary stent at Screening
10. History of recurrent bacterial cholangitis or recent episode within 3 months before Screening
11. Endoscopic interventions with therapeutic intent such as biliary duct dilation within 3 months before Screening or planned during the study
12. History of significant small bowel resection or short bowel syndrome
13. Presence of 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
14. Clinically relevant medical history, physical examination, vital sign, standard 12-lead electrocardiogram (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
15. Has any of the following laboratory results at Screening:
    a. Total bilirubin >2.0 mg/dL; total bilirubin >2.0 mg/dL is acceptable for subjects with medically documented Gilbert's syndrome if direct bilirubin is <0.3 mg/dL
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× ULN
    c. ALP >10× ULN
    d. International normalized ratio (INR) >1.3
    e. Platelet count <150,000/μL
    f. Urine albumin to creatinine ratio ≥30 mg/g
16. Estimated glomerular filtration rate <60 mL/min/1.73 m^2 as determined by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening
17. History of human immunodeficiency virus (HIV) or positive for HIV infection at Screening
18. Significant history of abuse of drugs, solvents, or moderate alcohol consumption (≥1 serving or unit/day on average for women and ≥2 servings or units/day on average for men; 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
19. Has received a prohibited medication within 2 weeks or 5 half-lives of Day 1, whichever is longer, as described in Section 8.4.1
20. 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 with an investigational or approved drug/device while enrolled in this study
21. History of known or suspected hypersensitivity to any component of the study drug

22. Female who is pregnant, nursing, or intends to become pregnant during the study
23. 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
24. 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.
25. Subject is, in the opinion of the Investigator, not suitable to participate in the study

8.3. Study Restrictions

During participation in the study, subjects must adhere to the following restrictions from Screening to the end of the Double-Blind Treatment Period unless subject safety is compromised:

- Do not use any drugs of abuse
- Do not use any investigational agents and/or devices
- Do not take any new prescribed medication, unless done so in consultation with the Medical Monitor
- Maintain current dose and regimen of all prescribed medication, unless changed in consultation with the Medical Monitor
- Do not undergo UVB treatment or plasmapheresis
- Do not change caffeine intake habits
- Do not add or change the frequency, dose, or time of administration of drugs that may cause sedation
- If routinely taking a bile acid sequestrant (eg, cholestyramine, colestipol, or colesevelam), hold the morning dose until 2 hours after study drug administration. If the bile acid sequestrant baseline dosing regimen does not allow for a 2-hour hold, hold dosing of these medications for a minimum of 1 hour after study drug administration. Alternatively, take the bile acid sequestrant at least 4 hours prior to study drug administration
- If taking antacids (eg, aluminum hydroxide, calcium carbonate, magnesium carbonate, sodium bicarbonate), withhold dosing of these medications at least 4 hours prior and 4 hours after each study drug administration

8.4. Concomitant Medications

Subjects are to follow the medication restrictions outlined in the inclusion and exclusion criteria (Section 8.1 and Section 8.2) and subject restrictions (Section 8.3) during the study. Dosages for concomitant medications are to remain constant during the study unless needed for subject safety and instructed otherwise by the Investigator or a treating physician.

Health authority authorized or approved coronavirus disease 2019 (COVID-19) vaccines are permitted. As implied in exclusion criterion 20, investigational severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines (ie, vaccines given as part of a clinical study) are not permitted. The SARS-CoV-2 vaccine should be recorded on the Concomitant Medication electronic case report form (eCRF).

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

All medications taken within 14 days before Screening and details of concomitant medications from Screening through the end of study participation should be recorded as should medications taken to treat a cholestatic disorder within 12 weeks before Screening and medications known to impact pruritus taken within 4 weeks before Screening.

8.4.1. Prohibited Concomitant Medications

Subjects taking immunosuppressant/immunomodulating agents may not receive live, attenuated vaccines during participation in this study. Medications with known nephrotoxic potential (eg, aminoglycosides, contrast dye, bisphosphonates, and nonsteroidal anti-inflammatory drugs) are prohibited from use during the study [redacted] Table 3 lists examples of excluded medications that are substrates for BCRP, OAT1, CYP2B6, or CYP2C8, or inhibitors of OAT3. If a subject receives a prohibited concomitant medication during the study, the Investigator, in consultation with the Medical Monitor, may interrupt or discontinue study drug as warranted for reasons of protecting subject safety.

8.5. Removal of Subjects from Therapy or Assessment

If a subject discontinues study drug and/or is withdrawn from the study, the reason will be recorded on the eCRF page and the Sponsor will be notified promptly.

8.5.1. Discontinuation of Study Drug

Study drug may be discontinued in the following instances:

- AE
- Withdrawal of consent
- Lost to follow-up
- Protocol deviation

- Investigator decision
- Sponsor decision
- Pregnancy during the study (Section 12.2.4)
- Criteria met from drug-induced liver injury (DILI) monitoring to discontinue study drug (Section 12.13.3)
- Other

If a subject experiences an AE that is Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 or higher, the study drug must be discontinued. AE grading for severity using CTCAE criteria is described in Section 12.1.2.

Subjects who terminate treatment with study drug early, regardless of the reason, will 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 of study drug.

Whenever possible, subjects should remain in the study and complete the remaining study visits and assessments even when study drug has been discontinued. Subjects who discontinue study drug for any reason and continue with the study visits as planned through the Week 12 visit (participating only in efficacy and safety, but not PK measures) will participate in the Safety Follow-Up Visit if the last dose of study drug was administered less than 2 weeks before the Week 12 visit to ensure that at least 2 weeks of follow-up data are collected for all randomized subjects.

If a subject discontinues study drug and chooses not to complete all of the remaining study visits, the subject will have a Follow-Up Visit approximately 2 weeks (±3 days) after the last dose of study drug if at least 2 weeks of follow-up data have not already been collected. If a subject fails to attend the follow-up visit and has not withdrawn consent, all reasonable efforts will be made to contact the subject to ensure that he/she is in satisfactory health. All contacts and contact attempts must be documented in the subject's medical record.

8.5.2. Discontinuation from the Study

Subjects may discontinue from the study at any time for any of the following reasons:

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

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

consent. The Investigator should make a reasonable attempt to document the specific reason why consent was withdrawn.

8.5.3. Safety Criteria for Study Drug Interruption

Study drug dosing will be interrupted for all subjects if 3 subjects develop AEs meeting CTCAE Grade 3 or higher that are considered related to study drug by the Investigator and/or Sponsor. AE grading for severity using CTCAE criteria is described in Section 12.1.2. All events with a CTCAE Grade of 3 or higher will be reviewed by the Data Monitoring Committee (DMC) (Section 12.3) to independently determine event relatedness and provide recommendations to the Sponsor.

9. TREATMENT OF SUBJECTS

9.1. Treatment Assignment

For the Double-Blind Treatment Period, eligible subjects will be centrally assigned to randomized study drug (100 mg doses of EP547 or placebo in a 1:1 ratio) using an IWRS and stratified based on type of cholestatic disease (PBC, PSC). During the Open-Label Extension Period, all eligible subjects will receive 100 mg doses of EP547 (no randomization). EP-547-201 treatment assignments by study period are presented in Table 4.

Table 4: EP-547-201 Treatment Assignments

Study Period	Study Days	Approx. No. of Subjects	Treatment Designation	Study Drug Dose Regimen
Screening	Day -28 to Day -1	58	Not applicable	None
6-Week, Double-Blind Treatment	Day 1 to Day 42	29	100 mg EP547	One 25 mg EP547 tablet and One 75 mg EP547 tablet PO QD
		29	Placebo	Two placebo tablets PO QD
6-Week, Open-Label Extension	Day 43 to Day 85	58	100 mg EP547	One 25 mg EP547 tablet and One 75 mg EP547 tablet PO QD
2-Week Safety Follow-Up	2 weeks after last study drug dose	58	Not applicable	None

PO = oral; QD = once daily.

Sites will request the allocated randomization and kit numbers in advance of dosing via IWRS.

9.2. Treatment Compliance

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

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

9.3. Randomization and Blinding

9.3.1. Randomization

All subjects who meet eligibility requirements will be enrolled into the study and randomized to receive double-blind, PO, QD doses of EP547 or placebo for 6 weeks beginning at Visit 2 (Day 1). Subjects will be randomized to receive either 100 mg doses of EP547 or placebo in a 1:1 ratio. Randomization will be conducted centrally via IWRS and stratified based on type of cholestatic disease (PBC, PSC).

All subjects who complete the Double-Blind Treatment Period and are still receiving study drug will receive open-label 100 mg doses of EP547 during the Open-Label Extension Period.

9.3.2. Blinding

The Sponsor, Medical Monitor, Contract Research Organization (CRO) staff, Investigators, site staff, and subjects will be blinded to subject's assigned treatment during the Double-Blind Treatment Period of the study until the database is locked except for CRO or vendor staff involved in the analysis of PK samples or safety reporting to regulatory agencies.

To address business needs, a limited number of study team members and senior stakeholders comprising the internal Data Review Team (DRT) may conduct and review an interim analysis of unblinded data from the Double-Blind Treatment Period (Section 14.13). The rest of the central study and project team members will remain blinded.

Treatment with 100 mg doses of EP547 during the Open-Label Extension Period will be conducted in an unblinded manner.

9.3.2.1. Emergency Unblinding

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

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

In all emergency cases, the reasons and rationale for unblinding will be documented in writing and maintained in the study file.

9.3.2.2. Unblinding for Regulatory Reporting

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

9.4. Study Visits

Subjects should fast for at least 8 hours before each dose of study drug and before study visits that require a blood sample for assessment of chemistry, PK (predose), or completion of questionnaires. The date, time, and type of any snack or meal provided at the site will be recorded. Water is acceptable in the morning of study visits to ensure the subject is hydrated for laboratory sample collection.

Questionnaires to be completed at the site should be administered in a quiet, private place at the study site before all other scheduled procedures.

For the hybrid model, Visits 1, 2, 6, and 8 (Screening, Day 1, Week 6, and Week 12) and early termination (if applicable) must be completed at the study site. All other study visits may be conducted remotely, where allowed per regulatory/local requirements. For the decentralized model, all visits will be conducted remotely.

For remote visits for both the hybrid and decentralized models, the home health nurse visit at the subject's home or work and the telemedicine visit with the study site staff for a given study visit may be conducted on different days but must be within the allowable visit window. The home health nurse will complete the study assessments that the site is physically unable to complete remotely (eg, blood and lab sample collection, vital signs, ECGs); the site will complete all other study assessments remotely during the telemedicine visit. Additional information for conducting remote visits will be provided in study-specific manual(s).

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

9.4.1. Screening Period

9.4.1.1. Visit 1 (Day -28 to Day -1)

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

The following assessments may be conducted over more than 1 day but must be completed between Day -28 and Day -1:

- Completion of informed consent before performance of any study procedures or assessments
- Medical history
- Height
- Assessment of baseline concomitant medications, including:
  - All medications taken within 14 days before Screening
  - Medications taken to treat a cholestatic disorder within 12 weeks before Screening

  - Medications known to impact pruritus within 4 weeks before Screening
- Assessment of AEs
- Partial Mayo Score (for subjects with UC only)
- CDAI (for subjects with CD only)
- Physical examination
- Vital signs
- Standard 12-lead ECG
- Transient elastography (TE; FibroScan; if an eligible historical TE is not available within 6 months of Screening)
- Laboratory assessments:
  - Urinalysis
  - HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis E virus (HEV) serology
  - Serum pregnancy test (females only)
  - Chemistry and hematology
  - Coagulation
  - IgG4
- Eligibility check
- Receive questionnaire training (to be conducted before completing the daily WI-NRS for Day -14)

Subjects will be instructed to complete the WI-NRS daily, in the morning, and at the same time of day, beginning at Day -14 to the Safety Follow-Up Visit. For days that coincide with a study visit (for Visit 2 and beyond), the WI-NRS is to be completed before the study visit.

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) for enrollment and randomization.

9.4.2. Double-Blind Treatment Period

9.4.2.1. Visit 2 (Day 1)

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

Subjects will undergo the following procedures at Visit 2 (Day 1):

- Confirm that the WI-NRS has been completed daily from Day -14 to the morning prior to this visit

- Questionnaires:
  - 5-D Itch Scale
  - PGI-S

- Assessment of concomitant medication usage
- Assessment of AEs
- Vital signs
- Standard 12-lead ECG
- Laboratory assessments:
  - Urine pregnancy test (females only)
  - Urinalysis
  - Kidney-related biomarkers (blood and urine)
  - Chemistry and hematology
  - Coagulation
  - Bile acids and heme metabolites
  - Retained samples for future analysis (blood and urine)
  - Genotyping (optional)
  - Thyroid hormones: thyroid-stimulating hormone (TSH) and free thyroxine (T4)
- Blood sample draw for PK assessment predose and [redacted] postdose
- Eligibility check
- Randomization to 100 mg EP457 or placebo in a 1:1 ratio via IWRS
- Dispense double-blind study drug

For the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. If enrollment/randomization is conducted on a separate day than dosing, the eligibility check should also be conducted during the same day as enrollment/randomization. Additionally, confirmation that WI-NRS has been completed daily and assessments of concomitant medication usage and AEs are to be conducted on both days (ie, date of enrollment/randomization and date of first dose). All other assessments listed above are to be conducted on the date of first dose only.

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

9.4.2.2. Visit 3 (Week 1)

The following assessments will be performed during Visit 3 (Week 1):

- Confirm that the WI-NRS has been completed daily from Visit 2 (Day 1) to the morning prior to this visit
- Assessment of concomitant medication usage
- Assessment of AEs
- Vital signs
- Laboratory assessments:
  - Urinalysis
  - Kidney-related biomarkers (blood and urine)
  - Chemistry and hematology
  - Coagulation
- Blood sample draw for PK assessment predose

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

9.4.2.3. Visit 4 (Week 2)

The following assessments will be performed during Visit 4 (Week 2):

- Confirm that the WI-NRS has been completed daily from Visit 3 (Week 1) to the morning prior to this visit
- Assessment of concomitant medication usage
- Assessment of AEs
- Vital signs
- Laboratory assessments:
  - Urinalysis
  - Kidney-related biomarkers (blood and urine)
  - Chemistry and hematology
  - Coagulation
- Blood sample draw for PK assessment predose

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

9.4.2.4. Visit 5 (Week 3)

Subjects will undergo the following assessments at Visit 5 (Week 3):

- Confirm that the WI-NRS has been completed daily from Visit 4 (Week 2) to the morning prior to this visit
- Assessment of concomitant medication usage
- Assessment of AEs
- Vital signs
- Laboratory assessments:
  - Urine pregnancy test (females only)
  - Urinalysis
  - Kidney-related biomarkers (blood and urine)
  - Chemistry and hematology
  - Coagulation
  - Retained samples for future analysis (blood and urine)
- Blood sample draw for PK assessment predose and [redacted] postdose
- Collect study drug kits and assess study drug accountability and compliance
- Dispense double-blind study drug

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

9.4.2.5. Visit 6 (Week 6)

Subjects will undergo the following assessments at Visit 6 (Week 6):

- Confirm that the WI-NRS has been completed daily from Visit 5 (Week 3) to the morning prior to this visit
- Questionnaires:
  - 5-D Itch Scale
  - PGI-C
  - PGI-S

- Assessment of concomitant medication usage

- Assessment of AEs
- Partial Mayo Score (for subjects with UC only)
- CDAI (for subjects with CD only)
- Vital signs
- Standard 12-lead ECG
- Laboratory assessments:
  - Urine pregnancy test (females only)
  - Urinalysis
  - Kidney-related biomarkers (blood and urine)
  - Chemistry and hematology
  - Coagulation
  - Bile acids and heme metabolites
  - Retained samples for future analysis (blood and urine)
  - Thyroid hormones: TSH and free T4
- Blood sample draw for PK assessment predose
- Collect study drug kits and assess study drug accountability and compliance
- Dispense open-label study drug

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

9.4.3. Open-Label Extension

9.4.3.1. Visit 7 (Week 9)

Subjects will undergo the following assessments at Visit 7 (Week 9):

- Confirm that the WI-NRS has been completed daily from Visit 6 (Week 6) to the morning prior to this visit
- Assessment of concomitant medication usage
- Assessment of AEs
- Vital signs
- Laboratory assessments:
  - Urine pregnancy test (females only)
  - Urinalysis
  - Kidney-related biomarkers (blood and urine)

  - Chemistry and hematology
  - Coagulation
  - Retained samples for future analysis (blood and urine)
- Collect study drug kits and assess study drug accountability and compliance
- Dispense open-label study drug

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

9.4.3.2. Visit 8 (Week 12)

Subjects will undergo the following assessments at Visit 8 (Week 12):

- Confirm that the WI-NRS has been completed daily from Visit 7 (Week 9) to the morning prior to this visit
- Questionnaires:
  - 5-D Itch Scale
  - PGI-C
  - PGI-S

- Assessment of concomitant medication usage
- Assessment of AEs
- Partial Mayo Score (for subjects with UC only)
- CDAI (for subjects with CD only)
- Physical examination
- Vital signs
- Standard 12-lead ECG
- Laboratory assessments:
  - Urine pregnancy test (females only)
  - Urinalysis
  - Kidney-related biomarkers (blood and urine)
  - Chemistry and hematology
  - Coagulation
  - Retained samples for future analysis (blood and urine)

  - Thyroid hormones: TSH and free T4
- Collect study drug kits and assess study drug accountability and compliance

9.4.4. Safety Follow-Up Period

9.4.4.1. Safety Follow-Up Visit (Visit 9)

Subjects will undergo the following assessments at the Safety Follow-Up Visit, approximately 2 weeks after the last dose of study drug:

- Confirm that the WI-NRS has been completed daily from the last visit to the morning prior to this visit
- Questionnaires:

- Assessment of concomitant medication usage
- Assessment of AEs
- Vital signs
- Standard 12-lead ECG
- Laboratory assessments:
  - Urine pregnancy test (females only)
  - Urinalysis
  - Kidney-related biomarkers (blood and urine)
  - Chemistry and hematology
  - Coagulation

9.4.5. 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 will undergo the following assessments during the Early Study Termination Visit:

- Confirm that the WI-NRS has been completed daily from the previous visit to the morning prior to this visit
- Questionnaires:

[redacted]

- Assessment of concomitant medication usage
- Assessment of AEs
- Partial Mayo Score (for subjects with UC only)
- CDAI (for subjects with CD only)
- Physical examination
- Vital signs
- Standard 12-lead ECG
- Laboratory assessments:
  - Urine pregnancy test (females only)
  - Urinalysis
  - Kidney-related biomarkers (blood and urine)
  - Chemistry and hematology
  - Coagulation
  - Thyroid hormones: TSH and free T4
- Collect study drug kits and assess study drug accountability and compliance

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drugs

For the Double-Blind Treatment Period, tablets containing 25 mg or 75 mg of EP547 or placebo will be supplied in a way to ensure the study blind. For the Open-Label Extension Period, tablets containing 25 mg or 75 mg of EP547 will be supplied. Subjects receiving EP547 will take one 25-mg and one 75-mg EP547 tablet per dose (for a total dose of 100 mg) and subjects receiving placebo will take 2 placebo tablets per dose.

10.2. Study Drug Packaging and Labeling

For the Double-Blind Treatment Period, study drug kits each containing 2 tablets per dose and packaged into blister card/wallets will be labeled with a unique number and will be supplied to study sites in a blinded manner.

Study drug kits for the Open-Label Extension Period will be packaged and labeled similarly as those for the Double-Blind Treatment Period but will be supplied to the sites in an unblinded manner.

10.3. Study Drug Storage

The study drug tablets should be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F), with excursions allowed between 15°C to 30°C (59°F to 86°F).

10.4. Study Drug Administration

Each study drug dose, containing 2 tablets, is to be administered orally as intact tablets (swallowed whole, not chewed or crushed), and taken with water. Doses are to be administered daily at approximately the same time of day after a fast of at least 8 hours.

10.4.1. Instructions for Missed Dose(s)

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

10.5. Study Drug Dispensing and Accountability

Subjects will complete dosing records, which will be reviewed at each study visit by study site staff.

Subjects should be instructed to retain the study drug kit (including blister cards/wallets), even if empty, and to return it and any remaining study drug to the study site at their next visit or to a direct-to-patient courier service. The study site staff should perform study drug accountability and, if applicable, follow-up with the subject to retrieve any remaining study drug that has not been returned.

10.6. Study Drug Handling and Disposal

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

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

To support remote study visits for the hybrid and decentralized models, the use of a direct-to-patient courier service to transport study drug between the study site or central drug depot and the subject's home may be arranged. The courier will be asked to collect the study drug kit dispensed by the study site staff or central drug depot and deliver it to the subject's home. The courier may also be asked to collect the used study drug kit with any unused study drug from the subject to be returned to the site or central drug depot for accountability and reconciliation. Chain of custody of the study drug transport will be documented. Additional study drug handling and disposal information for remote visits will be provided in study-specific manual(s).

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 site staff must maintain documentation of any missing or unreturned study drug. The final disposition of all study drug received at the site is to be documented.

10.7. Product Quality Complaints

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

All initial PQCs must be reported to the Sponsor or CRO by 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. EFFICACY AND PHARMACODYNAMIC ASSESSMENTS

Efficacy evaluations, including patient-reported assessments of pruritus (WI-NRS), pruritus-related quality of life (5-D Itch Scale), pruritus severity (PGI-S), overall response to therapy (PGI-C), sleep disturbance ([redacted]), fatigue ([redacted]), and overall quality of life ([redacted]) will be assessed.

PD assessments, including blood and/or urine sampling for genotyping (optional), pruritus-related biomarkers (bile acids and heme metabolites), kidney-related biomarkers, and future analysis will also be assessed.

All efficacy and PD assessments will be performed as indicated in the Schedule of Assessments (Appendix A).

11.1. Questionnaires

At Visit 1 (Screening) before completing the daily WI-NRS for Day -14, subjects will receive training on how to respond to questionnaires. Sites will review the responses from each subject at least twice a week to ensure proper compliance.

11.1.1. Worst Itch Numeric Rating Scale (WI-NRS)

Subjects will be asked to rate the severity of their worst level of itching in the past 24 hours in the morning, and at the same time of day, using the WI-NRS. The WI-NRS is an 11-point scale ranging from 0 (No Itching) to 10 (Worst Itching Imaginable) (Phan 2012) and requires approximately 1 minute to complete. Higher scores indicate greater itch severity. Itching severity scores collected via the WI-NRS have been categorized in the literature as mild (<4), moderate (≥4 to <7), or severe (≥7) (Fishbane 2020, Hirschfield 2020, Levy 2020, Stander 2020). An example of the WI-NRS is included in Appendix B.

Subjects will be instructed to complete the WI-NRS daily, in the morning, and at the same time of day, beginning at Day -14 to the Follow-Up Visit. For days that coincide with a study visit (for Visit 2 and beyond), the WI-NRS is to be completed before the visit.

The WI-NRS scores from Day -7 through Day -1 will be averaged together to confirm compliance and determine subject eligibility for continued participation regarding pruritus sensation. The average WI-NRS score using the daily values from the week before the first dose of study drug (Visit 2 [Day 1]) will serve as the baseline score. The 7 daily WI-NRS scores prior to Visit 6 (Week 6) will be averaged together for primary endpoint analyses. Data from at least 4 of the 7 days for each week are required to be considered an acceptable profile.

11.1.2. 5-D Itch Scale

The 5-D Itch Scale was developed as a brief but multidimensional questionnaire designed for pruritus that measures changes over time (Elman 2010). The 5 dimensions are degree, duration, direction, disability, and distribution. It requires approximately 1 to 2 minutes to complete, and scores can range between 5 (no pruritus) and 25 (most severe pruritus). The scores of each of the 5 domains are achieved separately and then summed together to obtain a total 5-D score. An example of the 5-D Itch Scale is included in Appendix C.

11.1.3. Patient Global Impression of Severity (PGI-S)

The PGI-S was validated in women with stress urinary incontinence, but may be used to rate the severity of other specific conditions (Yalcin 2003). For this questionnaire, the specific condition to be rated is pruritus. Subjects will be asked to rate the severity of their pruritus in the past 7 days using a 4-point scale from None to Severe. The PGI-S requires less than 1 minute to complete. An example of the PGI-S is included in Appendix D.

11.1.4. Patient Global Impression of Change (PGI-C)

Subjects will be asked to rate their impression of overall change in pruritus in the past 7 days compared to before they started taking study drug using the PGI-C. The PGI-C is a 7-point scale ranging from Much Improved to Much Worse and requires approximately 1 minute to complete (Guy 1976). Higher scores indicate less improvement in pruritus. An example of the PGI-C is included in Appendix E.

11.2. Blood and Urine Sampling for Pharmacodynamic Assessments

Blood samples for genotyping (optional) and pruritus-related biomarkers (bile acids and heme metabolites) and blood and urine samples for future analysis will be assessed. Samples for genotyping and future analysis may be stored for up to 10 years after completion of the study.

11.3. Blood and Urine Sampling for Analysis of Kidney-Related Biomarkers

Blood will be collected for analysis of kidney-related biomarkers such as cystatin-C and neutrophil gelatinase-associated lipocalin.

Urine will be collected for analysis of kidney-related biomarkers such as clusterin, cystatin-C, kidney injury molecule-1, N-acetyl-β-D-glucosaminidase, neutrophil gelatinase-associated lipocalin, and osteopontin.

11.4. Height

Height will be measured with no shoes.

12. SAFETY ASSESSMENTS

Safety evaluations, including AEs, concomitant medications, medical history, vital signs, physical examinations, standard 12-lead ECGs, laboratory evaluations of safety, and disease-specific assessments (Partial Mayo Score for subjects with UC and CDAI for subjects with CD) will be performed as indicated in the Schedule of Assessments (Appendix A).

For the decentralized model, the Investigator may require the subject to have an in-person consultation with a physician after virtually conducting safety assessments, if deemed necessary.

12.1. Adverse Events

12.1.1. Definition of an Adverse Event

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

Medical conditions present at baseline that worsen in severity or frequency after exposure to study drug are considered 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 serious AEs (SAEs). Events with emergency room visits that are less than 24 hours will also not be considered SAEs unless they meet one of the criteria listed in Section 12.2.1.

Clinically significant abnormal laboratory tests, 12-lead ECG assessments, or vital sign results may, 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.

12.1.2. Determining Severity of Adverse Events

AEs must be graded for severity (ie, intensity) using CTCAE, version 5.0 (HHS 2017). A severity category of mild, moderate, severe, life-threatening, or death, as defined below, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious". The assessment of severity is made regardless of the relationship to study drug or of the seriousness of the AE. When reporting AEs, reference should be made to the CTCAE manual for guidance on appropriate grading.

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

All CTCAE Grade 3 or higher must be reported to the Sponsor or designee using the SAE/AESI/Grade 3+ Report Form, according to the timelines described for SAEs in Section 12.2.2.

12.1.3. 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.

12.1.4. Recording Adverse Events

All AEs must be recorded in the source documents and in the eCRFs provided by the Sponsor from the signing of the Informed Consent Form (ICF) until the end of study participation. AEs will be assessed for likelihood of causal relationship to the study drug (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 12.4).

12.1.4.1. Special Instructions for Recording Adverse Events in the eCRF

Diagnosis versus Signs and Symptoms

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

Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, clinical sequelae or a cascade of events) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as an 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.

12.1.5. Adverse Events of Special Interest

[redacted]. The applicability of the finding in monkeys to humans is unknown. Notably, no adverse changes in serum chemistry markers (eg, creatinine and BUN) were observed with daily doses of EP547 as high as 225 mg for 1 week in healthy volunteers in the Phase 1 study. Any clinically meaningful new, worsening from baseline, or abnormal laboratory findings or symptoms suggestive of AKI (eg, 'blood urea increased' or 'protein urine present' AEs as identified by the SMQ 'Acute renal failure') will be considered AESI and should be reported on the SAE/AESI/Grade 3+ Report Form.

Acute renal failure is a syndrome characterized by a relatively rapid decline in renal function that leads to the accumulation of water, crystalloid solutes, and nitrogenous metabolites in the body. Other clinical features include increase in serum creatinine and urea nitrogen levels (azotemia) >0.5 and 10 mg/dL, respectively; oliguria; and changes in the rate of urine flow.

AESI must be reported to the Sponsor or designee using the SAE/AESI/Grade 3+ Report Form, according to the timelines described for SAEs in Section 12.2.2.

12.2. Serious Adverse Events

12.2.1. Definition of a Serious Adverse Event

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

- Results in death;
- Is life-threatening, ie, the subject is, in the opinion of the Investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death);
- Requires hospital admission or prolongs hospitalization. Planned hospital admissions or surgical procedures for an illness or a disease that existed before administration of study drug, and for which the condition has not worsened since starting study drug, are not to be considered SAEs. Emergency room visits that are less than 24 hours will also not be considered SAEs;
- 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 unless it fulfills one of the SAE criteria above. For example, a headache that persists for several hours may be considered a severe AE but not fulfill the criteria of an SAE. Conversely, a wound infection that may be considered minor could be an SAE if it prolonged hospitalization.

12.2.2. Reporting Serious Adverse Events

In the event of any SAE reported or observed after signing of the ICF until 30 days after the last dose of study drug, regardless of causality, site personnel will report it to [redacted] within 24 hours of the knowledge of the occurrence. 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. To report an SAE, complete the study-specific SAE/AESI/Grade 3+ Report Form electronically in the electronic data capture (EDC) system for the study. This will trigger an email notification alert to the study team at [redacted] that an SAE has occurred. If the event meets serious criteria and it is not possible to access the internet, send an email to [redacted] safety team [redacted] or call the [redacted] and fax/email the completed paper back-up SAE/AESI/Grade 3+ Report Form to [redacted] within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available. Incoming reports are reviewed during normal business hours.

Follow-up information to all SAEs should be submitted to the Sponsor, or designee, in the same timeframe as initial reports. Any supporting documentation (eg, medical records) sent to [redacted] with the SAE/AESI/Grade 3+ Report 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).

Reconciliation of SAE information in the EDC with the SAE information received and entered in the Argus Safety 8.2 database will be performed per the Data Management Plan.

Safety Contact Information:

The [redacted] team is available via email (preferred), at [redacted].

12.2.3. Reporting Serious and Unexpected Adverse Events Assessed as Related

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, as required.

12.2.4. Pregnancy

Pregnancy in and of itself is not an AE, although pregnancies occurring in subjects or partners of male subjects are considered immediately reportable events. If a pregnancy occurs in a subject, study drug must be discontinued immediately. The pregnancy must be reported to [redacted] 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 [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.

12.3. Data Monitoring Committee

The DMC is an independent group of external experts who will review safety data during the conduct of the study, as outlined in the DMC charter. The DMC will make a determination of

relatedness for all AEs with CTCAE Grade 3 or higher. The DMC will also meet on an ad hoc basis when at least 3 AEs of CTCAE Grade 3 or higher have accrued or when there has been a single CTCAE Grade 4 or higher. Based on review of the data, the DMC will provide recommendations to the Sponsor on whether the nature, frequency, and/or severity of AEs associated with study drug warrant modification to the study protocol, suspension of dosing, or study termination.

12.4. 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.

12.5. Vital Signs

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

Vital signs also include body weight, which should be measured with no shoes on and using a calibrated scale throughout the study.

12.6. Physical Examinations

Physical examinations will include, but are not limited to, an assessment of general appearance, skin, HEENT (head, eyes, ears, nose, throat), musculoskeletal, thyroid/endocrine, cardiovascular, chest/lung, neurologic, abdomen, and extremities/general body systems. Symptom directed physical examinations to assess clinically significant changes from Screening or any new signs or symptoms may be conducted at other visits as determined by the Investigator based on subject complaint.

For the decentralized model, the Investigator, assisted by the mobile nurse, will conduct physical examinations per protocol via telemedicine during a videoconference session.

12.7. Standard 12-Lead Electrocardiograms

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

12.8. Laboratory Evaluations of Safety

Samples for the following laboratory tests 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), glucose, 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 with differential (lymphocytes, neutrophils, monocytes, eosinophils, and basophils), red blood cell count, platelet count, and platelet volume. If a subject develops lymphopenia, blood lymphocytes will be tested to assess populations of circulating T cells (including CD4+ and CD8+ subtypes), B cells, and natural killer (NK) cells.
- Urinalysis: leukocyte esterase, nitrites, pH, protein, specific gravity, glucose, occult blood, ketones, bilirubin, urobilinogen, albumin, creatinine, sodium, chloride, and potassium; 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: required for all females; serum test at Screening (Visit 1) and urine test for all other visits where pregnancy testing is required
- Thyroid function tests: TSH and free T4

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

12.9. Other Laboratory Evaluations

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

- IgG4
- Serology: HIV, HAV, HBV, HCV, and HEV

Per exclusion criterion 6, subjects with uncontrolled viral hepatitis are not eligible to participate in this study. Active HAV infection is defined as a positive result for immunoglobulin M (IgM) anti-HAV or HAV ribonucleic acid (RNA). Current chronic HBV infection is defined as a positive result for hepatitis B surface antigen (HBsAg) or HBV deoxyribonucleic acid (DNA). Current chronic HCV infection is defined as a positive result for HCV antibody and HCV RNA at Screening. If HCV is cured, a negative HCV RNA confirmed within 1 year prior to Screening will be required. Active HEV infection is defined as a positive result for IgM anti-HEV or HEV RNA.

All serology laboratory evaluations will be conducted at a central laboratory. Details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

12.10. Transient Elastography

Transient elastography (FibroScan TE) is a validated, noninvasive technique used to assess hepatic stiffness (Corpechot 2016) that will be used to determine subject eligibility based on exclusion criterion 4. If an eligible historical TE within 6 months of Screening is not available, TE procedures will be conducted at study sites with the appropriate equipment and by adequately trained study site staff. Scheduling of the TE assessment should be within the Screening window (Day -28 to Day -1).

12.11. Partial Mayo Scoring Index (Subjects with Ulcerative Colitis Only)

The Partial Mayo Scoring Index is a non-invasive questionnaire used as an outcome measure for clinical studies assessing therapies for UC (Lewis 2008). The index is composed of 3 categories (Bleeding, Stool Frequency, and Physician Assessment) that are each rated from 0 to 3 and summed to give a total score that ranges from 0 to 9. The Partial Mayo Scoring Index will be used to monitor disease stability during the course of the study.

12.12. Crohn's Disease Activity Index (CDAI) (Subjects with Crohn's Disease Only)

The CDAI is a composite instrument used for evaluating the disease severity of CD that is scored on a scale from 0 to 1100 and includes abdominal pain, general well-being, complications, abdominal mass, anemia, and weight change. Subjects with CD can be divided into asymptomatic remission (CDAI <150), mild-to-moderate CD (150 to 219), moderate-to-severe CD (220 to 450), and severe-fulminant disease (>450) (Chen 2018). The CDAI will be used to monitor disease stability during the course of the study.

12.13. Subject Safety Guidelines

12.13.1. Potential Side Effects

Safety results from the Phase 1 Study EP-547-101 did not reveal any safety trends, and there were no TEAEs assessed as expected with the use of EP547. Refer to the Investigator's Brochure for additional EP547 information regarding potential side effects.

12.13.2. 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.

12.13.3. Monitoring and Management of Potential Drug-Induced Liver Injury

Subjects will be assessed for potential DILI during both the Double-Blind Treatment Period and Open-Label Extension Period according to the consensus guidelines for clinical trials in adults with chronic cholestatic liver disease (Palmer 2020). Monitoring, interrupting, and stopping rules based on multiples of ULN, threshold values, baseline values, and/or nadir values of ALT, AST, ALP, and total bilirubin and liver-related symptoms are described in the algorithms for treatment-emergent hepatocellular and cholestatic DILI signals presented below.

Elevated ALP values should be confirmed to be of hepatic origin with GGT. Examples of liver-related symptoms include severe fatigue, nausea, new onset of or worsening of pruritus, right upper quadrant pain, immunologic reaction (eg, rash, >5% eosinophilia), and hepatic decompensation. If the algorithm calls for repeat blood tests, the tests are to be performed within 2 to 5 calendar days after receipt of laboratory values by the site for hepatocellular DILI signals and within 7 to 10 calendar days after receipt of laboratory values by the site for cholestatic DILI signals. ALT, AST, ALP, and total bilirubin, at a minimum, will be assessed as part of the repeat blood tests.

Monitoring for Hepatocellular Injury

The algorithm for monitoring and interrupting study drug for treatment-emergent hepatocellular DILI signals in subjects with a normal ALT baseline value is provided in Table 5.

Table 5: Algorithm for Monitoring and Interrupting Study Drug for Treatment-Emergent Hepatocellular DILI Signals in Subjects with a Normal ALT Baseline Value

Treatment-Emergent ALT	Bilirubin	Liver-Related Symptoms	Action
ALT ≥5× ULN	Normal Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	Repeat blood tests and monitor for symptoms.
ALT ≥8× ULN	Normal or elevated	None or present	Interrupt study drug and repeat blood tests. Study drug can be restarted if another etiology (not hepatocellular injury) is identified and abnormalities return to baseline levels.
ALT ≥3× ULN	Total bilirubin ≥2× baseline Gilbert's syndrome or hemolysis: direct bilirubin >2× baseline if baseline >0.5 mg/dL	None or present	
ALT ≥5× ULN	Normal or elevated	Present	

ALT = alanine aminotransferase; DILI = drug induced liver injury; ULN = upper limit of normal.

The algorithm for monitoring and interrupting study drug for treatment-emergent hepatocellular DILI signals in subjects with an elevated ALT baseline value is provided in Table 6.

Table 6: Algorithm for Monitoring and Interrupting Study Drug for Treatment-Emergent Hepatocellular DILI Signals in Subjects with an Elevated ALT Baseline Value

Treatment-Emergent ALT	Bilirubin	Liver-Related Symptoms	Action
ALT ≥3× baseline	Normal Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	Repeat blood tests and monitor for symptoms.
ALT ≥5× baseline	Normal or elevated	None or present	Interrupt study drug and repeat blood tests. Study drug can be restarted if another etiology (not hepatocellular injury) is identified and abnormalities return to baseline levels.
ALT ≥2× baseline	Total bilirubin ≥2× baseline Gilbert's syndrome or hemolysis: direct bilirubin >2× baseline if baseline >0.5 mg/dL	None or present	
ALT ≥2× baseline	Normal or elevated	Present	

ALT = alanine aminotransferase; DILI = drug induced liver injury.

Monitoring for Cholestatic Injury

The algorithm for monitoring and interrupting study drug for treatment-emergent cholestatic DILI signals is provided in Table 7.

Table 7: Algorithm for Monitoring and Interrupting Study Drug for Treatment-Emergent Cholestatic DILI Signals

Treatment-Emergent ALP	Bilirubin	Liver-Related Symptoms	Action
ALP ≥2× baseline without alternative explanation	Normal Gilbert's syndrome or hemolysis: No change in baseline total bilirubin	None	Repeat blood tests and monitor for symptoms.
	Total bilirubin ≥2× baseline Gilbert's syndrome or hemolysis: direct bilirubin >2× baseline if baseline >0.5 mg/dL	None or present	Interrupt study drug and repeat blood tests. Study drug can be restarted if another etiology (not cholestatic injury) is identified and abnormalities return to baseline levels.
	Normal or elevated	Present	
ALP ≥3× baseline without alternative explanation	Normal or elevated	None or present	

ALP = alkaline phosphatase; DILI = drug induced liver injury.

In addition to the algorithms above, the Investigator may use clinical judgement to increase monitoring for DILI or interrupt or discontinue study drug as warranted for reasons of subject safety. An episode of DILI leading to hepatic decompensation in a study subject will result in permanent study drug discontinuation.

If a subject cannot return to the study site for a scheduled or unscheduled visit, or an immediate assessment is required, the use of a local laboratory is acceptable at the discretion of the Investigator. All local laboratory values obtained as part of DILI monitoring as well as their normal ranges are to be collected and entered into the clinical database.

12.13.4. Observation for Acute Kidney Injury

[redacted]. Notably, no adverse changes in serum chemistry markers (eg, creatinine and BUN) were observed with daily doses of EP547 as high as 225 mg for 1 week in healthy volunteers in the Phase 1 study. [redacted]

In subjects with the following serum creatinine levels, adapted from the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury

(KDIGO 2012), interruption of study drug and repeating blood tests should be considered, preferably within 3 to 7 days:

- Increase in serum creatinine by ≥0.3 mg/dL (≥26.5 µmol/L) from baseline: consider interrupting study drug, repeat blood test within 3 to 7 days
- Increase in serum creatinine to ≥1.5 × baseline (which is known or presumed to have occurred within the prior 7 days): interrupt study drug, repeat blood test within 3 to 5 days

These KDIGO guidelines typically apply to hospital settings, where baseline values within given timeframes (ie, the preceding 48 hours to 7 days) are available. However, in interventional studies such as the current study, values this recent will not likely be available in most cases. In such instances, the Investigator can refer to the baseline value (prior to starting study drug) and evaluate the change. In cases of AKI where an etiology is identified, the reported AE term should reflect the etiology for the impairment of renal function (eg, AKI due to hypovolemia).

Additionally, all abnormal complete blood count, serum creatinine, BUN, and urine albumin to creatinine ratio values during the Double-Blind Treatment Period and Open-Label Treatment Period are to be followed as deemed clinically necessary by the Investigator.

13. PHARMACOKINETICS ASSESSMENT

Blood sampling for PK of EP547 will be [redacted] to analyze EP547 concentrations; the metabolite profile may also be analyzed from these samples.

In the event of an SAE, the Investigator should collect, if at all possible, a blood PK sample at an unscheduled visit as part of SAE follow-up.

All PK laboratory evaluations will be conducted at a bioanalytical laboratory. Details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

14. STATISTICS

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

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

14.1. Analysis Sets

The following analysis sets will be considered:

- **Full Analysis Set**: All subjects who are randomized and take at least 1 dose of randomized study drug will be included in the Full Analysis Set (FAS). Subjects in the FAS will be analyzed according to randomized treatment assignment. If a subject is incorrectly stratified (ie, randomized according to an incorrect stratification), the subject will be analyzed under the randomized treatment for the stratum recorded in the IWRS. All efficacy and PD analyses will be based on the FAS.
- **Per Protocol Set**: The Per Protocol (PP) Set is a subset of the FAS containing subjects who meet study eligibility requirements and have no protocol deviations that might impact the assessment of efficacy measurements. Subjects will be analyzed according to randomized treatment assignment. The PP Set will be used for sensitivity analyses relating to efficacy and PD. The type of protocol deviations governing exclusion from the PP Set will be determined prior to database lock and primary analysis, and will be detailed in the SAP.
- **Safety Analysis Set:** All subjects who are randomized and take at least 1 dose of randomized study drug will be included in the Safety Analysis Set. Safety analyses will be based upon treatment actually received.
- **PK Set:** All subjects who receive at least 1 dose of EP547 and provide adequate blood samples for bioanalysis will be included in the PK Set.

14.2. Estimand

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

The primary estimand of the study is to assess the difference in severity of pruritus in subjects with cholestatic pruritus due to PBC or PSC treated with EP547 or placebo, as measured by change in weekly average WI-NRS after 6 weeks of randomized treatment, regardless of treatment discontinuation and use of prohibited and/or rescue medications.

The population targeted by the scientific question is defined via the inclusion and exclusion criteria as part of the protocol. A key aspect of eligibility is that subjects must have moderate-to-severe pruritus at baseline, as defined as a mean daily WI-NRS score of at least 4.

The primary endpoint to be obtained for each subject in this study to address the scientific question is the mean weekly WI-NRS score at Week 6.

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

14.3. Endpoints

14.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in WI-NRS at Week 6.

14.3.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Change from baseline in 5-D Itch Scale
- The proportion of subjects with improvement in pruritus as defined by PGI-C
- The proportion of subjects with improvement in pruritus severity from baseline as defined by change in PGI-S
- The proportion of subjects with a reduction in WI-NRS ≥2 from baseline
- The proportion of subjects with a reduction in WI-NRS ≥3 from baseline
- The proportion of subjects with a reduction in WI-NRS ≥4 from baseline
- The proportion of subjects with WI-NRS <4

14.3.3. Exploratory Endpoints

Exploratory endpoints include:

[redacted]

14.4. Sample Size Considerations

Assuming a standard deviation of 2.5 points, a sample size of 26 subjects per treatment group provides approximately [redacted]% power to detect a difference of [redacted] EP547 and placebo with respect to the change in weekly mean of the daily WI-NRS score based on a 2-sided, 2-sample comparison of means at the 5% significance level. With an anticipated early withdrawal rate of approximately 10%, the planned enrollment of 29 subjects per treatment group will ensure that at least 26 subjects complete the 6 weeks of double-blind treatment.

14.5. Demographic and Baseline Characteristics

Demographic data and baseline characteristics for the FAS, PP, and Safety Analysis Sets will be summarized by treatment group and overall using descriptive statistics.

14.6. Subject Disposition

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

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

14.7. Study Drug Usage and Compliance

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

Duration of treatment will also be summarized by treatment group for the Safety Analysis Set.

14.8. Efficacy and Pharmacodynamic Analysis

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

All efficacy and PD endpoints will be further evaluated during the Open-Label Extension Period. Summaries of change over time will evaluate both change from baseline (Visit 2 [Day 1]) and change from the initiation of the Open-Label Extension Period (Visit 6 [Week 6]).

For WI-NRS, a weekly score will be determined based on the average of all available daily scores of the week. The average WI-NRS score using the daily values from the week before the first dose of study drug will serve as the baseline score. For any given week, if more than 3 daily scores are missing, the weekly score is considered missing.

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

14.8.1. Analysis of the Primary Endpoint: Change from Baseline in Worst Itch Numeric Rating Scale (WI-NRS) at Week 6

WI-NRS data will be analyzed using a mixed effects model for repeated measures (MMRM) based on the data from all visits up to Visit 6 (Week 6). The model will include treatment, type of cholestatic disease (PBC, PSC), week, and treatment by week interaction as fixed effects, and baseline WI-NRS score as a covariate. The treatment effect will be the contrast between EP547 and placebo least-squares (LS) means. The LS means, treatment effect estimate, 95% confidence interval, and p-value will be presented. Testing of hypothesis is 2-sided at a 5% type I error level.

14.8.2. Analysis of Secondary and Pharmacodynamic Endpoints

All efficacy and PD endpoints described in Sections 14.3.2 and 14.3.3 will be summarized. Endpoints that are defined as continuous variables will be analyzed using a similar model as described for the primary efficacy endpoint if they are collected at multiple post-baseline visits; otherwise, they will be analyzed using analysis of covariance (ANCOVA) adjusted for randomization strata and baseline measurements of the response parameter of interest. Other endpoints defined as response proportions will be analyzed using a Cochran-Mantel-Haenszel test stratified by randomization strata.

Specifically for WI-NRS, data summaries will present scores, change from baseline, and response proportions by week. Percent change from baseline by week will also be summarized.

14.8.3. Primary and Sensitivity Analyses to Address Missing Data in the Primary Analysis

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

As a sensitivity analysis, the primary endpoint will also be analyzed with multiple imputation procedures (Rubin 1987). The SAP will provide full detail of the methodologies that will be used.

14.9. Safety Analysis

The Safety Analysis Set will be used for the summaries of the safety data according to the treatment received. Safety data will be summarized separately for the Double-Blind Treatment Period and Open-Label Extension Period by randomized Double-Blind treatment received.

The safety and tolerability of EP547 will be assessed by comparing the frequency, causality, and severity of AEs, as well as treatment discontinuations due to AEs. AEs will be coded using the MedDRA by System Organ Class and preferred term. AEs that begin after the first administration of study drug, or existing AEs that worsen after the first dose of study drug, are considered TEAEs. All AE summaries will include TEAEs, and all AEs will be presented in listings.

The World Health Organization (WHO) DRUG Dictionary will be used to categorize verbatim descriptions of non-study drug into the Anatomic Therapeutic Chemistry (ATC) classification system. Changes in vital signs, standard 12-lead ECGs, laboratory evaluations, and disease-specific assessments (Partial Mayo Score for subjects with UC and CDAI for subjects with CD) will be summarized by treatment group.

14.10. Pharmacokinetic Analysis

A descriptive summary of observed plasma concentrations of EP547 will be displayed by time and by treatment group. The plasma concentrations will be analyzed in the PK Set.

14.11. Subgroup Analyses

The primary efficacy endpoint and selected secondary efficacy endpoints will be analyzed based on age, gender, race/ethnicity, cholestatic liver disease type (PBC or PSC), presence of comorbidities (ie, IBD, CD, and/or UC), OCA use at baseline (yes or no), or other demographic/baseline characteristics, as appropriate. Additional details will be provided in the SAP.

14.12. Multiple Comparison/Multiplicity

This is the first study to explore the efficacy of EP547 for more than 7 days. The familywise error rate will be controlled for the primary efficacy endpoint at $\alpha = 5\%$. All other efficacy variables will be tested at the 0.05 level of significance without multiplicity adjustment.

14.13. Planned Interim, Primary, and Final Analysis

To address business needs, an interim analysis may be conducted after approximately 50% of randomized subjects have completed 4 weeks of randomized treatment. Only a limited number of study team members and senior management stakeholders comprising the internal DRT would review the results of the interim analysis of unblinded data from the Double-Blind Treatment Period. The interim analysis would evaluate the effect of EP547 on WI-NRS, select secondary endpoints, and safety.

Additional details about the interim analysis, if applicable, will be provided in the SAP, which is to be finalized before the database lock and unblinding of the study data, as applicable. The SAP will be amended if emerging data from the completed interim analysis leads to substantial change in the study protocol that has significant impact on the statistical analyses.

The primary analysis will be conducted after the last subject randomized has completed the Double-Blind Treatment Period to determine whether the primary efficacy endpoint of change from baseline in WI-NRS at Week 6 is statistically significant. Details regarding the primary analysis procedures, including database lock and unblinding procedures, will be finalized prior to analysis.

The final analysis will be conducted when all randomized subjects have completed the Open-Label Extension Period or are discontinued from the study, and the final database is locked.

15. QUALITY CONTROL AND DATA MANAGEMENT

15.1. 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

15.2. Data Management

Based on the final eCRF, a database will be designed and built to meet US Food and Drug Administration (FDA): 21 Code of Federal Regulations (CFR) 11 requirements. A Data

Management Plan will be written specifying the procedures that will be used for medical coding, SAE reconciliation, QC, laboratory data, and data cleaning that will occur for the study. A Data Validation Plan will be written and edit checks will be programmed and validated.

15.3. Monitoring

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

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

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

15.4. 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. The 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.

15.5. 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.

15.6. 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.

15.7. 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.

All clinical study documents must be retained in accordance with the ICH E6 guideline and in compliance with local data retention requirements.

15.8. 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 or designee 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 ICF should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF should receive IRB/IEC approval in advance of use. The subject will be informed in a timely manner if new information becomes available that may be relevant to the

subject's willingness to continue participation in the study. The communication of this information should be documented.

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.

15.9. Ethical Conduct of the Study

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

15.10. Institutional Review Board/Independent Ethics Committee

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

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

16. STUDY MANAGEMENT

16.1. 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 protocol deviations include the following:

- 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.

16.2. 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.

16.3. Change in Study Site Staff

If 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.

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APPENDIX A. SCHEDULE OF ASSESSMENTS

Assessment	Screening	Double-Blind Treatment					Open-Label Extension		Follow-Up	Early Study Term	Notes
Visit	Visit 1[a]	Visit 2 Day 1	Visit 3 Week 1	Visit 4 Week 2	Visit 5 Week 3	Visit 6 Week 6	Visit 7 Week 9	Visit 8 Week 12	Visit 9		
Study Day	Days -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 43	Day 64	Day 85	2 weeks (±3 days) after last dose	≤2 days after last dose	
Visit Window	None	None[b]	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days			
Visit Type for Hybrid Model[c]	Site only	Site only	Site or Remote	Site or Remote	Site or Remote	Site only	Site or Remote	Site only	Site or Remote	Site only	
General Assessments											
Informed consent	X										
Medical history	X										
Height	X										Measured with no shoes.
HIV, HAV, HBV, HCV, HEV serology	X										
IgG4	X										
Eligibility check	X	X									
Randomization via IWRS		X									Subjects will be randomized in a 1:1 ratio to 100 mg EP457 or placebo.
Dispense study drug / administer dose		X			X	X	X				Administer study drug QD as intact tablets with water. For remote visits, study drug dispensing will be conducted by a direct-to-patient courier service.
Collect study drug / assess study drug accountability and compliance					X	X	X	X		X	For remote visits, study drug collection will be conducted by a direct-to-patient courier service.
Provide questionnaire training	X										To be conducted before completing the daily WI-NRS for Day -14.

Assessment	Screening	Double-Blind Treatment					Open-Label Extension		Follow-Up	Early Study Term	Notes
Visit	Visit 1[a]	Visit 2 Day 1	Visit 3 Week 1	Visit 4 Week 2	Visit 5 Week 3	Visit 6 Week 6	Visit 7 Week 9	Visit 8 Week 12	Visit 9		
Study Day	Days -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 43	Day 64	Day 85	2 weeks (±3 days) after last dose	≤2 days after last dose	
Visit Window	None	None[b]	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days			
Visit Type for Hybrid Model[c]	Site only	Site only	Site or Remote	Site or Remote	Site or Remote	Site only	Site or Remote	Site only	Site or Remote	Site only	
Efficacy Assessments											
WI-NRS	X	X	X	X	X	X	X	X	X	X	To be completed daily, in the morning, and at the same time of day, from Day -14 to the Safety Follow-Up Visit. For days that coincide with a study visit (for Visit 2 and beyond), it is to be completed before the visit.
5-D Itch Scale		X				X		X	X	X	
PGI-C						X		X		X	
PGI-S		X				X		X		X	
[redacted]											
Pharmacodynamic Assessments											
Bile acids and heme metabolites		X				X					
Retained samples for future analysis		X			X	X	X	X			Blood and urine samples may be stored for up to 10 years after the completion of the study. See the Laboratory Manual for collection details.
Genotyping (optional)		X									
Kidney-related biomarkers		X	X	X	X	X	X	X	X	X	Blood and urine will be collected for analysis of kidney-related biomarkers as described in Section 11.3.
Safety Assessments											
Partial Mayo Score	X					X		X		X	To be completed for subjects with UC.
CDAI	X					X		X		X	To be completed for subjects with CD.

Assessment	Screening	Double-Blind Treatment					Open-Label Extension		Follow-Up	Early Study Term	Notes
Visit	Visit 1[a]	Visit 2 Day 1	Visit 3 Week 1	Visit 4 Week 2	Visit 5 Week 3	Visit 6 Week 6	Visit 7 Week 9	Visit 8 Week 12	Visit 9		
Study Day	Days -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 43	Day 64	Day 85	2 weeks (±3 days) after last dose	≤2 days after last dose	
Visit Window	None	None[b]	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days			
Visit Type for Hybrid Model[c]	Site only	Site only	Site or Remote	Site or Remote	Site or Remote	Site only	Site or Remote	Site only	Site or Remote	Site only	
TE (FibroScan)	X										If an eligible historical TE within 6 months of Screening is not available, TE procedures will be conducted at study sites. Scheduling of the TE assessment should be within the Screening window.
Serum pregnancy testing	X										Required for all females.
Urine pregnancy testing		X			X	X	X	X	X	X	Required for all females.
Physical examination	X							X		X	Symptom directed physical examinations to assess clinically significant changes from Screening or any new signs or symptoms may be conducted at other visits as determined by the Investigator based on subject complaint (Section 12.6).
Standard 12-lead ECG	X	X				X		X	X	X	To be performed in a supine position after ≥5 minutes of rest.
Vital signs	X	X	X	X	X	X	X	X	X	X	Includes sitting systolic and diastolic blood pressure, pulse rate, oxygen saturation, body temperature, and respiratory rate, measured after ≥5 minutes of rest. Also includes weight, which should be measured with no shoes on and using a calibrated scale throughout the study.
Chemistry, hematology, and urinalysis	X	X	X	X	X	X	X	X	X	X	Drawn after an overnight fast (≥8 hours) and predose as applicable. Refer to Section 12.8 for chemistry, hematology, and urinalysis assessments.
Coagulation	X	X	X	X	X	X	X	X	X	X	Refer to Section 12.8 for coagulation assessments.
Thyroid hormones		X				X		X		X	Refer to Section 12.8 for thyroid hormone assessments.

Assessment	Screening	Double-Blind Treatment					Open-Label Extension		Follow-Up	Early Study Term	Notes
Visit	Visit 1[a]	Visit 2 Day 1	Visit 3 Week 1	Visit 4 Week 2	Visit 5 Week 3	Visit 6 Week 6	Visit 7 Week 9	Visit 8 Week 12	Visit 9		
Study Day	Days -28 to -1	Day 1	Day 8	Day 15	Day 22	Day 43	Day 64	Day 85	2 weeks (±3 days) after last dose	≤2 days after last dose	
Visit Window	None	None[b]	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days			
Visit Type for Hybrid Model[c]	Site only	Site only	Site or Remote	Site or Remote	Site or Remote	Site only	Site or Remote	Site only	Site or Remote	Site only	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	Record all medications taken within 14 days before Screening and medications taken to treat a cholestatic disorder and any pruritus within 12 weeks and 4 weeks, respectively, before Screening.
AE assessment	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											
[redacted]											

AE = adverse event; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; [redacted]; ECG = electrocardiogram; [redacted]; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HEV = hepatitis E virus; HIV = human immunodeficiency virus; IgG4 = immunoglobulin G4; IWRS = Interactive Web Response System; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetic; [redacted]; TE = transient elastography; QD = once daily; Term = termination; UC = ulcerative colitis; WI-NRS = Worst Itch Numeric Rating Scale.

Subjects should fast for at least 8 hours before each dose of study drug and before study days that require a blood sample for assessment of chemistry, PK (predose), or completion of questionnaires.

[a] Visit 1 (Screening) may be conducted over more than 1 day but must be completed between Day -28 and Day -1.

[b] For the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. If enrollment/randomization is conducted on a separate day than dosing, the eligibility check should also be conducted during the same day as enrollment/randomization. Additionally, confirmation that WI-NRS has been completed daily and assessments of concomitant medication usage and AEs are to be conducted on both days (ie, date of enrollment/randomization and date of first dose). All other assessments listed are to be conducted on the date of first dose only.

[c] For the hybrid model, Visits 1, 2, 6, and 8 (Screening, Day 1, Week 6, and Week 12) and early termination (if applicable) must be completed at the study site. All other study visits may be conducted remotely, where allowed per regulatory/local requirements. For the decentralized model, all visits will be conducted remotely.

For remote visits for both the hybrid and decentralized models, the home health nurse visit at the subject's home or work and the telemedicine visit with the study site staff for a given study visit may be conducted on different days but must be within the allowable visit window. The home health nurse will complete the study assessments that the site is physically unable to complete remotely (eg, blood and lab sample collection, vital signs, ECGs); the site will complete all other study assessments remotely during the telemedicine visit. Additional information for conducting remote visits will be provided in study-specific manual(s).

APPENDIX B. WORST ITCH NUMERIC RATING SCALE (WI-NRS)

Please indicate the severity of the **WORST ITCHING** you experienced over the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
NO ITCHING										**WORST ITCHING IMAGINABLE**

APPENDIX C. 5-D ITCH SCALE

1. **Duration:** During the last 2 weeks, how many hours a day have you been itching?

Less than 6 hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree:** Please rate the intensity of your itching over the past 2 weeks.

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction:** Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability:** Rate the impact of your itching on the following activities over the last 2 weeks.

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/ Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/ School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/Clothing	☐
Thighs	☐	(eg, waistband, undergarment)	
Lower Legs	☐	Groin	☐
Tops of Feet/Toes	☐		

APPENDIX D. PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

How would you rate the severity of your itch in the past 7 days?

None

Mild

Moderate

Severe

APPENDIX E. PATIENT GLOBAL IMPRESSION OF CHANGE (PGI-C)

Compared to before you started taking the study drug, how would you rate your itch in the past 7 days:

Check one only:

Much Improved

Moderately Improved

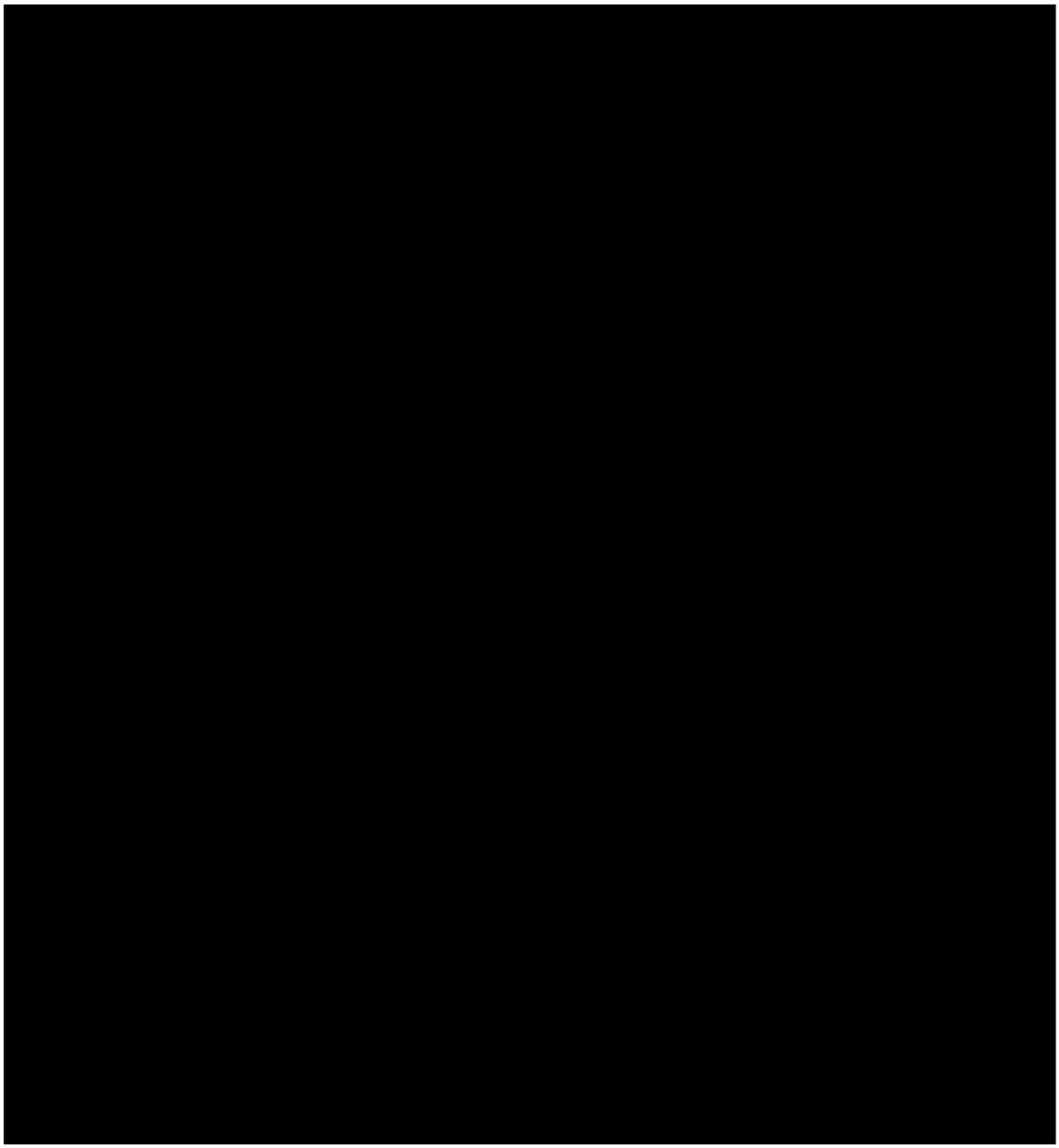
Minimally Improved

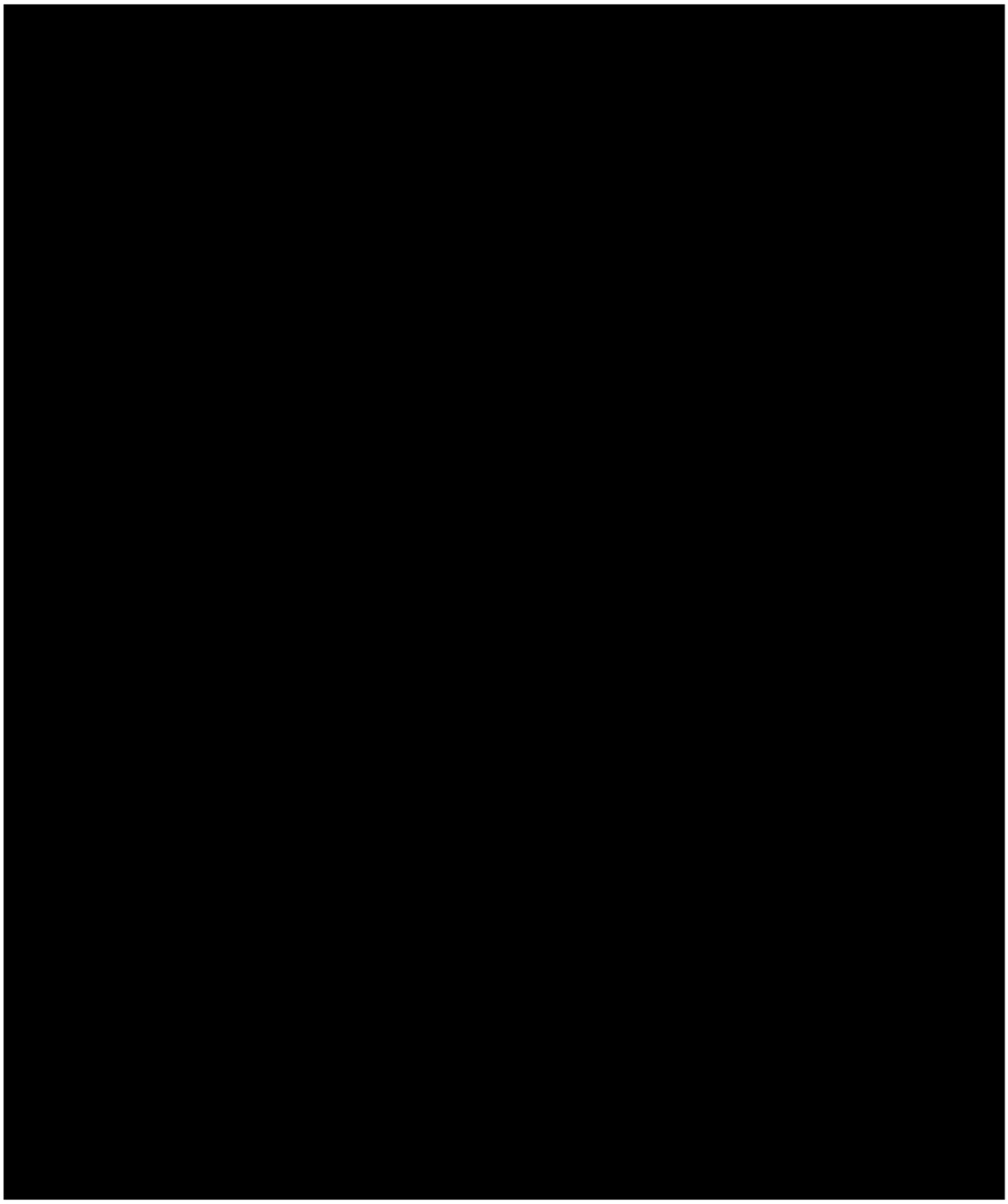
No Change

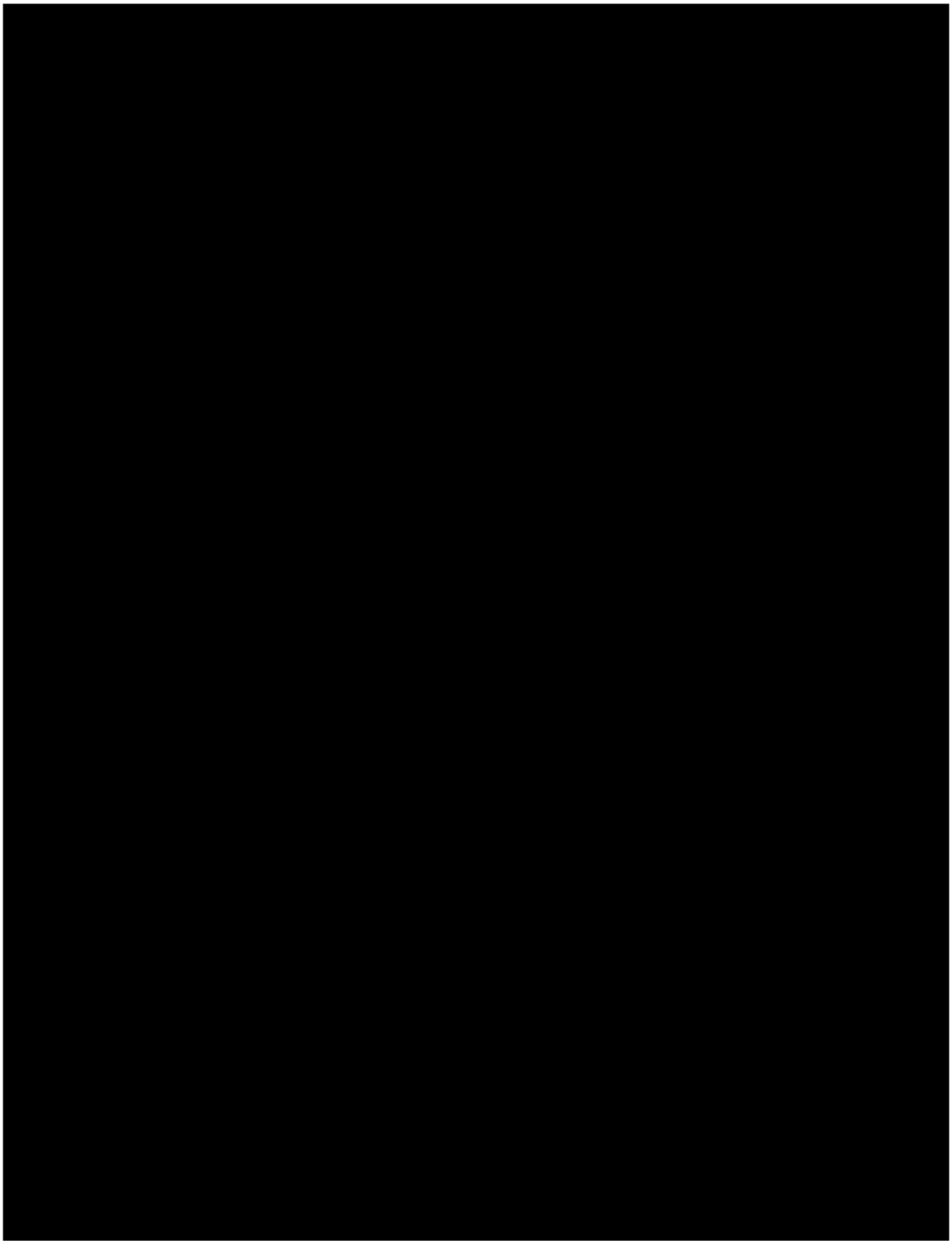
Minimally Worse

Moderately Worse

Much Worse







APPENDIX I. SUMMARY OF CHANGES BY AMENDMENT

Summary of Changes for Amendment 3.0 Dated 02 October 2023

Protocol EP-547-201 was amended primarily to:

- Adjust the eligibility criteria from an exclusionary estimated glomerular filtration rate of <90 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 and from a total bilirubin >ULN to >2.0 mg/dL (except for applicable subjects with Gilbert's syndrome) to further allow for EP262 to be evaluated in a study population that is meaningfully more characteristic of the broader population of pre-cirrhotic patients with PBC and PSC without impacting subject safety
- Change the contraceptive requirements in accordance with the Clinical Trial Facilitation Group recommendations related to contraception and pregnancy testing given the unlikely risk of human teratogenicity/fetotoxicity as determined from recently completed nonclinical studies
- Decrease the required duration of UDCA treatment from 1 year to 12 weeks for subjects treated with UDCA at Screening to increase eligibility for study participation without impacting safety
- [redacted]
- Remove the requirement for SARS-CoV-2 testing given recent advancements in the prevention and treatment of the virus
- Revise the description of the Worst Itch Numeric Rating Scale primary endpoint analysis to account for visit windows
- Remove the word "preliminary" when describing data from the recently completed Phase 1 Study EP-547-101
- Incorporate requests from the Personal Protection Committee West IV and the Agence nationale de sécurité du medicament et des produits de santé (ANSM) in France and the French Ethics Committee:
  - Describe and summarize the potential benefits and risks associated with study participation
  - Describe the ethical considerations for study conduct
  - Define the end of study as the date of the last study visit of the last subject in the study globally
  - Define women of childbearing potential

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

Section	Amendment 2.0	Amendment 3.0	Reason for Change
Title page Sponsor Statement	*New text*	**Study Acronym: PACIFIC Study**	The study acronym was added to further denote the study title.
Title Approval Page Procedures in Case of Emergency	[redacted], MD ~~President and~~ [redacted]	[redacted], MD [redacted]	Title was revised to reflect current role and responsibilities.
Synopsis (Inclusion Criteria) 8.1 Subject Inclusion Criteria	7. If female, must be willing to not donate eggs from Screening until ~~30 days~~ after the last dose of study drug and: a. Is surgically sterile; or b. Has been amenorrhoeic for ≥1 year without an alternative medical cause; or c. ~~Has a negative serum pregnancy test at Screening and agrees~~ to use ~~2 forms of contraception, which includes~~ at least 1 form of ~~highly effective and 1 effective~~ method of contraception from Screening until ~~30 days after~~ the last dose of study drug. ~~The following methods can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered highly effective~~ birth control methods: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation	7. If female, must **have a negative serum pregnancy test at Screening and** be willing to not donate eggs from Screening until after the last dose of study drug and: a. Is surgically sterile; or b. Has been amenorrhoeic for ≥1 year without an alternative medical cause; or c. **If of childbearing potential[1], must agree** to use at least 1 form of **an acceptable** method of contraception from Screening until the last dose of study drug. **Acceptable** birth control methods **include**: • **Barrier methods of contraception (eg, male condom, female condom, cervical cap or diaphragm, and contraceptive sponge)** • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Progestogen only hormonal contraception • Intrauterine device • Intrauterine hormone releasing system • Bilateral tubal occlusion	The ANSM requirement to define women of childbearing potential in the protocol was added. The contraceptive requirements were changed in accordance with the Clinical Trial Facilitation Group recommendations related to contraception and pregnancy testing given the unlikely risk of human teratogenicity/fetotoxicity as determined from recently completed nonclinical studies.

Section	Amendment 2.0	Amendment 3.0	Reason for Change
	• Progestogen only hormonal contraception ~~associated with inhibition of ovulation~~ • Intrauterine device • Intrauterine hormone releasing system • Bilateral tubal occlusion • Vasectomized partner • Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study drug), the reliability of which needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject ~~Effective methods of contraception include barrier methods of contraception (eg, male condom, female condom, cervical cap or diaphragm, and contraceptive sponge)~~	• Vasectomized partner • Sexual abstinence (complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study drug), the reliability of which needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject **[1]Women of childbearing potential are defined as those who are fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.**	
Synopsis (Inclusion Criteria) 8.1 Subject Inclusion Criteria	~~8. 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, or abstinence) from Screening through 30 days after the last dose of study drug~~	*Deleted text*	The contraceptive requirements were changed in accordance with the Clinical Trial Facilitation Group recommendations related to contraception and pregnancy testing given the unlikely risk of human teratogenicity/fetotoxicity as determined from recently completed nonclinical studies.

Section	Amendment 2.0	Amendment 3.0	Reason for Change
Synopsis (Inclusion Criteria) 8.1 Subject Inclusion Criteria	~~12~~. If currently taking ursodeoxycholic acid (UDCA), ~~must be treated for ≥1 year, and~~ must be on a stable dose of not more than 20 mg/kg/day for ≥12 weeks. If not currently taking UDCA, must not be treated with UDCA within 12 weeks before Screening or plan to be treated with UDCA during the study	**11**. If currently taking ursodeoxycholic acid (UDCA), must be on a stable dose of not more than 20 mg/kg/day for ≥12 weeks. If not currently taking UDCA, must not be treated with UDCA within 12 weeks before Screening or plan to be treated with UDCA during the study	Duration of UDCA treatment was decreased from 1 year to 12 weeks to increase eligibility for participation into the study without impacting safety.
Synopsis (Inclusion Criteria) 8.1 Subject Inclusion Criteria	~~14~~. If currently taking UDCA, ~~must be treated for ≥1 year, and~~ must be on a stable dose of not more than 23 mg/kg/day for ≥12 weeks. If not currently taking UDCA, must not be treated with UDCA within 12 weeks before Screening or plan to be treated with UDCA during the study	**13**. If currently taking UDCA, must be on a stable dose of not more than 23 mg/kg/day for ≥12 weeks. If not currently taking UDCA, must not be treated with UDCA within 12 weeks before Screening or plan to be treated with UDCA during the study	Duration of UDCA treatment was decreased from 1 year to 12 weeks to increase eligibility for participation into the study without impacting safety.
Synopsis (Exclusion Criteria) 8.2 Subject Exclusion Criteria	15. Has any of the following laboratory results at Screening: a. Total bilirubin >~~ULN~~; total bilirubin >~~ULN~~ is acceptable for subjects with medically documented Gilbert's syndrome if direct bilirubin is <0.3 mg/dL	15. Has any of the following laboratory results at Screening: a. Total bilirubin >**2.0 mg/dL**; total bilirubin >**2.0 mg/dL** is acceptable for subjects with medically documented Gilbert's syndrome if direct bilirubin is <0.3 mg/dL	To further allow for EP262 to be evaluated in a study population that is meaningfully more characteristic of the broader population of pre-cirrhotic patients with PBC and PSC without impacting subject safety.
Synopsis (Exclusion Criteria) 8.2 Subject Exclusion Criteria	16. Estimated glomerular filtration rate <~~90~~ mL/min/1.73 m^2 as determined by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening	16. Estimated glomerular filtration rate <**60** mL/min/1.73 m^2 as determined by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening	To further allow for EP262 to be evaluated in a study population that is meaningfully more characteristic of the broader population of pre-cirrhotic patients with PBC and PSC without impacting subject safety.
Synopsis (Exclusion Criteria) 8.2 Subject Exclusion Criteria	~~23. Positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription-polymerase chain reaction (RT-PCR) test at Screening~~	*Deleted text*	Testing for SARS-CoV-2 was removed given recent advancements in the prevention and treatment of the virus.

Section	Amendment 2.0	Amendment 3.0	Reason for Change
Synopsis (Worst Itch Numeric Rating Scale [WI-NRS]) 11.1.1 Worst Itch Numeric Rating Scale (WI-NRS)	The average WI-NRS score using the daily values from the week before the first dose of study drug (Visit 2 [Day 1]) will serve as the baseline score. The daily WI-NRS scores ~~from Day 36 through Day 43~~ will be averaged together for primary endpoint analyses.	The average WI-NRS score using the daily values from the week before the first dose of study drug (Visit 2 [Day 1]) will serve as the baseline score. The 7 daily WI-NRS scores **prior to Visit 6 (Week 6)** will be averaged together for primary endpoint analyses.	Using the 7 days prior to Visit 6 (Week 6) instead of a defined range of dates for the primary endpoint analyses allows for more flexibility as the date range may change depending on when the scheduled visit is conducted during the visit window.
5.3 EP547 and Study Rationale	Clinical safety and pharmacokinetics (PK) of EP547 are based on the ~~preliminary~~ results from Study EP-547-101, a first-in-human randomized, Phase 1 clinical study of oral single and multiple daily doses of EP547 in healthy subjects, in subjects with cholestatic disorders with pruritus, and in hemodialysis subjects with uremic pruritus.	Clinical safety and pharmacokinetics (PK) of EP547 are based on the results from Study EP-547-101, a first-in-human randomized, Phase 1 clinical study of oral single and multiple daily doses of EP547 in healthy subjects, in subjects with cholestatic disorders with pruritus, and in hemodialysis subjects with uremic pruritus.	"Preliminary" was removed as the Phase 1 Study EP-547-101 is complete and the results are final.
5.4 EP547 Dose Rationale	There were no ~~preliminary~~ safety or tolerability issues observed in the cholestatic pruritus population in the 75-mg single and 30-mg multiple dose evaluations.	There were no safety or tolerability issues observed in the cholestatic pruritus population in the 75-mg single and 30-mg multiple dose evaluations.	"Preliminary" was removed as the Phase 1 Study EP-547-101 is complete and the results are final.
5.5 Summary of Benefits and Risks	*New section added*	**5.5. Summary of Benefits and Risks** **5.5.1. Benefit Summary** **This study is investigating a potential benefit of EP547 to relieve or lessen cholestatic itch, which may also be associated with an improvement in fatigue, quality of sleep, and overall quality of life. EP547 is not intended to improve a subject's cholestatic liver disease.** **5.5.2. Risk Summary and Mitigation Strategy**	This change reflects the French Ethics Committee requirement to include a benefit:risk analysis.

Section	Amendment 2.0	Amendment 3.0	Reason for Change
		Safety results from the Phase 1 Study EP-547-101 did not reveal any adverse safety trends, and all doses tested were well tolerated. **Nonclinical safety pharmacology studies indicate no undesirable pharmacodynamic (PD) effects on respiratory, cardiovascular, and central nervous system (CNS) physiological functions when EP547 is administered at doses within and above the predicted therapeutic range. EP547 does not inhibit human ether-à-go-go-related gene (hERG) or NaV1.5, suggesting a low risk for electrophysiologic effects on the heart. In a standard battery of genotoxicity studies, EP547 was determined to be neither mutagenic nor clastogenic. Additionally, in vitro testing determined that EP547 is not phototoxic.** **Preliminary testing in human biomaterials suggests a low potential for most clinically significant perpetrator drug-drug interactions (DDIs) based on active transport or cytochrome P450 (CYP) inhibition/induction. Initial data suggest some potential for induction of CYP2B6 by EP547. The potential for inhibition of CYP2B6 and CYP2C8, and inhibition of breast cancer resistance protein (BCRP) organic anion transporter 1 (OAT1), exists at clinical doses of EP547.** [redacted] **Given the unknown clinical relevance of these observations, concomitant**	

Section	Amendment 2.0	Amendment 3.0	Reason for Change
		medications that are dependent on BCRP, OAT1, CYP2B6, or CYP2C8 for elimination should be carefully considered. Additionally, concomitant medications that are substrates for BCRP, OAT1, CYP2B6, or CYP2C8 should be monitored appropriately, and those with a narrow therapeutic window should have the timing of administration considered or the medication substituted if its use is prohibited in this study; concomitant medications that are inhibitors of OAT3 should be thoughtfully weighed for use with EP547 (Section 8.4.1). [redacted] **Notably, no adverse changes in serum chemistry markers (eg, creatinine and blood urea nitrogen [BUN]) were observed with daily doses of EP547 as high as 225 mg for 1 week in healthy volunteers in the Phase 1 study. Nonetheless, out of precaution, subjects participating in this study are required to have an estimated glomerular filtration rate ≥60 mL/min/1.73 m^2 as determined by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening, and medications with known nephrotoxic potential are prohibited from use during the study (Section 8.4.1). Additionally, any clinically meaningful new, worsening from baseline, or abnormal laboratory findings or symptoms suggestive of acute kidney injury (AKI) (eg, 'blood urea increased' or**	

Section	Amendment 2.0	Amendment 3.0	Reason for Change
		'protein urine present' adverse events [AEs] as identified by the Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ] 'Acute renal failure') will be considered AEs of special interest (AESI, Section 12.1.5). Subjects will be closely monitored for observations of AKI, and study drug may be interrupted for subjects who experience elevations in serum creatinine levels according to the algorithm described in Section 12.13.4. **5.5.3. Overall Benefit:Risk Conclusion** **Overall, the safety measures to be employed and the clinical experience to date with EP547 suggest minimal risk to subjects participating in Study EP-547-201. Although a variety of interventions for cholestatic pruritus have been explored, there is currently no medication approved for this indication in adults, and the need for improved treatments remains high. Therefore, development of additional safe and effective, mechanistically based therapeutic options for this condition is essential. If determined to be effective in this study, EP547 may ultimately have the potential to offer substantial relief for patients suffering from cholestatic pruritus, including those enrolled in this study. Considering all available safety information and measures taken to minimize risk to subjects, the overall benefit-risk profile of EP547 is deemed to be acceptable for the conduct of Study EP-547-201.**	

Section	Amendment 2.0	Amendment 3.0	Reason for Change
7.2 End of Study	*New section added*	**7.2. End of Study** **A subject is considered to have completed the study if he/she has completed all phases of the study, including the last study visit (ie, the Follow-Up Visit [Visit 9]).** **The end of the study is defined as the date of the last study visit of the last subject in the study globally.**	This change reflects the ANSM requirement to define the end of study in the protocol.
[redacted]			

Section	Amendment 2.0	Amendment 3.0	Reason for Change
8.4.1. Prohibited Concomitant Medications	Subjects taking immunosuppressant/immunomodulating agents may not receive live, attenuated vaccines during participation in this study. Medications with known nephrotoxic potential (eg, aminoglycosides, contrast dye, bisphosphonates, and nonsteroidal anti-inflammatory drugs) are prohibited from use during the study as are some medications that are substrates for BCRP, OAT1, CYP2B6, or CYP2C8. Table 3 lists examples of excluded medications that are substrates for BCRP, OAT1, CYP2B6 or CYP2C8. Table 3: Examples of Excluded Medications that are Substrates for BCRP, OAT1, CYP2B6, or CYP2C8	Subjects taking immunosuppressant/immunomodulating agents may not receive live, attenuated vaccines during participation in this study. Medications with known nephrotoxic potential (eg, aminoglycosides, contrast dye, bisphosphonates, and nonsteroidal anti-inflammatory drugs) are prohibited from use during the study as are some medications that are [redacted] *Added fibrates (eg, gemfibrozil), immunomodulators (eg, teriflunomide), and uricosurics (eg, probenecid) as examples of OAT3 inhibitors to Table 3.*	Updated to reflect the results from a recently completed nonclinical study suggesting that inhibition of OAT3 could increase exposure of EP3583.
9.4.1.1. Visit 1 (Day -28 to Day -1)	~~• SARS-CoV-2 RT-PCR test~~	*Deleted text*	Testing for SARS-CoV-2 was removed given recent advancements in the prevention and treatment of the virus.
12.11 SARS-CoV-2 Testing (*Deleted heading in Amendment 3.0*)	~~12.11 SARS-CoV-2 Testing~~ ~~Subjects will be tested for SARS-CoV-2 (COVID-19) at Screening via RT-PCR test. A positive test result for COVID-19 will exclude the subject from enrolling in the study, even if the subject is asymptomatic, regardless of vaccination status.~~	*Deleted text*	Testing for SARS-CoV-2 was removed given recent advancements in the prevention and treatment of the virus.

Section	Amendment 2.0	Amendment 3.0	Reason for Change
12.13.1 Potential Side Effects (*Previously 12.14.1 in Amendment 2.0*)	~~Preliminary~~ safety results from the Phase 1 Study EP-547-101 did not reveal any safety trends, and there were no TEAEs assessed as expected with the use of EP547. Refer to the Investigator's Brochure for additional EP547 information regarding potential side effects.	Safety results from the Phase 1 Study EP-547-101 did not reveal any safety trends, and there were no TEAEs assessed as expected with the use of EP547. Refer to the Investigator's Brochure for additional EP547 information regarding potential side effects.	"Preliminary" was removed as the Phase 1 Study EP-547-101 is complete and the results are final.
15.9 Ethical Conduct of the Study	*New section added*	**15.9. Ethical Conduct of the Study** **This study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP, ICH guidelines, other applicable regulatory requirements (eg, local requirements), the study protocol, and where applicable, Sponsor and/or CRO standard operating procedures.**	This change reflects the French Ethics Committee requirement to include references to the Declaration of Helsinki and Good Clinical Practice.
Appendix A. Schedule of Assessments	*SARS-CoV-2 RT-PCR testing was to be completed at Visit 1*	*SARS-CoV-2 RT-PCR testing was removed from Visit 1 and the definitions for SARS-CoV-2 and RT-PCR were removed from the list of abbreviations in the table footnotes.*	Testing for SARS-CoV-2 was removed given recent advancements in the prevention and treatment of the virus.
Appendix E. Patient Global Impression of Change (PGI-C)	Check one ~~box~~ only:	Check one only:	Revised to better reflect the information presented.

Summary of Changes for Amendment 2.0 Dated 20 April 2022

Protocol EP-547-201 was amended to increase opportunities for remote visits to ease subject burden associated with participating in this clinical study. Previously, subjects were able to attend study visits at a physical study site as well as remotely (hybrid model) where allowed per regulatory/local requirements. Amendment 2.0 introduces another option that allows all visits to be conducted remotely at a virtual site (decentralized model) where allowed per regulatory/local requirements. Changes to support the decentralized model include:

- Revising Visit 2 (Day 1) for subjects participating in the decentralized model so that enrollment/randomization and first dose can occur on different days to allow time for study drug to be delivered to a subject's home
- Clarifying that historical Fibroscan® assessments within 6 months of Screening are permitted to assess eligibility
- Allowing transport of study drug from a central drug depot to the subject's home to streamline drug transport for remote visits
- Removing the need to use a stadiometer to measure height as this device may not be readily available for use at remote visits

Refinements to the statistical assumptions allowed for a reduction in sample size from 62 subjects to 58 subjects for analysis of the primary endpoint. The enrollment target for subjects with cholestatic pruritus due to PBC and the enrollment cap for subjects receiving treatment with obeticholic acid at baseline were removed as they are not required to establish proof-of-concept and may limit the ability of the data to inform the population characteristics of subsequent clinical studies. Study drug storage conditions were also updated to match instructions on the labelling.

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

Section	Amendment 1.0	Amendment 2.0	Reason for Change
Global	~~site~~ visit	study visit	
Global	*Follow-up visit was referred to by name and not assigned a visit number.*	*The follow-up visit is now also referred to as Visit 9.*	A visit number for the follow-up visit was assigned for completeness and consistency with the naming convention of the other study visits.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
Global	*New text.*	IgG4	Given that IgG4 serum concentrations are required to determine eligibility, the assessment at Screening was added throughout for completeness.
Global	[redacted]	[redacted]	[redacted]
Global	SAE/AESI Report Form or SAE Report Form	SAE/AESI/Grade 3+ Report Form	The name of the report form for events that require reporting within 24 hours of the Investigator's knowledge was revised to include CTCAE Grade 3 (refer to Section 12.1.2 for new reporting requirement).
Synopsis (Methodology) 7.1. Overall Study Design	*New text.*	**Where allowed per regulatory/local requirements, subjects will be able to attend study visits at a physical study site as well as remotely (hybrid model) or at a virtual site where all visits will be conducted remotely (decentralized model). For both the hybrid and decentralized models, a home health nurse visit at the subject's home or work and a telemedicine visit with the study site staff (eg, smartphone or computer) will be arranged to conduct procedures for each remote study visit.**	Text was added to introduce the potential for remote participation earlier in the synopsis and protocol.
Synopsis (Methodology) 7.1. Overall Study Design	Approximately ~~62~~ subjects will be randomized to receive either 100 mg doses of EP547 or placebo orally (PO) once daily (QD) in a 1:1 ratio.	Approximately **58** subjects will be randomized to receive either 100 mg doses of EP547 or placebo orally (PO) once daily (QD) in a 1:1 ratio.	Refinements to the statistical assumptions allowed for a smaller sample size for analysis of the primary endpoint.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
Synopsis (Methodology Figure) 7.1. Overall Study Design (Figure 1)	*New footnote.*	**[a] For the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. When enrollment/randomization and first dose of study drug are on separate days, the first dose of study drug is considered Day 1.**	Text was added to allow time to transport study drug between the central drug depot and the subject's home after randomization for subjects participating in the decentralized model.
Synopsis (Double-Blind Treatment Period) 7.1.2. Double-Blind Treatment Period	Visit 2 (Day 1) will not have a visit window; ~~all~~ other visits in the Double-Blind Treatment Period will have a visit window of ±3 days.	Visit 2 (Day 1) will not have a visit window; **however, for the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. When enrollment/randomization and first dose of study drug are on separate days, the first dose of study drug is considered Day 1.** All other visits in the Double-Blind Treatment Period will have a visit window of ±3 days.	Text was added to allow time to transport study drug between the central drug depot and the subject's home after randomization for subjects participating in the decentralized model.
Synopsis (Double-Blind Treatment Period) 7.1.2. Double-Blind Treatment Period	~~Subjects are to return to the site to complete scheduled assessments. However, a home health nurse visit to the subject's home and a telehealth visit to communicate with study site staff using technology (eg, smartphone or computer) in lieu of a site visit may be permitted at certain visits if the subject is unable to visit the site but is willing to continue in the study.~~	*Deleted text.*	The text was deleted in this section and a revised version was included earlier in the synopsis and protocol.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
Synopsis (Number of Subjects [Planned]) 7.2. Number of Subjects	Approximately ~~62~~ subjects with cholestatic pruritus due to PBC or PSC will be randomized in the study. ~~At least 52 subjects with cholestatic pruritus due to PBC will be randomized. The number of subjects receiving treatment with obeticholic acid (OCA) at baseline will be capped at approximately 10 subjects.~~	Approximately **58** subjects with cholestatic pruritus due to PBC or PSC will be randomized in the study.	Refinements to the statistical assumptions allowed for a smaller sample size for analysis of the primary endpoint. Enrollment caps and targets for various populations were removed as they are not required to establish proof-of-concept and may limit the ability of the data to inform the population characteristics of subsequent clinical studies.
Synopsis (Exclusion Criteria) 8.2. Subject Exclusion Criteria	4. Evidence of compensated or decompensated cirrhosis based on ANY of the following: a. Historical liver biopsy demonstrating cirrhosis b. Liver stiffness as assessed by a FibroScan® score of ≥16.9 kPa for subjects with PBC or ≥14.4 kPa for subjects with PSC	4. Evidence of compensated or decompensated cirrhosis based on ANY of the following: a. Historical liver biopsy demonstrating cirrhosis b. Liver stiffness as assessed by a FibroScan® score of ≥16.9 kPa for subjects with PBC or ≥14.4 kPa for subjects with PSC **within 6 months of Screening**	Allowing Fibroscan® to be conducted within 6 months before Day 1 will increase eligibility for participation into the study without impacting safety and is commonly used in clinical studies.
Synopsis (Study Drug Storage) 10.3. Study Drug Storage	The study drug tablets should be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F).	The study drug tablets should be stored at controlled room temperature, 20°C to 25°C (68°F to 77°F), **with excursions allowed between 15°C to 30°C (59°F to 86°F)**.	Study drug storage conditions were updated to match instructions on the labelling.
Synopsis (Study Drug Dispensing and Accountability) 10.5. Study Drug Dispensing and Accountability	Subjects should be instructed to retain the study drug kit (including blister cards/wallets), even if empty, and to return it and any remaining study drug to the study site at their next visit.	Subjects should be instructed to retain the study drug kit (including blister cards/wallets), even if empty, and to return it and any remaining study drug to the study site at their next visit **or to a direct-to-patient courier service**.	The text was updated to allow transport of study drug kits between the subject's home and the central drug depot using a courier to better support remote visits.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
Synopsis (Discontinuation of Study Drug) 8.5.1. Discontinuation of Study Drug	~~If the subject is unable to visit the site but is willing to continue in the study, a home health nurse visit to the subject's home and a telehealth visit to communicate with study site staff using technology (eg, smartphone or computer) in lieu of a site visit may be permitted at certain visits.~~	*Deleted text.*	The text was deleted as this amendment allows for more opportunities to conduct visits remotely, regardless of discontinuation status.
Synopsis (Worst Itch Numeric Rating Scale [WI-NRS]:) 11.1.1. Worst Itch Numeric Rating Scale (WI-NRS) 14.8. Efficacy and Pharmacodynamic Analysis	The average WI NRS score using the daily values from the week before ~~randomization~~ will serve as the baseline score.	The average WI NRS score using the daily values from the week before **the first dose of study drug (Visit 2 [Day 1])** will serve as the baseline score.	Given that enrollment/ randomization and first dose of study drug may occur on different days for subjects participating in the decentralized model, the text was revised to clarify how the baseline score will be calculated.
Synopsis (Adverse Events of Special Interest) Synopsis (Observation for Acute Kidney Injury) 12.1.5. Adverse Events of Special Interest 12.14.4. Observation for Acute Kidney Injury	[redacted]		

<table>
<tr><th>Section</th><th>Amendment 1.0</th><th>Amendment 2.0</th><th>Reason for Change</th></tr>
<tr><td>Synopsis (Sample Size Considerations)
14.4. Sample Size Considerations</td><td>Assuming a standard deviation of 2.5 points, a sample size of 26 subjects per treatment group provides approximately 80% power to detect a difference of 2.0 points between EP547 and placebo with respect to the change in weekly mean of the daily WI-NRS score based on a 2-sided, 2-sample comparison of means at the 5% significance level. With an anticipated early withdrawal rate of approximately ~~5%~~, the planned enrollment of ~~31~~ subjects per treatment group will ensure that at least 26 subjects complete the 6 weeks of double-blind treatment.</td><td>Assuming a standard deviation of 2.5 points, a sample size of 26 subjects per treatment group provides approximately [redacted]% power to detect a [redacted] EP547 and placebo with respect to the change in weekly mean of the daily WI-NRS score based on a 2-sided, 2-sample comparison of means at the 5% significance level. With an anticipated early withdrawal rate of approximately 10%, the planned enrollment of 29 subjects per treatment group will ensure that at least 26 subjects complete the 6 weeks of double-blind treatment.</td><td>Refinements to the statistical assumptions allowed for a smaller sample size for analysis of the primary endpoint.</td></tr>
<tr><td>5.3. EP547 and Study Rationale</td><td>Study EP-547-201 is designed to evaluate the effects of EP547 on reducing the sensation of pruritus over 6 weeks in approximately ~~62~~ subjects diagnosed with cholestatic pruritus due to PBC or PSC.</td><td>Study EP-547-201 is designed to evaluate the effects of EP547 on reducing the sensation of pruritus over 6 weeks in approximately 58 subjects diagnosed with cholestatic pruritus due to PBC or PSC.</td><td>Refinements to the statistical assumptions allowed for a smaller sample size for analysis of the primary endpoint.</td></tr>
<tr><td>9.1. Treatment Assignment (Table 4)</td><td>
<table>
<tr><th>Study Period</th><th>Study Days</th><th>Approx. No. of Subjects</th><th>Treatment Designation</th><th>Study Drug Dose Regimen</th></tr>
<tr><td>Screening</td><td>Day -28 to Day -1</td><td>~~62~~</td><td>Not applicable</td><td>None</td></tr>
<tr><td rowspan="2">6-Week, Double-Blind Treatment</td><td rowspan="2">Day 1 to Day 42</td><td>~~31~~</td><td>100mgEP547</td><td>One 25 mg EP547 tablet and One 75 mg EP547 tablet PO QD</td></tr>
<tr><td>~~31~~</td><td>Placebo</td><td>Two placebo tablets PO QD</td></tr>
<tr><td>6-Week, Open-Label Extension</td><td>Day 43 to Day 85</td><td>~~62~~</td><td>100mgEP547</td><td>One 25 mg EP547 tablet and One 75 mg EP547 tablet PO QD</td></tr>
<tr><td>2-Week Safety Follow-Up</td><td>2 weeks after last study drug dose</td><td>~~63~~</td><td>Not applicable</td><td>None</td></tr>
</table>
</td><td>
<table>
<tr><th>Study Period</th><th>Study Days</th><th>Approx. No. of Subjects</th><th>Treatment Designation</th><th>Study Drug Dose Regimen</th></tr>
<tr><td>Screening</td><td>Day -28 to Day -1</td><td>58</td><td>Not applicable</td><td>None</td></tr>
<tr><td rowspan="2">6-Week, Double-Blind Treatment</td><td rowspan="2">Day 1 to Day 42</td><td>29</td><td>100mgEP547</td><td>One 25 mg EP547 tablet and One 75 mg EP547 tablet PO QD</td></tr>
<tr><td>29</td><td>Placebo</td><td>Two placebo tablets PO QD</td></tr>
<tr><td>6-Week, Open-Label Extension</td><td>Day 43 to Day 85</td><td>58</td><td>100mgEP547</td><td>One 25 mg EP547 tablet and One 75 mg EP547 tablet PO QD</td></tr>
<tr><td>2-Week Safety Follow-Up</td><td>2 weeks after last study drug dose</td><td>58</td><td>Not applicable</td><td>None</td></tr>
</table>
</td><td>Refinements to the statistical assumptions allowed for a smaller sample size for analysis of the primary endpoint.</td></tr>
</table>

Section	Amendment 1.0	Amendment 2.0	Reason for Change
9.4. Study Visits Appendix A. Schedule of Assessments	*New text.*	**For the hybrid model, Visits 1, 2, 6, and 8 (Screening, Day 1, Week 6, and Week 12) and early termination (if applicable) must be completed at the study site. All other study visits may be conducted remotely, where allowed per regulatory/local requirements. For the decentralized model, all visits will be conducted remotely.** **For remote visits for both the hybrid and decentralized models, the home health nurse visit at the subject's home or work and the telemedicine visit with the study site staff for a given study visit may be conducted on different days but must be within the allowable visit window. The home health nurse will complete the study assessments that the site is physically unable to complete remotely (eg, blood and lab sample collection, vital signs, ECGs); the site will complete all other study assessments remotely during the telemedicine visit. Additional information for conducting remote visits will be provided in study-specific manual(s).**	Added which visits can conducted remotely for the hybrid and decentralized models as well as which assessments the home health nurse and study site are responsible for remote visits for both the hybrid and decentralized models for completeness.
9.4.1.1. Visit 1 (Day -28 to Day -1)	• Transient elastography (TE; FibroScan)	Transient elastography (TE; FibroScan; **if an eligible historical TE is not available within 6 months of Screening)**	Allowing Fibroscan® to be conducted within 6 months before Day 1 will increase eligibility for participation into the study without impacting safety and is commonly used in clinical studies.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
9.4.2.1. Visit 2 (Day 1) Appendix A. Schedule of Assessments	*New text.*	**For the decentralized model, enrollment/randomization and the first dose of study drug may be separated by up to 10 additional calendar days to allow for home delivery of study drug. If enrollment/randomization is conducted on a separate day than dosing, the eligibility check should also be conducted during the same day as enrollment/randomization. Additionally, confirmation that WI-NRS has been completed daily and assessments of concomitant medication usage and AEs are to be conducted on both days (ie, date of enrollment/randomization and date of first dose). All other assessments listed above are to be conducted on the date of first dose only.**	The schedule of assessments was revised to account for the completion of enrollment/randomization and first dose of study drug on different calendar days for subjects participating in the decentralized model.
10.6. Study Drug Handling and Disposal	~~Where allowed, to~~ support ~~home~~ visits ~~by a home health nurse~~, the use of a direct-to-patient courier service to transport study drug between the study site and subject's home may be arranged ~~at certain visits~~. The courier will be asked to collect the study drug kit dispensed by the study site staff and deliver it to the subject's home. The courier may also be asked to collect the used study drug kit with any unused study drug from the subject to be returned to the site for accountability ~~with~~ reconciliation ~~to be completed by the study site staff~~.	**To** support **remote study** visits **for the hybrid and decentralized models**, the use of a direct-to-patient courier service to transport study drug between the study site **or central drug depot** and **the** subject's home may be arranged. The courier will be asked to collect the study drug kit dispensed by the study site staff **or central drug depot** and deliver it to the subject's home. The courier may also be asked to collect the used study drug kit with any unused study drug from the subject to be returned to the site **or central drug depot** for accountability **and** reconciliation. **Additional study drug handling and disposal information for remote visits will be provided in study-specific manual(s).**	The text was updated to allow transport of study drug between the central drug depot and the subject's home to better support remote visits.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
11.4. Height Appendix A. Schedule of Assessments	Height will be measured ~~using a stadiometer~~ with no shoes.	Height will be measured with no shoes.	The method in which height is to be measured was removed as stadiometers may not be readily available for use at remote visits.
12. Safety Assessments	*New text.*	**For the decentralized model, the Investigator may require the subject to have an in-person consultation with a physician after virtually conducting safety assessments, if deemed necessary.**	Allowing the Investigator to require the subject to have an in-person consultation with a physician for any subject after virtually conducting safety assessments for the decentralized model was added to ensure subject safety.
12.1.2. Determining Severity of Adverse Events	*New text.*	**All CTCAE Grade 3 or higher must be reported to the Sponsor or designee using the SAE/AESI/Grade 3+ Report Form, according to the timelines described for SAEs in Section 12.2.2.**	Reporting requirements for CTCAE Grade 3 or higher was specified as the DMC will make a determination of relatedness for all CTCAE Grade 3 or higher.
12.6. Physical Examinations	*New text.*	**For the decentralized model, the Investigator, assisted by the mobile nurse, will conduct physical examinations per protocol via telemedicine during a videoconference session.**	The logistics for conducting the physical exam for the decentralized model was added for completeness.
12.10. Transient Elastography	TE procedures will be conducted at study sites with the appropriate equipment and by adequately trained study site staff.	**If an eligible historical TE within 6 months of Day 1 is not available,** TE procedures will be conducted at study sites with the appropriate equipment and by adequately trained study site staff. **Scheduling of the TE assessment should be within the Screening window (Day -28 to Day -1).**	Allowing historical Fibroscan® assessments and expanding the Fibroscan® assessment window to 6 months before Screening will ease overall burden and scheduling constraints.

Section	Amendment 1.0	Amendment 2.0	Reason for Change
14.9. Safety Analysis	Changes in vital signs, standard 12 lead ECGs, laboratory evaluations, and disease-specific assessments (Partial Mayo Score for subjects with UC and CDAI for subjects with CD) will be ~~compared across doses and to placebo~~.	Changes in vital signs, standard 12 lead ECGs, laboratory evaluations, and disease-specific assessments (Partial Mayo Score for subjects with UC and CDAI for subjects with CD) **will be summarized by treatment group**.	The text was corrected to reflect the intended analysis of safety data.
Appendix A. Schedule of Assessments	*Next text.*	*Added which visits can conducted remotely for the hybrid model.*	Added which visits can be conducted remotely for the hybrid model for completeness.
Appendix A. Schedule of Assessments	*New text.*	**If a historical TE within 6 months of Day 1 is not available, TE procedures will be conducted at study sites. Scheduling of the TE assessment should be within the Screening window.**	Allowing historical Fibroscan® assessments and expanding the Fibroscan® assessment window to 6 months before Screening will ease overall burden and scheduling constraints.
Appendix A. Schedule of Assessments	*New text.*	**For remote visits, study drug dispensing will be conducted by a direct-to-patient courier service.**	Added to reflect study drug dispensing procedures for remote visits.
Appendix A. Schedule of Assessments	*New text.*	**For remote visits, study drug collection will be conducted by a direct-to-patient courier service.**	Added to reflect study drug collection procedures for remote visits.

Summary of Changes for Amendment 1.0 Dated 17 November 2021

Protocol EP-547-201 was amended to implement changes to the study population, include additional safety monitoring, and incorporate operational changes, which include the following:

Study Population Changes

- Modified the inclusion/exclusion criteria to refine subject selection by excluding subjects with compensated cirrhosis, impaired renal function, moderate alcohol consumption, a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test, and active hepatitis A virus (HAV) or hepatitis E virus (HEV) infections

Changes to Safety Monitoring

- Added individual and overall study stopping criteria
- Added screening assessments for cirrhosis (Fibroscan®), SARS-CoV-2, HAV, and HEV
- Added thyroid-stimulating hormone and free thyroxine monitoring
- Included a Data Monitoring Committee to independently determine adverse event relatedness and advise the Sponsor regarding potential modifications to the study protocol, suspension of dosing, or study termination
- Added total lymphocyte count monitoring and additional blood lymphocyte population assessments for subjects who develop lymphopenia
- Requested that Investigators attempt to collect a blood pharmacokinetic sample at an unscheduled visit as part of serious adverse event follow-up to assess drug levels at the time of the event
- Added that all abnormal complete blood count, serum creatinine, blood urea nitrogen, and urine albumin to creatinine ratio values during treatment be followed as deemed clinically necessary by the Investigator

Operational Changes

- Removed patient interviews, global metabolomic analysis, autotaxin, lysophosphatidic acid, and cytokines markers from the study as these pharmacodynamic assessments are not required to establish early proof of concept
- Removed the Child-Pugh assessment as it is no longer relevant given that patients with cirrhosis are no longer eligible for study participation
- Replaced daily dosing diaries with dosing records to allow more flexibility in recording subject dosing
- Added instructions for use of a direct-to-patient courier service to support drug dispensing during home health nurse visits

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

Section	Original	Amendment 1.0	Reason for Change
Global	*Included patient interviews, global metabolomic analysis, autotaxin, lysophosphatidic acid, and cytokines markers (eg, interleukin 8 [IL-8], tumor necrosis factor alpha [TNF-α]) as part of the pharmacodynamic assessments*	*Removed patient interviews, global metabolomic analysis, autotaxin, lysophosphatidic acid, and cytokines markers (eg, interleukin 8 [IL-8], tumor necrosis factor alpha [TNF-α]) from the list of pharmacodynamic assessments*	Given that the primary purpose of EP-547-201 is to establish early proof of concept, these pharmacodynamic assessments have been removed but may be incorporated into a future study.
Synopsis (Double-Blind Treatment Period) 7.1.2 Double-Blind Treatment Period	However, a home health nurse visit to the subject's home and a telehealth visit to communicate with study site staff using technology (eg, smartphone or computer) in lieu of a site visit may be permitted ~~on a case-by-case basis~~ if the subject is unable to visit the site but is willing to continue in the study.	However, a home health nurse visit to the subject's home and a telehealth visit to communicate with study site staff using technology (eg, smartphone or computer) in lieu of a site visit may be permitted at certain visits if the subject is unable to visit the site but is willing to continue in the study.	Using "case-by-case basis" for allowing alternative visit types in lieu of a site visit was removed as it was thought to discourage their use. Because health nurse visits are feasible only at specific visits based on the required procedures, this clarification was added to the protocol.
Synopsis (Inclusion Criteria) 8.1 Subject Inclusion Criteria	3. Has a mean daily WI-NRS score indicative of moderate to severe pruritus (score ≥4) ~~as recorded using a study-issued electronic device or application (app)~~ during Screening (Day -7 through Day -1); data from at least 4 of the 7 days are required to be considered an acceptable profile	3. Has a mean daily WI-NRS score indicative of moderate to severe pruritus (score ≥4) during Screening (Day -7 through Day -1); data from at least 4 of the 7 days are required to be considered an acceptable profile	The specificity of using a study-issued electronic device or app was removed to allow more flexibility for how questionnaire results are to be recorded.

Section	Original	Amendment 1.0	Reason for Change
Synopsis (Exclusion Criteria) 8.2 Subject Exclusion Criteria	4. ~~History or presence of decompensated cirrhosis as evidenced by known portal hypertension with complications, including known gastric or esophageal varices, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, history of variceal bleeds, moderate to severe hepatic impairment (Child-Pugh Classes B or C), or related therapeutic or prophylactic interventions (eg, non-selective beta blockers being used to prevent complications of portal hypertension [propranolol or carvedilol], insertion of variceal bands, transjugular intrahepatic portosystemic shunt or direct intrahepatic portocaval shunt)~~	4. Evidence of compensated or decompensated cirrhosis based on ANY of the following: a. Historical liver biopsy demonstrating cirrhosis b. Liver stiffness as assessed by a FibroScan® score of ≥16.9 kPa for subjects with PBC or ≥14.4 kPa for subjects with PSC c History or presence of portal hypertension with complications, including known gastric or esophageal varices, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, history of variceal bleeds, or related therapeutic or prophylactic interventions (eg, non-selective beta blockers being used to prevent complications of portal hypertension [propranolol, nadolol, or carvedilol], insertion of variceal bands, transjugular intrahepatic portosystemic shunt, or direct intrahepatic portocaval shunt)	Exclusion criterion 4 was revised to exclude cirrhotic subjects with Child-Pugh A (ie, compensated cirrhosis) to increase subject safety, and allow for the use of Fibroscan as a non-invasive assessment of cirrhosis.
Synopsis (Exclusion Criteria) 8.2 Subject Exclusion Criteria	15. Has any of the following laboratory results at Screening: b. Total bilirubin >~~2×~~ ULN; total bilirubin >~~2×~~ ULN is acceptable for Gilbert's syndrome if ~~fractionated and~~ direct bilirubin <~~50%~~	15. Has any of the following laboratory results at Screening: b. Total bilirubin >ULN; total bilirubin >ULN is acceptable for subjects with medically documented Gilbert's syndrome if direct bilirubin is <0.3 mg/dL	Exclusion criterion 15a was updated to exclude subjects who have total bilirubin >ULN to increase subject safety but allow those with documented Gilbert's syndrome who have direct bilirubin <0.3 mg/dL to be able to participate.
Synopsis (Exclusion Criteria) 8.2 Subject Exclusion Criteria	16. Estimated glomerular filtration rate <~~60~~ mL/min/1.73 m^2 as determined by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening	16. Estimated glomerular filtration rate <90 mL/min/1.73 m^2 as determined by the Chronic Kidney Disease Epidemiology Collaboration equation at Screening	Exclusion criterion 16 was revised to exclude subjects with estimated glomerular filtration rate <90 mL/min/1.73 m^2 to increase subject safety.

Section	Original	Amendment 1.0	Reason for Change
Synopsis (Exclusion Criteria) 8.2 Subject Exclusion Criteria	18. Significant history of abuse of drugs, solvents, or alcohol (~~>3~~ servings~~s~~ or unit~~s~~/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	18. Significant history of abuse of drugs, solvents, or moderate alcohol consumption (≥1 serving or unit/day on average for women and ≥2 servings or units/day on average for men; 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	Exclusion criterion 18 was revised to exclude subjects with moderate alcohol consumption to increase subject safety.
Synopsis (Exclusion Criteria) 8.2 Subject Exclusion Criteria	*New text*	23. Positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription- polymerase chain reaction (RT-PCR) test at Screening	Subjects who test positive for SARS-CoV-2 will be excluded from participating in the study.
Synopsis (Study Drug Dispensing and Accountability) 10.5 Study Drug Dispensing and Accountability	Subjects will ~~record tablet self-administration daily in a dosing diary that~~ will be reviewed at each study visit by study site staff.	Subjects will complete dosing records, which will be reviewed at each study visit by study site staff.	Daily dosing diaries were replaced with dosing records to allow more flexibility in recording subject dosing.
Synopsis (Discontinuation of Study Drug) 8.5.1 Discontinuation of Study Drug	If the subject is unable to visit the site but is willing to continue in the study, a home health nurse visit to the subject's home and a telehealth visit to communicate with study site staff using technology (eg, smartphone or computer) in lieu of a site visit may be permitted ~~on a case-by-case basis~~.	If the subject is unable to visit the site but is willing to continue in the study, a home health nurse visit to the subject's home and a telehealth visit to communicate with study site staff using technology (eg, smartphone or computer) in lieu of a site visit may be permitted at certain visits.	Using "case-by-case basis" for allowing alternative visit types in lieu of a site visit was removed as it was thought to discourage their use. Because health nurse visits are feasible only at specific visits based on the required procedures, this clarification was added to the protocol.

Section	Original	Amendment 1.0	Reason for Change
Synopsis (Questionnaires) 11.1 Questionnaires	~~Reponses to all questionnaires administered throughout the study will be recorded using a study-issued electronic device or app.~~ At Visit 1 (Screening) before completing the daily WI-NRS for Day -14, subjects will receive training on how ~~to use the electronic device or app~~ to respond to questionnaires. Sites will review the responses from each subject at least twice a week to ensure proper compliance. ~~All subjects who were given a study-issued device, including those who fail Screening, will be required to return it to the site once their participation in the study is complete.~~	At Visit 1 (Screening) before completing the daily WI-NRS for Day -14, subjects will receive training on how to respond to questionnaires. Sites will review the responses from each subject at least twice a week to ensure proper compliance.	The specificity of using a study-issued electronic device or app was removed to allow more flexibility for how questionnaire results are to be recorded.
Synopsis (Worst Itch Numeric Rating Scale [WI-NRS]) 11.1.1 Worst Itch Numeric Rating Scale (WI-NRS)	Subjects will be instructed to complete the WI-NRS daily, in the morning, and at the same time of day, ~~using their study-issued electronic device or app~~ beginning at Day -14 to the Follow-Up Visit.	Subjects will be instructed to complete the WI-NRS daily, in the morning, and at the same time of day, beginning at Day -14 to the Follow-Up Visit.	
Synopsis (Worst Itch Numeric Rating Scale [WI-NRS]) 11.1.1 Worst Itch Numeric Rating Scale (WI-NRS)	The WI-NRS scores from Day -7 through Day -1 will be averaged together to confirm compliance ~~with the study-issued electronic device or app~~ and determine subject eligibility for continued participation regarding pruritus sensation.	The WI-NRS scores from Day -7 through Day -1 will be averaged together to confirm compliance and determine subject eligibility for continued participation regarding pruritus sensation.	
Synopsis (Observation for Acute Kidney Injury) 12.14.4 Observation for Acute Kidney Injury	*New text*	<u>Additionally, all abnormal complete blood count, serum creatinine, BUN, and urine albumin to creatinine ratio values during the Double-Blind Treatment Period and Open-Label Treatment Period are to be followed as deemed clinically necessary by the Investigator.</u>	Added to reinforce the importance of a timely response for any complete blood count, serum creatinine, BUN, or urine albumin value during treatment.

Section	Original	Amendment 1.0	Reason for Change
5.4 EP547 Dose Rationale	[redacted]		
7.3 Dose Adjustment Criteria	Dosages for study drug should be maintained constant during the study. ~~There are no prespecified safety criteria or PK criteria for stopping doses for individual subjects.~~	Dosages for study drug should be maintained constant during the study. However, dosing of study drug may be interrupted or discontinued due to safety findings. Refer to Section 8.5 for guidance on mandatory discontinuation of study drug due to severe and related adverse events (AEs).	Individual subject and study stopping criteria were added to the protocol to enhance general oversite of safety.
8.5.1 Discontinuation of Study Drug	*New text.*	If a subject experiences an AE that is Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 or higher, the study drug must be discontinued. AE grading for severity using CTCAE criteria is described in Section 12.1.2.	Individual subject and study stopping criteria were added to the protocol to enhance general oversite of safety.
8.5.3 Safety Criteria for Study Drug Interruption	*New section.*	**8.5.3 Safety Criteria for Study Drug Interruption** Study drug dosing will be interrupted for all subjects if 3 subjects develop AEs meeting CTCAE Grade 3 or higher that are considered related to study drug by the Investigator and/or Sponsor. AE grading for severity using CTCAE criteria is described in Section 12.1.2. All events with a CTCAE Grade of 3 or higher will be reviewed by the Data Monitoring Committee (DMC) (Section 12.3) to independently determine event relatedness and provide recommendations to the Sponsor.	

Section	Original	Amendment 1.0	Reason for Change
9.2 Treatment Compliance	The Investigator should assess the subject's compliance with dosing of study drug by counting returned study drug tablets and reviewing the subject's ~~daily~~ dosing ~~diary~~ as indicated in the Schedule of Assessments (Appendix A).	The Investigator should assess the subject's compliance with dosing of study drug by counting returned study drug tablets and reviewing the subject's dosing records as indicated in the Schedule of Assessments (Appendix A).	Daily dosing diaries were replaced with dosing records to allow more flexibility in recording subject dosing.
9.4.1.1 Visit 1 (Day -28 to Day -1)	*New text.*	• Transient elastography (TE; FibroScan) • SARS-CoV-2 RT-PCR test	TE and SARS-CoV-2 RT-PCR testing were added at Screening to the protocol.
9.4.1.1 Visit 1 (Day -28 to Day -1)	- HIV, hepatitis B virus (HBV), ~~and~~ hepatitis C virus (HCV) serology	- HIV, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis E virus (HEV) serology	The exclusion of subjects with uncontrolled viral hepatitis was expanded to include active hepatitis A and hepatitis E infections.
9.4.1.1 Visit 1 (Day -28 to Day -1)	• Receive training ~~for the study issued electronic device or app~~ (to be conducted before completing the daily WI-NRS for Day -14) Subjects will be instructed to complete the WI-NRS daily, in the morning, and at the same time of day, ~~using their study issued electronic device or app~~ beginning at Day -14 to the Safety Follow-Up Visit.	• Receive questionnaire training (to be conducted before completing the daily WI-NRS for Day -14) Subjects will be instructed to complete the WI-NRS daily, in the morning, and at the same time of day, beginning at Day -14 to the Safety Follow-Up Visit.	The specificity of using a study-issued electronic device or app was removed to allow more flexibility for how questionnaire results are to be recorded.
9.4.2.1 Visit 2 (Day 1) 9.4.2.5 Visit 6 (Week 6) 9.4.3.2 Visit 8 (Week 12) 9.4.5 Early Study Termination Visit 12.8 Laboratory Evaluations of Safety	*New text*	- Thyroid hormones: TSH and free T4	TSH and free T4 monitoring were added to the protocol to increase subject safety.

Section	Original	Amendment 1.0	Reason for Change
10.6 Study Drug Handling and Disposal	*New text*	Where allowed, to support home visits by a home health nurse, the use of a direct-to-patient courier service to transport study drug between the study site and subject's home may be arranged at certain visits. The courier will be asked to collect the study drug kit dispensed by the study site staff and deliver it to the subject's home. The courier may also be asked to collect the used study drug kit with any unused study drug from the subject to be returned to the site for accountability with reconciliation to be completed by the study site staff. Chain of custody of the study drug transport will be documented.	A direct-to-patient courier service may be provided to support drug dispensing during home health nurse visits.
12.1.2 Determining Severity of Adverse Events	AEs must be graded for severity (ie, intensity) using ~~Common Terminology Criteria for Adverse Events (CTCAE)~~.	AEs must be graded for severity (ie, intensity) using Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (HHS 2017).	The hyperlink for the CTCAE criteria was replaced with a reference and the CTCAE criteria version was specified to allow for easier referencing of the criteria.
12.2.2 Reporting Serious Adverse Events	To report an SAE, complete the study-specific ~~Serious Adverse Event Report (~~SAE~~R)~~ Form electronically in the electronic data capture (EDC) system for the study.	To report an SAE, complete the study-specific SAE/AESI Report Form electronically in the electronic data capture (EDC) system for the study.	The name of the SAER FORM was changed to SAE/AESI Report FORM to reflect its current naming convention.
12.2.2 Reporting Serious Adverse Events	Any supporting documentation (eg, medical records) sent to Covance with the SAE~~R~~ Form must have subject identifying information (eg, subject names, subject addresses, and medical records number) redacted by the site.	Any supporting documentation (eg, medical records) sent to Covance with the SAE/AESI Report Form must have subject identifying information (eg, subject names, subject addresses, and medical records number) redacted by the site.	The name of the SAER FORM was changed to SAE/AESI Report FORM to reflect its current naming convention.
12.2.3 Reporting Serious and Unexpected Adverse Events Assessed as Related	**12.2.3. Reporting Serious and Unexpected Adverse Events**	**12.2.3. Reporting Serious and Unexpected Adverse Events Assessed as Related**	The title of Section 12.2.3 was revised to better reflect the types of AEs that require reporting in this section.

Section	Original	Amendment 1.0	Reason for Change
12.3 Data Monitoring Committee	*New section*	**12.3 Data Monitoring Committee** The DMC is an independent group of external experts who will review safety data during the conduct of the study, as outlined in the DMC charter. The DMC will make a determination of relatedness for all AEs with CTCAE Grade 3 or higher. The DMC will also meet on an ad hoc basis when at least 3 AEs of CTCAE Grade 3 or higher have accrued or when there has been a single CTCAE Grade 4 or higher. Based on review of the data, the DMC will provide recommendations to the Sponsor on whether the nature, frequency, and/or severity of AEs associated with study drug warrant modification to the study protocol, suspension of dosing, or study termination.	The DMC was added to independently determine AE relatedness and advise the Sponsor regarding potential modifications to the study protocol, suspension of dosing, or study termination.
12.8 Laboratory Evaluations of Safety	Hematology: hemoglobin, hematocrit, white blood cell (WBC) count ~~total and differential~~), red blood cell count, platelet count, and platelet volume	Hematology: hemoglobin, hematocrit, white blood cell (WBC) count with differential (lymphocytes, neutrophils, monocytes, eosinophils, and basophils), red blood cell count, platelet count, and platelet volume. If a subject develops lymphopenia, blood lymphocytes will be tested to assess populations of circulating T cells (including CD4+ and CD8+ subtypes), B cells, and natural killer (NK) cells.	Total lymphocyte count monitoring and additional blood lymphocyte population assessments for subjects who develop lymphopenia were added to the protocol to increase subject safety.

Section	Original	Amendment 1.0	Reason for Change
12.9 Other Laboratory Evaluations	• Serology: HIV, HBV, HCV Per exclusion criterion 6, subjects with uncontrolled viral hepatitis are not eligible to participate in this study. Current chronic HBV infection is defined as a positive result for hepatitis B surface antigen (HBsAg) or HBV deoxyribonucleic acid (DNA). Current chronic HCV infection is defined as a positive result for HCV antibody and HCV ~~ribonucleic acid (~~RNA~~)~~ at Screening. If HCV is cured, a negative HCV RNA confirmed within 1 year prior to Screening will be required.	• Serology: HIV, HAV, HBV, HCV, and HEV Per exclusion criterion 6, subjects with uncontrolled viral hepatitis are not eligible to participate in this study. Active HAV infection is defined as a positive result for immunoglobulin M (IgM) anti-HAV or HAV ribonucleic acid (RNA). Current chronic HBV infection is defined as a positive result for hepatitis B surface antigen (HBsAg) or HBV deoxyribonucleic acid (DNA). Current chronic HCV infection is defined as a positive result for HCV antibody and HCV RNA at Screening. If HCV is cured, a negative HCV RNA confirmed within 1 year prior to Screening will be required. Active HEV infection is defined as a positive result for IgM anti-HEV or HEV RNA.	The exclusion of subjects with uncontrolled viral hepatitis was expanded to include active hepatitis A and hepatitis E infections to increase subject safety.
12.10 Transient Elastography	*New text*	**12.10 Transient Elastography** Transient elastography (FibroScan TE) is a validated, noninvasive technique used to assess hepatic stiffness (Corpechot 2016) that will be used to determine subject eligibility based on exclusion criterion 4. TE procedures will be conducted at study sites with the appropriate equipment and by adequately trained study site staff.	TE testing was added at Screening to the protocol to exclude subjects with evidence of cirrhosis.
12.9 Child-Pugh Assessment	~~**12.9 Child-Pugh Assessment**~~ ~~The Child-Pugh score is used to assess the prognosis of chronic liver disease, particularly cirrhosis (Pugh 1973, Lucey 1997). The score uses 5 clinical measures of liver disease (total bilirubin, serum albumin, PT or INR, ascites, and hepatic encephalopathy), each scored 1 to 3, with 3~~	*Deleted text*	The Child-Pugh assessment was removed as it is no longer relevant given that patients with cirrhosis are no longer eligible for study participation.

<table>
<tr><th>Section</th><th>Original</th><th>Amendment 1.0</th><th>Reason for Change</th></tr>
<tr><td></td><td>~~indicating most severe. Chronic liver disease is classified into Child-Pugh Class A to Class C as indicated in Table 5, and will be used to determine subject eligibility for exclusion criterion 4.~~

~~**Table 5: Child-Pugh Scoring System**~~
<table><tr><th>~~Factor~~</th><th colspan="3">~~Points~~</th></tr><tr><td></td><td>~~1~~</td><td>~~2~~</td><td>~~3~~</td></tr><tr><td>~~Bilirubin (mg/dL)~~</td><td>~~<2~~</td><td>~~2-3~~</td><td>~~>3~~</td></tr><tr><td>~~Albumin (g/dL)~~</td><td>~~>3.5~~</td><td>~~3.5-2.8~~</td><td>~~<2.8~~</td></tr><tr><td rowspan="2">~~Prothrombin time (sec prolonged) or INR~~</td><td>~~0-3~~</td><td>~~4-6~~</td><td>~~>6~~</td></tr><tr><td>~~<1.7~~</td><td>~~1.7-2.3~~</td><td>~~>2.3~~</td></tr><tr><td>~~Ascites~~</td><td>~~None~~</td><td>~~Mild~~</td><td>~~Moderate - Severe~~</td></tr><tr><td>~~Hepatic Encephalopathy~~</td><td>~~None~~</td><td>~~Grade 1 or 2~~</td><td>~~Grade 3 or 4~~</td></tr></table>~~INR = international normalized ratio.~~

~~The Child-Pugh score is calculated by adding the scores for the 5 factors and can range from 5 to 15. Child-Pugh score class is either A (a score of 5 to 6), B (7 to 9), or C (10 or above). Decompensation indicates cirrhosis with a Child-Pugh score of 7 or more (Class B). This level has been the accepted criterion for listing for liver transplantation (Pugh 1973, Lucey 1997).~~</td><td></td><td></td></tr>
</table>

Section	Original	Amendment 1.0	Reason for Change
12.11 SARS-CoV-2 Testing	*New section*	12.11 SARS-CoV-2 Testing Subjects will be tested for SARS-CoV-2 (COVID-19) at Screening via RT-PCR test. A positive test result for COVID-19 will exclude the subject from enrolling in the study, even if the subject is asymptomatic, regardless of vaccination status.	SARS-CoV-2 RT-PCR testing will be conducted at Screening and subjects who test positive for the virus will be excluded from participating in the study to increase subject safety.
13 Pharmacokinetics Assessment	*New text*	In the event of an SAE, the Investigator should collect, if at all possible, a blood PK sample at an unscheduled visit as part of SAE follow-up.	Investigators are to attempt to collect a blood PK sample at an unscheduled visit as part of SAE follow-up to assess drug levels at the time of the event.
17 List of References	~~Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the Oesophagus for Bleeding Oesophageal Varices. Br J Surg. 1973;60(8):646-9.~~ ~~Lucey MR, Brown KA, Everson GT, et al. Minimal Criteria for Placement of Adults on the Liver Transplant Waiting List: A Report of a National Conference Organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Liver Transpl Surg. 1997;3(6):628-37.~~	Corpechot C. Utility of Noninvasive Markers of Fibrosis in Cholestatic Liver Diseases. Clin Liver Dis. 2016;20(1):143-58. HHS. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 2017. p. 1-155.	References for Child-Pugh scoring were removed as this assessment is no longer being conducted and the reference for transient elastography was added for this newly added assessment. The hyperlink for the CTCAE criteria was replaced with a reference.
Appendix A. Schedule of Assessments	*Included patient interviews, global metabolomic analysis, autotaxin, lysophosphatidic acid, and cytokine markers.* *Mentioned use of an electronic device or app for completing questionnaires.*	*Removed patient interviews, global metabolomic analysis, autotaxin, lysophosphatidic acid, and cytokine markers.* *Added HAV, HEV, SARS-CoV-2 RT-PCR, and TE (FibroScan) testing to Visit 1.* *Added thyroid hormone testing to Visits 2, 6, 8 and early termination.* *Removed mention of an electronic device or app for completing questionnaires.*	Changes were made to reflect edits described for earlier sections of the protocol.

Section	Original	Amendment 1.0	Reason for Change
[redacted]			