ENANTA
Pharmaceuticals

CLINICAL STUDY PROTOCOL

A PHASE 2 DOSE RANGING, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND EFFICACY OF EDP-305 IN SUBJECTS WITH PRIMARY BILIARY CHOLANGITIS (PBC) WITH OR WITHOUT AN INADEQUATE RESPONSE TO URSODEOXYCHOLIC ACID (UDCA)

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CONFIDENTIAL

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CONTACT INFORMATION

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator:

Signed: Date:

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LIST OF ABBREVIATIONS

ADaM	analysis data model
AE, AR	adverse event(s), adverse reaction(s)
ALT	alanine aminotransferase
APRI	AST to platelet ratio index
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BP	blood pressure
CL/F	apparent total clearance after oral administration
C_{max}	maximum concentration
eCRF	electronic case report form
CRO	contract research organization
CS, NCS	clinically significant, non-clinically significant
CV	cardiovascular
CYP450, CYP3A4	cytochrome P450, cytochrome P450 3A4
CYP7A1	cholesterol 7α-hydroxylase
EC	ethics committee
ECG	electrocardiogram
EOS	end-of-study
EOT	end-of-treatment
F	oral bioavailability
FDA	Food and Drug Administration
FIB-4	fibrosis 4 index
FXR	farnesoid X receptor
GCP, GMP, GLP	good clinical practice, good manufacturing practice, good laboratory practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-C	high density lipoprotein cholesterol
HDPE	high density polyethylene
hERG	human *Ether-à-go-go*-related gene
HIV	human immunodeficiency virus
HR	heart rate
hs-CRP	high-sensitivity C-reactive protein
HV	healthy volunteers
IB	investigator's brochure
ICF	informed consent form
ICH	International Council on Harmonisation
INR	international normalized ratio
IRB	institutional review board
IU	international units
IUD, IUS	intrauterine device, intrauterine system
IWRS	interactive web response system
MAD	multiple ascending dose
MedDRA	medical dictionary for regulatory activities
NAFL, NAFLD	non-alcoholic fatty liver, non-alcoholic fatty liver disease

NASH	non-alcoholic steatohepatitis
NCI CTCAE	National Cancer Institute, Common Terminology Criteria for Adverse Events
NFS	NAFLD fibrosis score
NOAEL/NOEL	no observed adverse effect level / no observed effect level
OCA	obeticholic acid
PBC	primary biliary cholangitis
PBC-ANAb	PBC-specific antinuclear antibodies
PD	pharmacodynamics
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetics
PN	presumptive NAFLD (non-alcoholic fatty liver disease)
po	oral administration (by mouth, per os)
PT/PTT	prothrombin time / partial thromboplastin time
QD	once daily
SAD	single ascending dose
SAE	serious adverse event(s)
SAP	statistical analysis plan
SHP	small heterodimer partner
SOC	system organ class
SUSAR	suspected, unexpected, serious adverse reaction
$t_{1/2}$	plasma half-life
TB	total bilirubin
TEAE	treatment emergent adverse event(s)
T_{max}	time to maximum concentration
UDCA	ursodeoxycholic acid
ULN	upper limit of normal

PROTOCOL SYNOPSIS

Sponsor: Enanta Pharmaceuticals, Inc.

Name of Investigational Product: EDP-305

Study Title: A Phase 2 Dose Ranging, Randomized, Double Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of EDP-305 in Subjects with Primary Biliary Cholangitis (PBC) with or without an Inadequate Response to Ursodeoxycholic Acid (UDCA)

Protocol Number: EDP 305-201

Phase of Development: 2

Study Centers: The study will be conducted at approximately 65 sites located in both the US as well as international locations.

Number of Subjects Planned: Approximately 119 subjects will be enrolled.

Investigational Product, Dosage, and Mode of Administration: EDP-305 will be supplied as 1mg and 2.5mg tablets for oral administration; doses administered will be 1 mg, 2.5 mg, or placebo taken once daily (QD) for 12 weeks.

Duration of Treatment: 12 weeks.

Objectives:

Primary Objective:

- To evaluate the effect of EDP-305 on alkaline phosphatase (ALP) levels.

Secondary Objective:

- To evaluate the safety and tolerability of EDP-305
- To evaluate the effect of EDP-305 on bilirubin levels
- To evaluate the effects of EDP-305 on other markers of liver function
- To evaluate the effects of EDP-305 on non-invasive markers of liver fibrosis
- To evaluate the effects of EDP-305 on inflammatory markers
- To evaluate the effects of EDP-305 on lipids
- To evaluate the effects of EDP-305 on pruritus
- To evaluate the effects of EDP-305 on Quality of Life (QoL)
- To evaluate the pharmacokinetics (PK) of EDP-305 and metabolites in plasma
- To evaluate the pharmacodynamics (PD) of EDP-305

Criteria for Evaluation:

Primary Endpoint:

- Proportion of subjects with at least 20% reduction in ALP from pretreatment value or normalization of ALP at Week 12

Secondary Endpoints:

- Frequency of adverse events (AEs), serious AEs, and AEs leading to discontinuation through Week 12

- Bilirubin (Total, Conjugated, Unconjugated) decline from Baseline at Week 12
- Change from Baseline in Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST), Gamma-Glutamyl transferase (GGT) at Week 12
- Change from Baseline of noninvasive liver fibrosis markers (Enhanced Liver Fibrosis [ELF] panel, PRO C3, AST to Platelet Ratio Index [APRI] and fibrosis-4 [FIB-4]) at Week 12
- Change from Baseline in fibrinogen, CRP, IL6, IL1β, TNF-α, TNF-β , alpha2 macroglobulin and haptoglobin levels at Week 12
- Change from Baseline in Triglycerides (TG), Total Cholesterol (TC), High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C) at Week 12
- Change from Baseline in 5D-itch scale and Visual Analog Score (VAS) at Week 12
- Change from Baseline in PBC-40 Quality of Life (QoL) at Week 12
- Pharmacokinetic parameters of EDP-305 (and metabolites): C_{max}, T_{max}, and AUC_{last}.
- Pharmacodynamic parameters of EDP-305: FGF19, C4 and Bile Acid (BA) at Week 12

Study Design:

This is a multicenter, double blind, placebo controlled, dose ranging Phase 2 study assessing the safety and efficacy of two doses of orally administered EDP-305. The total maximum length of time for participation for each subject enrolled in the study will be approximately 20 weeks. The study will consist of a Screening Period, Treatment Period and a Follow-up Period as shown in the following table.

Study Period	**Duration**
Screening	Up to 4 weeks (28 Days)
Treatment	12 weeks
Follow-up	4 weeks
Total approximate maximum duration of participation	up to 20 weeks

Screening Period: After reviewing and signing the Informed Consent Form (ICF), subjects will be screened and must meet all criteria for entry into the study. The Screening Visit must occur between Days -28 and -1 (up to 4 weeks). All Screening assessments must occur within the -28 to -1 window.

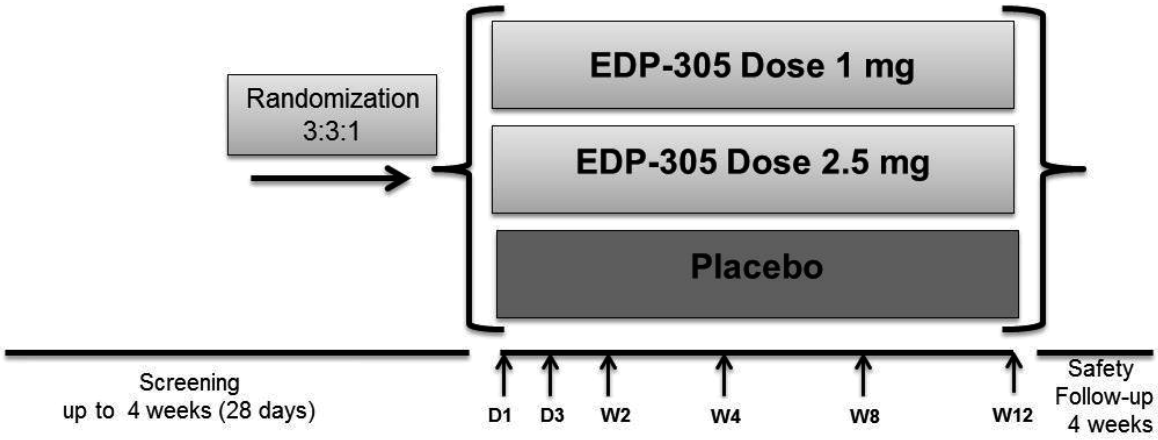
Treatment Period: Subjects who have met all study criteria will report to the site on the morning of Day 1. Subjects must have fasted for at least 8 hours prior to dosing. Subjects will be randomized in a 3:3:1 manner to receive one of two doses of EDP-305 or placebo QD. Procedures performed are specified in the Schedule of Assessments (Appendix 1). Predose assessments will be conducted (including laboratory sample collection) before the subject

receives the first dose of study drug in the clinic. Following dosing, PK and biomarker samples will be collected. Prior to leaving the clinic on Day 1, study drug will be dispensed to the subjects and the subjects will be given instructions for taking study drug at home. Subjects will take study drug once daily for a total of 12 weeks returning to the clinic for efficacy and safety assessments on Day 3 and Weeks 2, 4, 8 and 12. On study days when there is a clinic visit, subjects will be administered their daily dose in the clinic. Additional PK and PD samples will be collected over a period of 8 hours on Day 1 and Week 12 (Day 84/End of Treatment, [EOT]) from subjects at a subset of sites that have the technical capability to collect and process intensive (longer duration) PK and PD samples (PK/PD Sub-study).

Safety Follow-up and Early Termination Visit: The safety follow-up visit (or End of Study [EOS] visit) will occur 4 weeks after the last dose of study drug for all subjects, including those who discontinue treatment early (ie, prior to completing 12 weeks of dosing). Final study assessments will be completed at that visit.

Subjects who discontinue treatment early should return to the clinic as soon as possible following the last dose of study drug for an EOT visit. They should then return for the EOS visit 4 weeks following last dose of study drug.

Study Design:



Abbreviations: D=Day; W=Week

Eligibility Criteria:

Inclusion Criteria

Subjects must meet all of the following criteria to be eligible to participate:

1. An informed consent document must be signed and dated by the subject
2. Male and female subjects of any ethnic origin between the ages of 18 and 75 years, inclusive
3. Male or female with a diagnosis of PBC by at least two of the following criteria:
   - History of ALP above ULN for at least 6 months

- Positive Anti-Mitochondrial Antibodies (AMA) titers (>1/40 on immunofluorescence or M2 positive by enzyme linked immunosorbent assay [ELISA] or positive PBC-specific antinuclear antibodies [PBC- ANAb])
- Documented liver biopsy result consistent with PBC (with no cirrhosis)

4. For subjects with no documented liver biopsy performed within 2 years, subjects must undergo a transient elastography (Fibroscan) showing liver stiffness <14.0 kPA
5. Must be on a stable dose of UDCA12-20 mg/kg/day for at least 6 months prior to Screening or intolerant of UDCA in the opinion of the Investigator (no UDCA for at least 12 weeks prior to Screening)
6. Alkaline Phosphatase (ALP) ≥1.67 × ULN and/or total bilirubin >ULN but <2 × ULN (<2.4 mg/dL)
7. Subjects must have Screening laboratory values for Hepatitis B surface antigen (HBsAg), anti-HCV antibodies and HCV RNA negative, and Human Immunodeficiency Virus (HIV) 1 and 2 antibodies (Ab) as seronegative. NOTE: Subjects previously infected by chronic hepatitis C and treated with direct acting antivirals (DAAs) with sustained virologic response (SVR) for at least 3 years will be allowed.
8. Female subjects of childbearing potential must agree to use two effective methods of contraception from the date of Screening until 90 days after the last dose of EDP-305. Effective methods of contraception are defined as:
   - a condom for the male partner and at least one of the following for the female participant:
     - Intrauterine device
     - Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive

   Note: The above does not apply to female subjects of non-childbearing potential (ie, physiologically incapable of becoming pregnant) defined as:
   - has had a complete hysterectomy greater than or equal to 3 months prior to dosing or
   - has had a bilateral oophorectomy (ovariectomy) or
   - has had a bilateral tubal ligation or fallopian tube inserts or
   - is postmenopausal (a demonstration of a total cessation of menses for ≥1 year with an FSH level of >35 mIU/mL).
9. All male participants who have not had a vasectomy must use effective contraception from Day -1 to 90 days after their last dose of study drug. Effective contraception is defined as a condom and spermicide for the male, or condom and at least one of the following for a female partner:
   - Intrauterine device
   - Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive
   - Be of non-childbearing potential
10. Male subjects must agree to refrain from sperm donation from the date of Screening until 90 days after their last dose of study drug
11. Screening body mass index (BMI) of ≥18 kg/m^2
12. Subject must be willing and able to adhere to the assessments, visit schedule, prohibitions and restrictions, as described in this protocol

Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate:

1. Laboratory Screening Results:
   - AST >5 × ULN

- ALT >5 × ULN
- Patients with Gilbert's syndrome will not be allowed due to interpretability of bilirubin levels
- Total white blood cells (WBC) <3000 cells/mm^3
- Absolute neutrophil count (ANC) <1500 cells/mm^3
- Platelet count <140,000/mm^3
- Prothrombin time (international normalized ratio, INR) >1.2
- Serum creatinine >2 mg/dL or creatinine clearance <60 mL/min (based on Cockroft-Gault Method)

2. Suspected to have relevant nonalcoholic fatty liver disease (NAFLD) as based on the judgment of the Investigator at Screening
3. Known history of alpha-1-Antitrypsin deficiency
4. Use of immunosuppressants known to have an effect on the liver of patients with PBC (eg, colchicine, methotrexate, or azathioprine) in the 3 months preceding Screening.
5. Current use of fibrates, including fenofibrates. NOTE: Subjects who discontinued fibrates for at least 3 months before Screening can participate
6. Use of an experimental treatment for PBC within the past 6 months
7. Prior use and/or concomitant treatment with obeticholic acid (OCA)
8. Use of experimental or unapproved drugs within 1 year of Screening
9. Any other condition(s) that would compromise the safety of the subject or compromise the quality of the clinical study, as judged by the Principal Investigator (PI)
10. Pregnant or nursing females
11. Recipients of liver or other organ transplantation or anticipated need for orthotropic organ transplantation in one year as determined by a Model for End-Stage Liver Disease (MELD) Score ≥15
12. Co-existing liver or biliary diseases, such as primary sclerosing cholangitis, choledocholithiasis, acute or chronic hepatitis, autoimmune hepatitis, alcoholic liver disease, nonalcoholic steatohepatitis (NASH), acute infection of bile duct system or gall bladder, history of gastrointestinal bleeding (secondary to portal hypertension), cirrhosis, cholangiocarcinoma diagnosed or suspected liver cancers
13. Cirrhosis with or without complications, including history or presence of: spontaneous bacterial peritonitis, hepatocellular carcinoma
14. Hepatorenal syndrome (type I or II) or Screening serum creatinine >2 mg/dL (178 µmol/L)
15. Prior variceal hemorrhage, uncontrolled encephalopathy, Child-Pugh Class A, B and C, esophageal varices, or refractory ascites within the previous 6 months of Screening (defined as date informed consent signed)
16. Patients with a history of severe pruritus requiring current or prior systemic treatment (e.g., with BAS or rifampicin)
17. Medical conditions that may cause nonhepatic increases in ALP (e.g., Paget's disease)
18. Any condition possibly affecting drug absorption (eg, gastrectomy <3 years prior to Screening. NOTE: Subjects who have undergone gastric surgeries known to not affect drug absorption such as gastric band or gastric sleeve will be allowed if they are stable for at least 1 year prior to Screening.
19. History of regular alcohol consumption exceeding 14 drinks/week for females and 21 drinks/week for males within 6 months of Screening. One drink is defined as 5 ounces

(150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor)

20. Participation in a clinical trial within 30 days prior to study drug administration
21. Clinically significant electrocardiogram (ECG) abnormalities or QTcF greater than 450 ms for males and 470 ms for females at either Screening or Baseline, or any prior history of QT abnormality
22. Use of CYP3A4 and P-gp inducers and inhibitors within 14 days prior to the first dose of study medication and throughout study duration
23. Clinically significant history of drug sensitivity or allergy, as determined by the PI
24. Subject has received an investigational agent or investigational vaccine within 30 days, or a biological product within 3 months or 5 elimination half-lives (whichever is longer) prior to the planned intake of study drug
25. Use of a new statin regimen from Screening and throughout study duration.
    NOTE: Subjects on a stable dose of statins for at least 3 months prior to Screening are allowed. No dose modification during the study will be allowed.
26. Use of immunosuppressants (eg, systemic corticosteroids) for more than 2 consecutive weeks in duration within 1 year prior to Screening.

Subject Withdrawal:

Subjects may choose to discontinue from the study at any time. Subjects may also be discontinued from the study at any time if the subject, Investigator or Sponsor determines that it is not in the best interest of the subject to continue participation. Subjects who prematurely withdraw from the study for any reason after having been randomized will not be replaced. Subjects who prematurely discontinue treatment early and received at least one dose of study drug should return to the clinic as soon as possible to complete the EOT Visit and for the Safety Follow-up Visit 4 weeks after their last dose.

Individual subjects who meet the following Stopping Rules will be discontinued from further dosing and thorough evaluation and follow-up will be performed:

- If ALT or aspartate aminotransferase (AST) increases to >5 × Baseline.
- If ALT or AST increase >2 × Baseline AND the increase is accompanied by a concomitant total bilirubin (TB) increase >2 × Baseline OR the INR concomitantly increases by >0.2
- If elevations of ALT/AST are accompanied by signs or symptoms of right upper quadrant abdominal pain, anorexia, nausea, vomiting fever, eosinophilia, and/or rash.

Statistical Methods:

Detailed statistical analysis will be outlined in the statistical analysis plan (SAP).

Analysis Populations

- *Safety Population:* All subjects who receive at least one dose of study medication. Subjects will be included in the treatment group that corresponds to the study medication received during the study.
- *Efficacy Population:* All subjects who receive at least one dose of study medication. Subjects will be included in the randomized treatment group.

- *Pharmacokinetic Population:* All subjects receiving active study medication and having any measurable plasma concentration of study medication at any timepoint.

Safety Analyses: Statistical methods for the safety analyses will be primarily descriptive in nature. No formal statistical comparisons of EDP-305 dose levels will be made. Safety data, including adverse events (AEs), vital signs, ECGs, concomitant medications, and laboratory values will be summarized separately for each treatment group. Change from Baseline will be included in summary tables for vital signs, ECG parameters, and laboratory parameters. Shift tables will also be generated for safety laboratory parameters by visit and treatment group. All laboratory data will be included in the data listings and all test values outside the normal range will be flagged. AEs will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term by treatment group.

Efficacy Analyses: Proportion of subjects with at least 20% reduction in ALP from pretreatment value or normalization of ALP at Week 12. Treatment comparisons will be made using a Mantel-Haenszel test comparing each of the active treatment groups to placebo, respectively.

Pharmacokinetic Analyses: Plasma PK parameters for each dose level will be calculated from the concentrations of EDP-305 and its major metabolites (as applicable) measured in predose and postdose plasma samples. For each EDP-305 dose level, descriptive statistics (sample size, arithmetic means, geometric means, standard deviation, % coefficient of variation, minimum, median, and maximum) will be presented. Figures will be created to display mean and individual subject EDP-305 concentration time curves in plasma on both a linear and logarithmic scale. The following PK parameters will be calculated as indicated for plasma EDP-305 and its major metabolites: AUC_{0-t}, C_{max}, and T_{max}.

Sample Size Consideration: The planned sample size is approximately 105 subjects. Group sample sizes of 45 in each active arm and 15 in the placebo arm achieve 83.552% power to detect a ratio of the group proportions of 40%. The proportion in the smallest active arm is assumed to be 0.4000 under the null hypothesis and 0.0400 under the alternative hypothesis. The proportion in the placebo arm is 10%. The test statistic used is the two-sided Mantel-Haenszel test. The significance level of the test is 0.05. To account for a 10% discontinuation rate, 14 additional subjects will be enrolled to attempt to have 105 who complete treatment, bringing the total number of subjects enrolled to 119.

1. INTRODUCTION

1.1 Overview

EDP-305 (also known as EPS-2305, EPC-2305 or EP-022305) is a Farnesoid X Receptor (FXR) agonist being investigated as a potential treatment for Nonalcoholic Steatohepatitis (NASH) with liver fibrosis and Primary Biliary Cholangitis (PBC). This study, EDP 305-201, is a randomized, double-blind, placebo-controlled, Phase 2 study designed to assess the safety, tolerability, and effectiveness of EDP-305 in subjects with PBC with or without an inadequate response to ursodeoxycholic acid (UDCA).

1.2 Background

1.2.1 PBC and Farnesoid X Receptor (FXR)

Bile acids play a key role in regulating liver and metabolic homeostasis including regulation of lipid and glucose metabolism mediated through two receptor pathways, FXR and TGR5 (*Matsubara, Li, & Gonzalez, 2013*). FXR is a member of the nuclear hormone receptor superfamily and is considered a master regulator of many bile acid activities including feedback regulation of bile acid synthesis, gluconeogenesis and glycogenolysis in the liver, and peripheral insulin sensitivity in adipose tissue (*McMahan et al., 2013*). Given the critical role bile acids play in liver homeostasis and the role of FXR in regulating bile acid biosynthesis, FXR has become a target for therapeutic intervention in numerous liver diseases including NASH and PBC.

Primary biliary cirrhosis is an important but uncommon autoimmune disease which predominantly affects women. Based on well-defined assessment of cases, the incidence and prevalence rates for PBC in Europe, North America, Asia, and Australia are reported as ranging from 0.33 to 5.8 per 100,000 inhabitants and 1.91 to 40.2 per 100,000 inhabitants, respectively *(Boonstra, Beuers, & Ponsioen, 2012)*. Kim et al estimated that there were 47,000 prevalent cases of PBC in the United States white population and that approximately 3500 new cases are diagnosed each year *(Kim et al., 2000)*. PBC disproportionately affects women (10:1 women to men ratio) although some recent data suggest an increasing male prevalence *(Lleo et al., 2016)*. The typical age of diagnosis is between 40 and 60 years; recent data suggest that young age at diagnosis (ie, < 30 years of age) and male gender indicate a poor prognosis *(Boonstra et al., 2012)*. Racial and ethnic differences in PBC patients have not been clearly identified. It is a globally recognized autoimmune cholestatic liver disease *(Beuers, Trauner, Jansen, & Poupon, 2015; Hirschfield & Gershwin, 2013; Selmi, Mackay, & Gershwin, 2011; Webb & Hirschfield, 2017)* with several characteristics, including: cholestasis, serologic reactivity to antimitochondrial antibodies (AMA) or specific antinuclear antibody (ANA) reactivity, with accompanying histologic evidence of chronic non-suppurative, granulomatous, lymphocytic small bile duct cholangitis. Without treatment, the disease progresses to cirrhosis and, as the liver

fails, complications develop including those related to cirrhosis, portal hypertension and hepatocellular carcinoma *(Carbone et al., 2013; Huet et al., 2008; Kuiper et al., 2010; Lammers et al., 2014; Trivedi et al., 2016)*, liver transplantation or death ensue.

It is believed that a key result of the immunologic injury in PBC is a rise in the endogenous hepatocellular bile acids to cytotoxic levels, causing inflammatory damage, an increase in hepatocellular enzymes and apoptosis which over time results in hepatic fibrosis and cirrhosis *(Beuers, 2006)*. Disease progression may take decades from diagnosis to the development of the clinical events associated with hepatic decompensation. Early on, patients are typically asymptomatic, and suspicion of a potential PBC diagnosis is raised by an elevation of alkaline phosphatase noted on screening blood tests obtained during routine office visits. Currently, patients are more likely to be diagnosed at earlier stages of the disease, secondary to the current practice guideline that include screening of liver biochemistries during routine physical exams *(Floreani et al., 2011; Prince, Chetwynd, Craig, Metcalf, & James, 2004)*.

Clinically, PBC is monitored by assessing alkaline phosphatase (ALP) levels. ALP is used universally in the diagnosis of the disease (as noted in both the US and recent European treatment guidelines *(European Association for the Study of the Liver, 2017; Lindor et al., 2009)*. However, other liver enzymes including gamma-glutamyltransferase (GGT), alanine aminotransferases (ALT) and aspartate aminotransferase (AST) are also used in the clinical assessment and care of patients. As the disease progresses and hepatocellular function is impaired, bilirubin levels (a direct measurement of hepatic degradation) rise and albumin and prothrombin time (assays of hepatic synthesis) are impaired.

1.2.2 Rationale for Development of EDP-305 for PBC

Until most recently, there has been one approved treatment for PBC, ursodeoxycholic acid (UDCA), which was approved by the FDA in 1997. UDCA is effective in more than 50 percent of patients, but up to 40 percent of patients do not achieve an adequate reduction in blood chemistries (eg, ALP and/or total bilirubin) with UDCA, while 5% to 10% are unable to tolerate UDCA. While UDCA therapy has a marked impact on clinical outcomes in PBC, up to 40% of UDCA-treated patients have a suboptimal or absent response to UDCA and, as such, are at significantly increased risk of an adverse outcome (death, requiring a liver transplant, or other clinical complications) *(Carbone et al., 2013; Corpechot et al., 2008; ter Borg, Schalm, Hansen, & van Buuren, 2006)*. Several studies have shown that UDCA-treated patients with early stage disease, who respond biochemically to UDCA treatment, have survival rates comparable with a standardized general population *(Carbone et al., 2013; Corpechot et al., 2008; ter Borg et al., 2006)*. In 2016, the U.S. Food and Drug Administration granted accelerated approval for the FXR agonist Ocaliva® (obeticholic acid, OCA) for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as a single therapy in adults unable to tolerate UDCA *(U.S. Food and Drug Administration, 2016)*.

Several animal models have demonstrated that the FXR has a protective effect in various diseases, including cholestatic and autoimmune liver diseases, alcoholic liver disease, fatty liver, gallstone formation, portal hypertension, and hepatocellular carcinoma. It has been recently reported that EDP-305 potently suppresses liver injury and fibrosis in mouse models of biliary and metabolic liver disease *(An et al., 2017)*. Furthermore, in the MCD diet mouse model of steatohepatitis and perisinusoidal fibrosis, EDP-305 outperformed OCA in attenuating MCD diet-induced liver injury and fibrosis.

In conclusion, there remains an unmet medical need for better therapies in patients with an inadequate response to UDCA or those who cannot tolerate the drug, and those with a more advanced fibrosis stage. Results from *in vitro* pharmacology and animal model studies suggest that EDP-305 has the potential to satisfy this unmet medical need.

1.3 Nonclinical Studies

1.3.1 Mechanism of Action and Pharmacology

A summary of pharmacology studies is presented below. Additional details for each study as well as details on additional studies can be found in the Investigator's Brochure (IB). As noted for each study, the natural agonist of FXR, chenodeoxycholic acid (CDCA) and/or it's close synthetic analog obeticholic acid (OCA), were used as controls. OCA has recently been approved for the treatment of PBC.

1.3.1.1 Mechanism of Action

EDP-305 is an FXR agonist which, as discussed above, plays an essential role in the feedback regulation of bile acid biosynthesis. The efficacy and potency of EDP-305 was demonstrated in several *in vitro* assays.

- In FXR Chinese Hamster Ovary (CHO) cell reporter assays and full-length FXR Human Embryonic Kidney 293 (HEK 293) cell reporter assays, EDP-305 and its major metabolites were potent stimulators of FXR activity.
- In human Huh7.5 hepatocyte cells, EDP-305 effected a dose-dependent increase in SHP gene expression and decrease in CYP7A1 mRNA expression.
- In reporter gene assays measuring activation of 25 different nuclear receptors, only FXR was activated following incubation with EDP-305.

1.3.1.2 In Vitro Pharmacology

The ability of EDP-305 to regulate over 30 key genes involved in bile acid and lipid metabolism, inflammation, fibrosis, and glucose metabolism was evaluated using *in vitro* systems. OCA was used as a comparator/control in all cases. The results, which are described in the IB, demonstrated that EDP-305 affected the expression of 38 genes important in bile acid (5 genes)

and lipid (9 genes) metabolism, inflammation (10 genes), fibrosis (8 genes) and glucose metabolism (6 genes).

1.3.1.3 In Vivo Pharmacology

The efficacy of EDP-305 was demonstrated in animal models of disease:

- The regulation of FXR downstream genes critical for bile acid metabolism was assessed in C57BL/6 mice treated with EDP-305 or OCA orally for five days. EDP-305 induced a dose-dependent increase in FGF15 and SHP gene expression in the ileum, and dose-dependent increases in SHP and BSEP mRNA and decreases in CYP7A1 mRNA in the liver. In all cases, EDP-305 was more active than OCA.
- STAM mice develop NASH, fibrosis and ultimately hepatocellular carcinoma, in a manner replicating the pathological progression seen in the human disease. Treatment of STAM mice with EDP-305 for 4 weeks resulted in a significant reduction in non-fasted blood glucose levels, significant improvement in the NAFLD activity score (NAS), and significant reductions in key genes associated with fibrosis (ie, smooth muscle actin), and lipogenesis (sterol regulatory element binding protein 1c). In all cases, EDP-305 was more active than OCA.
- The effects of preventative and therapeutic treatment with EDP-305 and OCA on hepatic lipids were assessed in a hamster model of dyslipidemia. In this study, treatment began concurrently with the start of a 4-week high fat/high cholesterol diet (preventative model) or two weeks later (therapeutic model). EDP-305 and OCA stimulated significant reductions in hepatic lipid levels in both the therapeutic and preventative treatment protocols. Additionally, both EDP-305 and OCA showed a moderate reduction in HOMA-IR and plasma insulin levels in the therapeutic model, suggesting the potential for improvement in insulin sensitivity.
- Mdr2-/- mice develop progressive biliary-type (periportal) fibrosis resembling that observed in PSC, PBC, CFLD and congenital biliary cirrhosis (*Ikenaga et al., 2015*). In Mdr2-/- mice with pre-established fibrosis, administration of EDP-305 (10 or 30 mg) resulted in significant decreases in serum ALT and AST levels compared to vehicle controls. Mice receiving OCA (30 mg/kg) had a significant decrease in AST but not ALT levels. Histologically, treatment with EDP-305 resulted in a marked attenuation of fibrosis compared to placebo control mice with a 39% reduction in hepatic collagen content. Treatment with OCA at 30 mg/kg did not result in a histological improvement in fibrosis, and had no significant impact on hepatic collagen levels. Thus, treatment with EDP-305 potently improved pre-established liver injury and hepatic fibrosis in Mdr2-/- mice outperforming OCA in all parameters measured.

1.3.2 Safety Pharmacology

EDP-305 was tested in a battery of safety and secondary pharmacology studies. The results of the safety pharmacology tests are shown below in Table 1. A detailed description of the studies and results can be found in the IB.

Table 1: Safety Pharmacology Studies

System / Study	Test System (route)	Dose or Concentration	Results
CV/ Radioligand hERG Binding Assay	HEK293 Cells (*in vitro*)	3 and 10 µM	EDP-305 was inactive in this assay.
CV / hERG Patch Clamp Assay	HEK293 Cells (*in vitro*)	0.3, 1, 3, 10 µM	IC_{50} was estimated to be > 1 µM due to disruption of the giga-ohm seal required for successful recordings at 3 and
CV / Pharmacology & TK Study	Cynomolgus monkeys (oral)	100, 200, 400 mg/kg	NOEL was 400 mg/kg; EDP-305 did not elicit adverse clinical observations, alter body weight, or affect survival, body temperature, blood pressure, heart rate or ECG.
CNS / Safety Pharmacology Study	Crl:CD1® (ICR) mice (oral)	25, 50, 100	NOEL was 100 mg/kg; EDP-305 did not elicit any adverse effects as assessed via FOB evaluations
Respiratory / Safety Pharmacology Study	Crl:CD1® (ICR) mice (oral)	25, 50, 100	NOEL was 100 mg/kg; EDP-305 did not affect respiratory rate, tidal volume or minute volume

Abbreviations: Human embryonic kidney (HEK), Cardiovascular (CV), Toxicokinetics (TK), No-observed-effect-level (NOEL), Central nervous system (CNS), Functional observation battery (FOB), Electrocardiogram (ECG)

1.3.3 Pharmacokinetics

A series of nonclinical studies were conducted to assess the pharmacokinetics and metabolism of EDP-305.

1.3.3.1 Absorption

The absorption of a single oral dose of EDP-305 was evaluated in CD-1 mice, Sprague-Dawley rats, Beagle dogs, and Cynomolgus monkeys. The studies showed that EDP-305 was well absorbed with a calculated oral bioavailability of 9.0% in monkeys, 26.0% in mice, 29.2% in dogs, and 33.3% in rats. An evaluation of membrane permeability to EDP-305 was performed using Caco-2 cells and showed a high *in vitro* permeability of 8.7×10^{-6} to 10.8×10^{-6} cm/sec at concentrations tested from 0.5 µM to 10 µM. Based on the outcome of these absorption studies, EDP-305 is projected to have a good oral absorption in humans.

1.3.3.2 Distribution

Drug concentrations in the plasma, liver, and kidney were measured following 5-day oral administrations of EDP-305 to mice at 25, 50 or 100 mg/kg. Results showed that EDP-305 preferentially penetrated into the liver, which is the target organ of NASH and PBC. The liver-to-plasma exposure ratio ranged from 6.0 – 13.8.

As determined by equilibrium dialysis, plasma protein binding of EDP-305 (1 µg/mL) was >99.9% in mouse, rat, dog, monkey, and human. The *in vitro* partitioning of EDP-305 between plasma and formed elements (erythrocytes, leukocytes, and platelets) of whole blood was also evaluated. The blood-to-plasma concentration ratios ranged from 0.46 –0.57 in human, indicating that EDP-305 had a preferential distribution into the plasma compartment. The blood

to plasma partition ratio was independent of the concentrations evaluated (0.1, 0.5, 1 and 2 µg/mL).

1.3.3.3 Metabolism

The metabolic stability of EDP-305 was examined in liver microsomes across different species including rat, dog, monkey and human. Results showed that EDP-305 had the highest intrinsic clearance (Cl_{int}) of 41.0 µL/min/kg in monkey liver microsomes, and had the lowest intrinsic clearance of 6.5µL/min/kg and 6.9 µL/min/kg in rat and human liver microsomes, respectively. [redacted] The human metabolites observed in *in vitro* liver microsome incubations were also formed in mouse and/or monkey, the primary species for general toxicology studies. Thus, no metabolites unique to humans have been observed to date.

1.3.3.4 Drug Interactions

Based on preclinical evaluation, EDP-305 has low potential to inhibit CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or to induce CYP 1A2, 2B6 and 3A4. However, incubation in the presence of EDP-305 resulted in a concentration-dependent down-regulation of mRNA for CYP1A2 and CYP3A4.

The *in vitro* studies suggest that there is potential for EDP-305 to inhibit organic anion-transporting polypeptide (OATP)1B1 and OATP1B3. EDP-305 has low potential to inhibit BSEP, multidrug resistance-associated protein 2 (MRP2), P-glycoprotein (P-gP), and breast cancer resistance protein (BCRP) transporters. EDP-305 is unlikely to be a BCRP substrate but has potential to be a P-gP substrate.

1.3.4 Toxicology

The nonclinical safety assessment program evaluated the potential toxicity of EDP-305 in pivotal GLP studies (mouse and monkey) and in non-pivotal studies (rat, mouse, and monkey). In all studies, the vehicle was 0.5% (w/v) methylcellulose in water (ultrapure, reverse osmosis or NANOpure). The mouse was chosen as the rodent species for the definitive studies based on the presence of a gallbladder in this species versus the rat. The monkey was chosen as the non-rodent species owing to the similar metabolic profiles between monkey and human. Results of key studies are presented below while details of all studies can be found in the IB.

1.3.4.1 Repeat-dose Toxicology Studies

[redacted]

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In conclusion, an EDP-305 dose-limiting toxicity was not observed in mice or monkeys following repeat-dose administration for up to 91 days. The NOAEL for all studies was the highest dose tested. [redacted]

1.3.4.2 Genetic Toxicity/Carcinogenesis

[redacted]

[redacted] Thus, these results support the conclusion that EDP-305 is non-genotoxic.

1.4 Clinical Studies

Five Phase 1 clinical studies have been conducted and/or are ongoing with EDP-305 including a First-in-Human (FIH) study in healthy volunteers (HV) and in subjects with presumptive NAFLD (PN), a hepatic impairment study, two drug: drug interaction (DDI) studies, and a bioavailability (BA) study (Table 4).

Table 4: Clinical Studies with EDP-305

Study ID	Phase / Type	Population Planned/Actual (N)	Title
EDP 305-001	1 / FIH	HV & PN / N=42/50(HV), N=48/96(PN)	A Randomized, Double-Blind, Placebo-Controlled, First-In-Human Study of Orally Administered EDP-305 to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses (SAD), Multiple Ascending Doses (MAD) and the Effect of Food on EDP-305 Pharmacokinetics in Healthy Subjects, and of Multiple Ascending Doses (MAD) in Subjects with Presumptive NAFLD
EDP 305-003	1 / HI	HV, mild & moderate HI / N=30/29	A Phase 1, Open-Label, Parallel Group, Single Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of EDP-305 in Subjects with Varying Degrees of Hepatic Function
EDP 305-004	1 / DDI	HV / N=24/24	A Non-Randomized, Multiple-Dose, Open-Label, Single Sequence Study to Evaluate the Effect of Concomitant Administration of EDP-305 on the Pharmacokinetics and Safety of Midazolam, Caffeine, and Rosuvastatin in Healthy Human Volunteers
EDP 305-005	1 / DDI	HV / N=48/48	A Non-Randomized, Open-Label, Two-Part, Drug-Drug Interaction Study to Evaluate the Effects of Itraconazole and Rifampin on the Pharmacokinetics and Safety of EDP-305 in Healthy Volunteers
EDP 305-006	1 / BA	HV / N=18/18	A Randomized, Single-Dose, Open-Label, 3-Way, 3-Period Crossover, 6-Sequence Bioavailability Study Comparing the Pharmacokinetics of EDP-305 Suspension (reference) to Tablet (test) in Healthy Human Volunteers under Fed and Fasted Conditions
Abbreviations: Pop. (study population); FIH (first-in-human); HV (healthy volunteer(s)); PN (presumptive NAFLD); HI (hepatic impairment); DDI (drug:drug interaction); BA (bioavailability)			

1.4.1 Study EDP 305-001

A Randomized, Double-Blind, Placebo-Controlled, First-In-Human Study of Orally Administered EDP-305 to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses (SAD), Multiple Ascending Doses (MAD) and the Effect of Food on EDP-305 Pharmacokinetics in Healthy Subjects, and of Multiple Ascending Doses (MAD) in Subjects with Presumptive NAFLD

A Phase 1 FIH study (EDP 305-001) to evaluate the safety, tolerability, and pharmacokinetics of EDP-305 in healthy volunteers (HV) and subjects with presumptive NAFLD (PN) was conducted. The study included 2 phases: a Single Ascending Dose (SAD) phase enrolling healthy adult subjects, including a "fasted" versus "fed" two-part cohort to assess food effect (SAD/FE), and a Multiple Ascending Dose (MAD) phase enrolling healthy adult subjects into 3 cohorts, and subjects with PN into 3 cohorts. A total of 42 HV were planned to be enrolled into 6 SAD cohorts at doses of 1, 5, 10, 20, and 40 mg EDP-305/placebo and a total of 48 subjects were planned to be enrolled into 3 MAD-HV cohorts (5, 10, 20 mg EDP-305/placebo) and 3 MAD-PN cohorts (5, 10, 20 mg EDP-305/placebo). The study was amended to add a 80 mg cohort in the SAD phase, and 6 MAD cohorts (3 HV and 3 PN) assessing 3 lower doses of EDP-305, 0.5mg, 1mg, and 2.5mg, in each subject population. In all cohorts except SAD/FE, 8 subjects were enrolled at a randomization ratio of 3:1 (6 receiving EDP-305 and 2 receiving placebo (PBO)). Ten subjects were enrolled in the SAD/FE cohort and randomized 4:1, EDP-305 to PBO.

A total of 146 subjects have been enrolled and received at least one dose of EDP-305 or placebo, and were included in the safety analyses: 50 healthy subjects in the SAD phase, and 48 healthy subjects and 48 subjects with presumptive NAFLD in the MAD phase.

EDP-305 was generally well tolerated at single doses up to 80 mg and at multiple doses up to 20 mg for 14 days. TEAEs occurring in ≥ 2 EDP-305 treated subjects in MAD were: headache and pruritus in HV, and constipation and pruritus in PN. No SAEs or Grade 4 AEs were reported. Drug related pruritus was reported after multiple dosing at the higher doses of EDP-305 10 mg (n=2) and 20 mg (n=7), and PBO (n=1), with 1 discontinuation at 20 mg in HV (moderate). Majority of drug related pruritus were mild to moderate (except one subject with severe). No pruritus was observed at lower doses (below 10 mg). No clinically significant laboratories were reported except one transient Grade 2 ALT/AST elevation in one subject (MAD-HV-20 mg) that led to drug discontinuation. Total, LDL-, HDL- cholesterol and triglycerides did not differ between EDP-305 and placebo in either healthy or PN subjects at any dose, except at 20 mg in PN for cholesterol and HDL.

A dose proportional increase in exposure was observed following single and multiple doses of EDP-305. Pharmacokinetic (PK) profiles following single doses of EDP-305, indicated linear, one-compartment PK, with monophasic decline. Half-life was similar following single doses with a mean ranging from 11 to 16 hours. A high fat meal increased EDP-305 exposure by approximately 200%. Half-life ranged from 10-23 hours following multiple doses of EDP-305. There was more drug accumulation (~3-fold) observed following 20 mg dose compared to lower doses. Similar exposures were observed in both HV and PN subjects. The metabolite (EP-022571, EP-022572 and EP-022679) levels were generally low (<5% of parent drug), following single and multiple doses of EDP-305. EDP-305 and metabolite levels in the urine were low and

generally below limit of quantification suggesting that urinary excretion is a minor elimination pathway.

Significant elevations of FGF19 and diminutions in C4 demonstrated potent engagement of the FXR receptor at doses that neither elicit adverse effects on lipids nor result in pruritus.

In summary:

- EDP-305 was generally safe over a broad range of single and multiple doses with PK suitable for once daily oral dosing.
- Overall PK/pharmacodynamic (PD) profiles were similar between HV and PN, with a more pronounced PD effect at all doses compared to PBO in PN

These results support clinical evaluation of EDP-305 administered once daily in patients with PBC.

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1.5 Potential Risks and Benefits

Potential risks to subjects receiving EDP-305 have been estimated based on results from the repeat dose toxicity studies and safety data from the Phase 1 study (EDP 305-001) conducted in healthy volunteers and subjects with presumptive NAFLD (PN).

[redacted]

Safety data from EDP 305-001:

- EDP-305 was generally well tolerated at single doses up to 80 mg and at multiple doses up to 20 mg for 14 days.
- TEAEs occurring in ≥ 2 EDP-305 treated subjects were: headache and pruritus in HV, and constipation and pruritus in PN.
- No clinically significant laboratories were reported except one transient Grade 2 ALT/AST elevation in n=1 (MAD-HV-20mg) that led to drug discontinuation.
- No effects on lipids were observed after 14 days except for cholesterol and HDL at 20 mg in PN.
- Majority of drug related pruritus were mild to moderate (except n=1) and reported after multiple dosing at the higher doses of EDP-305 10 mg (n=2/12) and 20 mg (n=7/12), and PBO (n=1/24), with 1 drug discontinuation at 20 mg in HV. No pruritus was observed at any multiple doses below 10mg.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of the study is to evaluate the effect of EDP-305 on ALP levels.

2.1.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the safety and tolerability of EDP-305
- To evaluate the effect of EDP-305 on bilirubin levels
- To evaluate the effects of EDP-305 on other markers of liver function
- To evaluate the effects of EDP-305 on non-invasive markers of liver fibrosis
- To evaluate the effects of EDP-305 on inflammatory markers
- To evaluate the effects of EDP-305 on lipids
- To evaluate the effects of EDP-305 on pruritus
- To evaluate the effects of EDP-305 on Quality of Life (QoL)
- To evaluate the PK of EDP-305 and metabolites in plasma
- To evaluate the PD of EDP-305

2.2 Endpoints

2.2.1 Primary Endpoints

The primary endpoint of the study is the proportion of subjects with at least 20% reduction in ALP from pretreatment values or normalization of ALP at Week 12.

2.2.2 Secondary Endpoints

The secondary endpoints are as follows:

- Frequency of adverse events (AEs), serious AEs, and AEs leading to discontinuation through Week 12
- Bilirubin (Total, Conjugated, Unconjugated) decline from Baseline at Week 12
- Change from Baseline in Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST), Gamma-Glutamyl transferase (GGT) at Week 12
- Change from Baseline of noninvasive liver fibrosis markers (Enhanced Liver Fibrosis [ELF] panel, PRO C3, AST to Platelet Ratio Index [APRI] and fibrosis-4 [FIB-4]) at Week 12

- Change from Baseline in fibrinogen, CRP, IL6, IL1β, TNF-α, TNF-β , alpha2 macroglobulin and haptoglobin levels at Week 12
- Change from Baseline in Triglycerides (TG), Total Cholesterol (TC), High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C) at Week 12
- Change from Baseline in 5D-itch scale and Visual Analog Score (VAS) at Week 12
- Change from Baseline in PBC-40 Quality of Life (QoL) at Week 12
- Pharmacokinetic parameters of EDP-305 (and metabolites): C_{max}, T_{max}, and AUC_{last}
- Pharmacodynamic parameters of EDP-305: FGF19, C4, and Bile Acid (BA) at Week 12

3. SELECTION OF SUBJECTS

A total of approximately 119 subjects with a diagnosis of PBC are planned for enrollment into this study.

3.1 Subject Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled into this study:

1. An informed consent document must be signed and dated by the subject
2. Male and female subjects of any ethnic origin between the ages of 18 and 75 years, inclusive
3. Male or female with a diagnosis of PBC by at least two of the following criteria:
   - History of ALP above ULN for at least 6 months
   - Positive Anti-Mitochondrial Antibodies (AMA) titers (>1/40 on immunofluorescence or M2 positive by enzyme linked immunosorbent assay [ELISA] or positive PBC-specific antinuclear antibodies [PBC-ANAb])
   - Documented liver biopsy result consistent with PBC (with no cirrhosis)
4. For subjects with no documented liver biopsy performed within 2 years, subjects must undergo a transient elastography (Fibroscan) showing liver stiffness <14.0 kPA
5. Must be on a stable dose of UDCA 12-20 mg/kg/day for at least 6 months prior to Screening or intolerant of UDCA in the opinion of the Investigator (no UDCA for at least 12 weeks prior to Screening)
6. Alkaline Phosphatase (ALP) ≥1.67 × ULN and/or total bilirubin >ULN but <2 × ULN (<2.4 mg/dL)
7. Subjects must have Screening laboratory values for Hepatitis B surface antigen (HBsAg), anti-HCV antibodies and HCV RNA negative, and Human Immunodeficiency Virus (HIV) 1 and 2 antibodies (Ab) as seronegative. NOTE: Subjects previously infected by chronic hepatitis C and treated with direct acting antivirals (DAAs) with sustained virologic response (SVR) for at least 3 years will be allowed.
8. Female subjects of childbearing potential must agree to use two effective methods of contraception from the date of Screening until 90 days after the last dose of EDP-305. Effective methods of contraception are defined as:
   - a condom for the male partner and at least one of the following for the female participant:
     - Intrauterine device
     - Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive

   Note: The above does not apply to female subjects of non-childbearing potential (ie, physiologically incapable of becoming pregnant) defined as:
   - has had a complete hysterectomy greater than or equal to 3 months prior to dosing or
   - has had a bilateral oophorectomy (ovariectomy) or
   - has had a bilateral tubal ligation or fallopian tube inserts or

- is postmenopausal (a demonstration of a total cessation of menses for ≥1 year with an FSH level of >35 mIU/mL).

9. All male participants who have not had a vasectomy must use effective contraception from Day -1 to 90 days after their last dose of study drug. Effective contraception is defined as a condom and spermicide for the male, or condom and at least one of the following for a female partner:
   - Intrauterine device
   - Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive
   - Be of non-childbearing potential
10. Male subjects must agree to refrain from sperm donation from the date of Screening until 90 days after their last dose of study drug
11. Screening body mass index (BMI) of ≥18 kg/m^2
12. Subject must be willing and able to adhere to the assessments, visit schedule, prohibitions and restrictions, as described in this protocol

3.2 Subject Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Laboratory Screening Results:
   - AST >5 × ULN
   - ALT >5 × ULN
   - Patients with Gilbert's syndrome will not be allowed due to interpretability of bilirubin levels
   - Total white blood cells (WBC) <3000 cells/mm^3
   - Absolute neutrophil count (ANC) <1500 cells/mm^3
   - Platelet count <140,000/mm^3
   - Prothrombin time (international normalized ratio, INR) >1.2
   - Serum creatinine >2 mg/dL or clearance creatinine <60 mL/min (based on Cockroft-Gault Method)
2. Suspected to have relevant nonalcoholic fatty liver disease (NAFLD) as based on the judgment of the Investigator at Screening
3. Known history of alpha-1-Antitrypsin deficiency
4. Use of immunosuppressants known to have an effect on the liver of patients with PBC (eg, colchicine, methotrexate, or azathioprine) in the 3 months preceding Screening.
5. Current use of fibrates, including fenofibrates. NOTE: Subjects who discontinued fibrates for at least 3 months before Screening can participate
6. Use of an experimental treatment for PBC within the past 6 months
7. Prior use and/or concomitant treatment with OCA
8. Use of experimental or unapproved drugs within 1 year of Screening

9. Any other condition(s) that would compromise the safety of the subject or compromise the quality of the clinical study, as judged by the Principal Investigator (PI)
10. Pregnant or nursing females
11. Recipients of liver or other organ transplantation or anticipated need for orthotropic organ transplantation in one year as determined by a Model for End-Stage Liver Disease (MELD) Score ≥15
12. Co-existing liver or biliary diseases, such as primary sclerosing cholangitis, choledocholithiasis, acute or chronic hepatitis, autoimmune hepatitis, alcoholic liver disease, nonalcoholic steatohepatitis (NASH), acute infection of bile duct system or gall bladder, history of gastrointestinal bleeding (secondary to portal hypertension), cirrhosis, cholangiocarcinoma diagnosed or suspected liver cancers
13. Cirrhosis with or without complications, including history or presence of: spontaneous bacterial peritonitis, hepatocellular carcinoma
14. Hepatorenal syndrome (type I or II) or Screening serum creatinine >2 mg/dL (178 µmol/L)
15. Prior variceal hemorrhage, uncontrolled encephalopathy, Child-Pugh Class A, B and C, esophageal varices, or refractory ascites within the previous 6 months of Screening (defined as date informed consent signed)
16. Patients with a history of severe pruritus requiring current or prior systemic treatment (e.g., with BAS or rifampicin)
17. Medical conditions that may cause non-hepatic increases in ALP (e.g., Paget's disease)
18. Any condition possibly affecting drug absorption (eg, gastrectomy <3 years prior to Screening). NOTE: Subjects who have undergone gastric surgeries known to not affect drug absorption such as gastric band or gastric sleeve will be allowed if they are stable for at least 1 year prior to Screening.
19. History of regular alcohol consumption exceeding 14 drinks/week for females and 21 drinks/week for males within 6 months of Screening. One drink is defined as 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor)
20. Participation in a clinical trial within 30 days prior to study drug administration
21. Clinically significant electrocardiogram (ECG) abnormalities or QTcF greater than 450 ms for males and 470 ms for females at either Screening or Baseline, or any prior history of QT abnormality
22. Use of CYP3A4 and P-gp inducers and inhibitors within 14 days prior to the first dose of study medication and throughout study duration
23. Clinically significant history of drug sensitivity or allergy, as determined by the PI
24. Subject has received an investigational agent or investigational vaccine within 30 days, or a biological product within 3 months or 5 elimination half-lives (whichever is longer) prior to the planned intake of study drug
25. Use of a new statin regimen from Screening and throughout study duration.
    NOTE: Subjects on a stable dose of statins for at least 3 months prior to Screening are allowed. No dose modification during the study will be allowed.
26. Use of immunosuppressants (eg, systemic corticosteroids) for more than 2 consecutive weeks in duration within 1 year prior to Screening.

4. STUDY DESIGN

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study assessing the safety, tolerability, pharmacokinetics, and efficacy of two doses of EDP-305 in subjects with PBC with or without an inadequate response to UDCA.

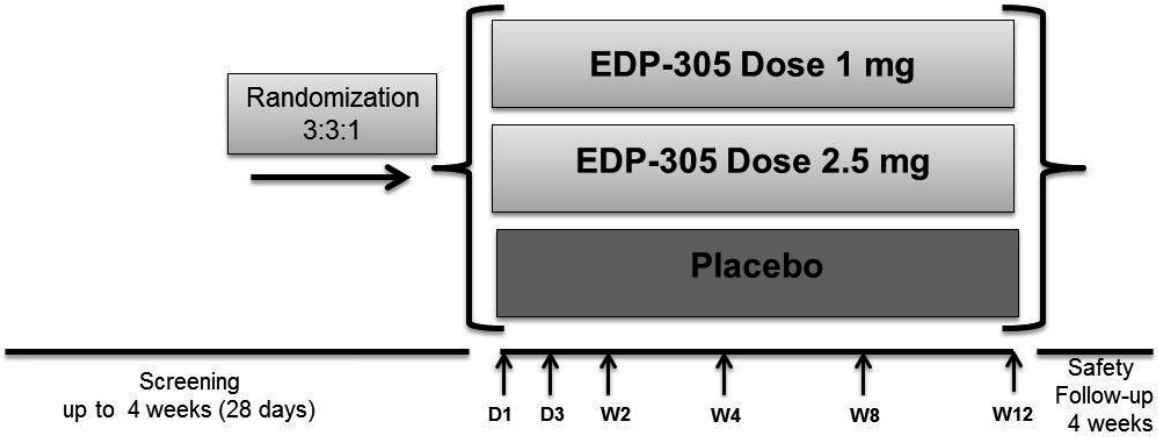
The study is composed of 3 phases or periods:

- Screening period which includes the Screening Visit and may occur over a time period of 28 days prior to the first dose of study drug
- Treatment period which begins with the first dose of study drug on Day 1 and concludes with the End of Treatment (EOT) Visit on Day 84 (Week12)
- Safety Follow-up period which includes the End of Study (EOS) Visit on Day 112.

4.1 Dose and Treatment Schedule

Subjects will be randomized in a 3:3:1 ratio to one of two doses of EDP-305 and placebo. Every subject will receive a single daily dose of blinded study drug for a total of 12 weeks. An overview of the study design is shown in Figure 1. Study visits and assessments are detailed in the Schedule of Assessment (SoA) in Appendix 1.

Figure 1: Study Design



Abbreviations: D=Day; W=Week

4.2 Rationale for Study Design

This proposed trial will evaluate EDP-305 in patients with PBC who will be randomized to one of three treatment groups: (1) 1 mg EDP-305, (2) 2.5 mg EDP-305, or (3) placebo in a 3:3:1 ratio.

4.2.1 Justification of Design and Control Group

Until recently, ursodeoxycholic acid (UDCA) has been the only approved treatment for PBC, which was approved by the FDA in 1997. While UDCA therapy has a marked impact on clinical outcomes in PBC, up to 40% of UDCA-treated patients have a suboptimal or absent response to UDCA and, as such, are at significantly increased risk of an adverse outcome (death, requiring a liver transplant, or other clinical complications) (*Carbone et al., 2013*; *Corpechot et al., 2008*; *ter Borg et al., 2006*) (U.S. Department of HHS Organ Procurement and Transplantation Network.) (*https://optn.transplant.hrsa.gov*, Sept 5, 2016). In May 2016, the U.S. Food and Drug Administration granted accelerated approval for the FXR agonist Ocaliva® (obeticholic acid, OCA) for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as a single therapy in adults unable to tolerate UDCA (U.S. Food and Drug Administration, 2016). The confirmatory trials are ongoing.

This Phase 2 double-blind, parallel dose group study evaluating 3 doses of EDP-305 compared to placebo was designed to assess the safety, efficacy, and PK of EDP-305 for the treatment of subjects with PBC over a 12-week treatment period. This trial will establish the effect of adding EDP-305 to the PBC standard of care treatment, UDCA on the ALP change. Patients will continue their pre-study stable dose of UDCA throughout the trial. Accordingly, patients will not have any standard therapies withheld in the trial. The use of placebo is implemented to maintain the study blind and scientific validity of the trial. Some patients cannot tolerate UDCA; their standard of care does not include UDCA. Patients taking drugs that might have effects in PBC or recently conditionally approved (i.e., OCA) are being excluded from the trial to ensure that the trial provides the clearest comparison of the effects of EDP-305 with placebo.

4.2.2 Justification of EDP-305 Dose

This phase 2 trial has been designed to assess the efficacy, safety and tolerability of 2 doses (1 mg, and 2.5 mg) of EDP-305 in patients with PBC so as to provide proof of concept data to support Phase 3 in this indication.

Study EDP 305-001 characterized a broad range of single and multiple doses: from 1 to 80 mg in the SAD part, and from 0.5 to 20 mg in the MAD part, and administered as an oral suspension. The safety and tolerability of EDP-305 has been established not only in healthy subjects but also in subjects with presumptive NAFLD at doses up to 80 mg single dose and up to 20 mg once daily for 14 consecutive days.

As demonstrated in study EDP 305-001, EDP-305 was generally well tolerated at single doses up to 80 mg and at multiple doses up to 20 mg for 14 days. No SAEs or Grade 4 AEs were reported. No clinically significant laboratories were reported except one transient Grade 2 ALT/AST elevation in n=1 (MAD-HV-20mg) that led to drug discontinuation. Drug related pruritus was reported after multiple dosing at the higher doses of EDP-305 10 mg (n=2) and 20 mg (n=7), and PBO (n=1), with 1 discontinuation at 20 mg in HV. Total, LDL-, HDL- cholesterol and triglycerides did not differ between EDP-305 and placebo in healthy at any dose or PN subjects at any dose, except for cholesterol and HDL at 20mg.

The pharmacokinetics of EDP-305 was profiled over a broad range of single and multiple doses. A dose proportional increase in exposure was observed over the broad dose range studied. Half-life ranged from 11-16 hours and from 10-23 hours following single and multiple doses of EDP-305, respectively. There was more drug accumulation observed following 20 mg dose compared to lower doses, indicating a potential change in the PK profile at 20 mg.

[redacted]

Based on observed safety profile to date, pharmacokinetics profile and changes in C4 and FGF-19 in study EDP 305-001 and relative bioavailability data from study 006, (Section 1.4.2.4), EDP-305 doses of 1 and 2.5 mg once daily using the tablet formulation are selected for this study. The exposures associated with this dose range are expected to result in clinically meaningful changes in C4 and other relevant markers of FXR activity (FGF-19), while minimizing the incidence of potential adverse events (i.e. pruritus).

[redacted] Doses of 1 and 2.5 mg using the tablet formulation in the fasted state (comparable to approximately 2.5 and 5 mg using the suspension formulation in the fasted state)

are expected to provide exposures associated with clinically meaningful changes in C4 and FGF-19, while minimizing the incidence of potential adverse events (i.e. pruritus).

In summary, based on data from studies 001, 004, and 006, doses of 1 and 2.5 mg are expected to provide:

- A safe and tolerable regimen with lowest chance to induce pruritus
- Plasma exposures representing linear, time-independent PK and correlated with desirable dose dependent changes in PD markers suitable for a once daily dosing
- Maximal decreases in C4 ranging from approximately 67% to 85% at steady state and associated increases in FGF-19 ranging from approximately 1000% to 1700% at steady state. Given the similarity in the MOA between EDP-305 and OCA, the expected changes in C4/FGF-19 over the selected dose range for EDP-305 in phase 2 studies, are expected to be associated with relevant downstream pharmacological effects clinically relevant changes in liver markers.

5. STUDY DRUG AND TREATMENT OF SUBJECTS

5.1 Description of Study Drug

EDP-305 drug product tablets consist of 1 mg, and 2.5 mg strengths supplied as round, white to off-white tablets debossed with I, and II respectively, to differentiate strength on one side of the tablet. Matching placebos for the two strengths will also be supplied as round, white to off-white tablets debossed with I, and II for 1mg, and 2.5 mg strengths respectively. Study drug and matching placebo tablets will be supplied by Enanta.

The matching placebo will contain all the excipients present in the EDP-305 drug product tablets with the exception of the active drug. [redacted]

EDP-305 drug product tablets and matching placebo tablets should be stored under refrigerated conditions (2°C – 8°C) at all times.

Additional information will be provided in the Pharmacy Manual.

5.2 Packaging and Labeling

EDP-305 tablets and matching placebo will be supplied in [redacted] All bottles containing clinical trial material will be labeled according to study drug labeling in compliance with applicable local and national regulations for labeling of investigational products.

EDP-305 tablets are packaged in a [redacted] The bottles will be induction sealed.

5.3 Storage

EDP-305 drug product tablets and placebo tablets in bottles will be shipped to the clinical site and stored under refrigerated conditions (2°C–8°C).

5.4 Accountability

Study drug may be dispensed only under the supervision of the Investigator or authorized designee and only to study subjects. The Pharmacist or designated study staff will maintain

adequate records of 1) study drug received, 2) study drug dispensed to the subjects, and 3) drug returned by the subjects. Subjects will be instructed to return all used and unused study drug to the site. All used and unused study drug will be retained at the site according to instructions provided by Enanta or designee until monitored by the study monitor. The study monitor will review study drug records and inventory throughout the study.

5.5 Handling and Disposal

Study drug must not be used for any purpose other than for administration to subjects enrolled into this clinical study. All study drug bottles that are opened and returned by subjects as well as those that are not opened or assigned to subjects will be retained at the site according to instructions provided by Enanta or designee until monitored by the study monitor. Full accountability of all study drug distributed to subjects will be documented per Section 5.4.

At the end of the study, Enanta will provide instructions for the destruction of any unused study drug. If Enanta authorizes destruction at the study site, the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy and any special instructions provided by Enanta, and, that the destruction was adequately documented.

5.6 Treatment Assignment and Randomization

Subjects will be randomized to study treatment using an Integrated Web Response System (IWRS). Subjects will be stratified initially by participation in the PK/PD substudy and then by a) prior use of fibrates and b) prior and/or current use of UDCA. Subjects will be randomized to the treatment groups shown below:

- Treatment Group 1 (N=45); EDP-305 1 mg orally for 12 weeks
- Treatment Group 2 (N=45); EDP-305 2.5 mg orally for 12 weeks
- Treatment Group 3 (N=15); Placebo (PBO) orally for 12 weeks

A minimum of 10 subjects per treatment group will be included in the PK/PD substudy. The randomization code will be produced by Enanta (or designee). The Enanta unblinded biostatistician or designee will review and approve the final randomization list.

During the Screening Period, subjects will be identified by a unique screening number assigned by the clinical site. Subjects who have completed screening assessments and are eligible for participation in the study will be randomized before the first dose of study drug (Day −1 or Day 1) and assigned a unique subject number which will be used to identify the subject throughout the study.

5.7 Study Drug Dose and Administration

Complete instructions for dispensing and administering study drug are presented in the study specific Pharmacy Manual.

The subject will be instructed to take all study drug doses at home except when study drug will be administered in the clinic (ie, at the Days 1 and 3, and Weeks 2, 4, 8 and 12 visits). The subject will be instructed to take the study drug approximately at the same time every day (ie, orally in the morning after fasting overnight for a minimum of 8 hours). If a subject forgets to take their study drug at their scheduled time, the dose may be taken later that day following a minimum of 4 hours fast; however, no more than 1 dose should be taken on any calendar day and a minimum of 16 hours between doses should be maintained.

Stopping rules for study drug administration are provided in Section 10.1.

5.7.1 Dispensing of Study Drug

When drug is dispensed at the clinic, study drug may be dispensed only under the supervision of a qualified pharmacist or an authorized designee and only for administration to the study subjects.

A 4-week supply of blinded study drug in individually labelled bottles will be dispensed by qualified site personnel to the subject at the visit on Day 1, Week 4, and 8. The bottle number dispensed to the subject and the number of tablets dispensed will be recorded in the site source documents. Subjects will be instructed to store study drug in the original bottle under refrigerated conditions. Subjects will be provided with a cooler bag to bring the study drug home. Once returning home, the subject will be instructed to refrigerate the study medication, removing it only for dosing.

5.7.2 Treatment Compliance

The subject will be instructed to bring all study drug (including empty bottles) to the clinic at each study visit. Both accountability and study drug compliance will be reviewed at each visit as indicated in the SoA (Appendix 1). The number of tablets will be counted and the study personnel will ask the subjects why any doses were missed, if applicable. Any potential reasons for lack of compliance with dosing will be monitored and followed up by the study personnel.

For any subject demonstrating continued noncompliance of study drug dosing despite continued educational efforts, the Investigator should contact the study medical monitor to discuss possible discontinuation of the subject from the study.

5.8 Concomitant Medications

Subjects taking UDCA at the start of the study must remain on the same dose of UDCA throughout the 12-week dosing period. If the Investigator believes that dosing with UDCA should be stopped due to adverse reactions, then the Medical Monitor should be consulted prior to discontinuing the drug. Subjects who were not taking UDCA at the start of the study will not be allowed to initiate treatment during the study.

All subjects enrolled in the study must abstain from taking any prohibited concomitant medication through the end of study.

Details of prior and concomitant medication use will be recorded in the source documentation and the electronic case report form (eCRF) as indicated in the SoA (Appendix 1).

5.8.1 Co-administration of EDP-305 and Ursodiol (ursodeoxycholic acid, UDCA)

Drug-drug interaction between EDP-305 and UDCA is not anticipated based on available EDP-305 drug-drug interaction (see Section 1.4.2), and on UDCA metabolic profile from the literature. In the liver, ursodiol is conjugated with glycine or taurine, then secreted into bile. These conjugates of ursodiol are absorbed in the small intestine by passive and active mechanisms. The conjugates can also be deconjugated in the ileum by intestinal enzymes, leading to the formation of free ursodiol that can be reabsorbed and reconjugated in the liver. Nonabsorbed ursodiol passes into the colon where it is mostly 7- dehydroxylated to lithocholic acid. Some ursodiol is epimerized to chenodiol (CDCA) via a 7-oxo intermediate. Chenodiol also undergoes 7-dehydroxylation to form lithocholic acid. These metabolites are poorly soluble and excreted in the feces. A small portion of lithocholic acid is reabsorbed, conjugated in the liver with glycine, or taurine and sulfated at the 3 position. The resulting sulfated lithocholic acid conjugates are excreted in bile and then lost in feces (*Axcan Scandipharm Inc., 2007*).

As UDCA is primarily metabolized through conjugation, EDP-305 is not expected to have an impact on the metabolism of UDCA.

Available data from Study EDP 305-005 indicated that CYP3A4 is a major pathway for EDP-305 metabolism, as is also supported by preclinical phenotyping data (refer to the Investigator's Brochure for additional detail). As reported in the literature, UDCA did not have an effect on midazolam pharmacokinetics (a sensitive CYP3A4 substrate) (*Becquemont et al., 2006*; *Dilger, Denk, Heeg, & Beuers, 2005*). [redacted] UDCA had limited effect on digoxin (a sensitive P-gp substrate) (*Becquemont et al., 2006*). Based on this information, UDCA is not expected to have an effect on EDP-305 pharmacokinetics during co-administration.

5.9 Prohibited Medications

[redacted]

Use of a new statin regimen is prohibited from Screening and throughout study duration. Subjects on a stable dose of statins for at least three months prior to Screening are allowed. However, no dose modification during the study will be allowed.

5.10 [redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

6. BLINDING

The study will be double-blinded meaning the subjects, Investigators, and site staff will be blinded to treatment assignment until the completion of the study.

All study personnel will be blinded to treatment assignment except for the following individuals:

- Unblinded Enanta/CRO statistician for purpose of generating and monitoring the randomization list
- Unblinded Drug Supply Chain personnel for the purpose of monitoring drug supplies
- Enanta/CRO Pharmacovigilance Group and Regulatory Affairs representatives when required to satisfy regulatory reporting requirements
- Bioanalytical Laboratory for the purpose of measuring drug concentrations

6.1 Blinding of Study Samples

6.1.1 Blinding of Biomarker, Fibrosis and Inflammatory Markers and Laboratory Liver Test Results

Investigators, site personnel and CRO/Sponsor will be blinded to the following laboratory tests post-Baseline:

- Biomarker laboratory data
  - FGF19,
  - total bile acids (BA),
  - C4 [7α-OH-4-cholesten-3-one],
- Fibrosis and inflammatory markers
  - ELF Panel (ie, hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], and tissue inhibitor of metalloproteinase 1 [TIMP-1])
  - PRO C3
  - Fibrinogen, CRP, alpha2 macroglobulin and haptoglobin
  - Tumor necrosis factor alpha and beta (TNF-α and β)
  - Interleukin (IL)-6, IL1β
  - AST to Platelet Ratio Index (APRI)
  - Fibrosis 4 (FIB-4) Index
- Liver Tests
  - ALP

6.1.2 Blinding of Pharmacokinetic Samples

All PK sample concentration measurements will be blinded to the Investigators, site staff, and study subjects. The laboratory performing bioanalytical analysis, however, will be provided the randomization scheme.

6.2 Unblinding

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The unblinding method will use the IWRS process.

Unblinding of individual subject treatment by the Investigator should be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, the Investigator must first attempt to contact the study Medical Monitor to discuss and agree to the need for unblinding. In situations in which the Investigator has attempted and failed to contact the Medical Monitor, and/or the urgency of the case required immediate action, he/she should use his/her best judgment, based on the nature and urgency of the clinical situation, and proceed with unblinding.

- [redacted]
- [redacted]

Once a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the Medical Monitor and study coordinator should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (the reason, date, etc.) should be clearly recorded in the subject's study file. In addition, the Investigator should consider whether the clinical event that prompted unblinding should be considered a serious adverse event (SAE), according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report as described in Section 9.2.

CRO pharmacovigilance will also unblind any SAE reports in compliance with Regulatory reporting requirements. In addition, Enanta may unblind individual subjects at any time for matters relating to safety concerns.

7. STUDY CONDUCT AND VISIT SCHEDULE

7.1 Study Visits

Details of assessments at each visit are presented in the SoA (Appendix 1).

7.1.1 Screening

Screening procedures will occur after the subject signs and dates an Institutional Review Board (IRB) or Ethics Committee (EC) approved ICF and provides authorization to use protected health information (See Section 12.1.3). The ICF will be completed prior to conduct of any study-specific procedures.

Screening procedures will be conducted as listed in the SoA (Appendix 1). Screening will occur over a period lasting no more than 28 days. For each subject, Screening can occur on one day or over multiple days. All Screening assessments must occur no earlier than 28 days before the first dose of study drug at the Day 1 visit. If any Screening assessment falls outside of that window, the Investigator should consult with the Sponsor's Medical Monitor to determine if the assessment needs to be repeated.

If a subject does not qualify for study entry due to an out-of-range lab value that is not consistent with the subject's medical history or appears spurious, with the approval of the Medical Monitor, the subject may retest that lab parameter once if the Investigator believes that he/she would qualify upon retest.

At the completion of Screening procedures/assessments, subjects who qualify for the study should be given detailed instructions on fasting requirements prior to the first dose and when to return to the clinic for the Day 1 visit.

7.1.2 Rescreening

Subjects who met all eligibility criteria that were current at the time of their Screening Visit may be re screened under the following circumstances and with the approval of the medical monitor:

- Subjects within the Screening Period who met all eligibility criteria, but are not able to obtain required documentation within the allotted window for the Screening Period.
- Subjects who are eligible, but transiently (for personal reasons) unable to commit to all study procedures

7.1.3 Baseline Visit (Day1)

Subjects who meet all inclusion criteria and none of the exclusion criteria will report to the clinic on the morning of Study Day 1 after fasting overnight for a minimum of 8 hours. After a review

of applicable inclusion/exclusion criteria, subjects who continue to satisfy eligibility requirements will be randomized in a 3:3:1 ratio to their treatment group. Predose assessments and procedures will be conducted as noted in the SoA (Appendix 1) and considered Baseline values.

After predose/Baseline study procedures are completed, subjects will receive the first dose of study drug in the clinic on Day 1 followed by PK and biomarker blood draws. Additional PK, C4, FGF19 and Bile Acid samples will be collected from subjects at a subset of sites (PK/PD Substudy) that have the technical capability to collect and process intensive (longer duration) sampling. PK and PD samples will be collected as described in Section 8.4.

Before leaving the clinic, subjects will receive study medication and instructions on how to take the medication at home.

7.1.4 Treatment Period Visits (Day 3, Weeks 2, 4, 8 and 12 /EOT)

Except for days when there is a clinic visit, subjects will take their daily dose of study drug at home for 12 weeks. Throughout the 12-week treatment period, subjects will return to the clinic as shown in the SoA (Appendix 1) for study assessments. Prior to each visit, subjects will be instructed to fast for a minimum of 8 hrs prior to the scheduled visit time.

At the end of the treatment period, subjects will complete the EOT visit. Subjects who complete 12 weeks of treatment will complete the EOT assessments at the Day 84 visit/Week 12. Subjects who discontinue treatment early should complete EOT assessments at the time of discontinuation (if in the clinic) or as soon thereafter as possible if the subject discontinues treatment while not in the clinic. Procedures performed are specified in the SoA (Appendix 1).

Population PK and PK/PD samples will be collected as specified in the SoA (Appendix 1) and as described in Section 8.4.

Subjects should discontinue drug on Day 84. Subjects, who return for their EOT Visit after Day 84, should stop dosing on Day 84 (Week 12 Visit).

7.1.5 Safety Follow-up Period (End of Study Visit)

All subjects, including those who discontinue treatment early, should return to the clinic for the End of Study (EOS) visit 4 weeks after the last dose of study drug for safety assessments (Appendix 1). For subjects who complete the study, the EOS visit would be scheduled on Day 112. Following completion of study procedures, subjects will be terminated from the study.

Any subject with ongoing AEs/SAEs (serious adverse events) at the EOS visit should be followed until resolution of their AE/SAE or until the Investigator has determined that the event has stabilized as discussed in Section 9.3.

7.2 Subject Withdrawal / Early Termination

Subjects are free to withdraw their participation at any time during this clinical trial. The Investigator has the right to remove any subject from treatment with study drug or participation in the study. However, the Investigator should consult with the Sponsor's Medical Monitor before prematurely removing a subject. For any subject who decides to withdraw from the study, the Investigator should inquire about the reason for withdrawal, request that the subject to return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events. Although a subject may discontinue study treatment, every effort must be made to continue the subject on the study, returning for the EOT visit (if prematurely discontinuing treatment) and the safety follow-up visit.

If a subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. Enanta may retain and continue to use any data collected before such withdrawal of consent.

For safety monitoring purposes, subjects who withdraw after receiving study drug should return to the clinic as soon as possible and undergo the EOT evaluations (SoA , Appendix 1). Subjects should then return for the Safety Follow Up assessments 4 weeks after the last dose of study drug. Any subject who withdraws with ongoing AEs/SAEs should be followed until resolution of their AE(s) or until the Investigator has determined that the AE(s) has stabilized.

Site personnel will attempt to contact any subject who does not return to the clinic for the EOS visit at least three times using the subject's preferred method of communication, followed by a certified letter if the three attempts were unsuccessful. Any subject who still cannot be reached following those attempts will be considered Lost to Follow-up. These subjects will be included in the analysis as indicated in Section 11.3.

7.2.1 Withdrawal Criteria

The primary consideration in any determination to discontinue a subject's participation must be the health and welfare of the subject. Reasons for withdrawal may include, but are not limited, to the following:

- Adverse Event
- Noncompliance with study drug dosing or study procedures
- Lack of efficacy
- Lost to follow-up
- Withdrawal by subject
- Protocol deviation

- Pregnancy
- Sponsor's decision to terminate the study
- Other

Subject-specific stopping rules due to AEs and/or laboratory abnormalities are outlined in Section 10.1.

Subjects who prematurely withdraw from the study for any reason after having been randomized will not be replaced.

7.2.2 Documentation of Withdrawal of Subjects

The reason for early withdrawal/termination/lost-to-follow-up of any subject from the study must be documented on the appropriate eCRF. If the reason for early withdrawal is an AE or an abnormal laboratory value, the specific event or test result, if available, should be recorded on the AE eCRF and the subject should be monitored until the event is resolved or deemed stable by the Investigator.

7.3 Site or Study Discontinuation

7.3.1 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- A decision from the IRB/EC or regulatory authority to terminate the study.

If the study is suspended or terminated for safety reasons, Enanta Pharmaceuticals, Inc. will promptly notify the Investigator and will also inform the regulatory authorities of the suspension or termination of the study and the reasons for the action. The Investigator is responsible for promptly informing the IRB/EC, and providing the reasons for the suspension or termination of the study.

7.3.2 Site Termination

A single site may warrant termination under the following conditions:

- Failure of the site to enroll subjects into the study at an acceptable rate.
- Failure of the site to comply with pertinent governmental regulations as appropriate.
- Submission of knowingly false information from the research facility to the Sponsor, clinical monitor, or governmental authority.

- Failure to adhere to the protocol requirements.
- Data recording is inaccurate or incomplete.
- PI does not adhere to the protocol or applicable regulatory guidelines in conducting the study.

7.3.3 Study Termination Procedures

If the study is terminated by Enanta Pharmaceuticals, Inc. for one of the reasons listed above, or upon completion of the study, the following activities must be conducted by the study monitor and/or site personnel:

- Return of all study data to Enanta Pharmaceuticals, Inc. or designee.
- Respond to and complete all requests for data clarifications.
- Accountability and final disposition of used and unused study drug.
- Review of site records for completeness.
- Shipment of all applicable biological samples (including PK samples) to the designated laboratory.

8. STUDY PROCEDURES/EVALUATIONS

All visits and assessments should be conducted as shown in the SoA (Appendix 1).

8.1 Demographics and Medical History

Demographics and baseline characteristics including date of birth, gender, race, ethnicity and medical history will be obtained from each subject and entered in the eCRF as reported. As a general rule, all medical events occurring within the last 6 months should be recorded. For events which occurred more than 6 months ago (and which are not ongoing), only significant or relevant events should be entered on the eCRF. Any items in the history that are still ongoing should be noted as such in the eCRF. All surgeries occurring in adulthood should be recorded in the eCRF while methods of contraception, if applicable, should only be documented in the source documents. If possible, the date of diagnosis of PBC should be recorded.

8.2 Clinical Evaluations

8.2.1 Vital Sign Measurements and ECGs

Vital signs will include heart rate (HR), respiratory rate, blood pressure (BP) and oral temperature. Vital signs will be measured at times shown in the SoA (Appendix 1) after the subject has been supine for 5 minutes. Temperature should be taken at the Screening, Day 1 and EOS visits.

Resting 12-lead ECGs will be done locally and recorded at the times indicated in the SoA after the subject has been supine for 5 minutes. A standard bedside 12-lead ECG machine that calculates heart rate and measures the PR, QRS, QT, RR, and QTc (QTcF) intervals will be utilized. If a blood draw and ECG are scheduled at the same time, then the ECG should be obtained first.

The Investigator or designee should review the ECGs in real-time for gross abnormalities and interval measurements of concern (absolute readings and for postdose ECGs, change from Baseline). Clinical interpretation of the ECGs by the Investigator or designee should be recorded on a hard copy of the ECGs.

The Investigator or designee should repeat any ECG with a change from baseline in QTcF >60 msec or a QTcF interval >500 msec. Also, ECGs may be repeated at the discretion of the Investigator to account for erroneous readings.

Prior to dosing the Baseline ECG must be reviewed to confirm that no clinically significant cardiac abnormalities are present.

8.2.2 Physical Examination

The Investigator or designee will perform the physical examination. A full physical examination will be conducted at Screening and EOS as indicated in the SoA (Appendix 1) and will include examination of the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; chest, lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. All subsequent physical examinations will be targeted to new signs and symptoms including specific assessments of any changes from previous status. Only clinically significant abnormalities should be recorded in the eCRF (eg, use of contact lenses does not need to be recorded).

8.2.3 Weight and Body Mass Index (BMI)

Height should be recorded once at the Screening visit while weight should be recorded at the Screening and EOS visits. BMI should be calculated at the times shown in the SoA (Appendix 1) according to the following equation: BMI=weight (kg)/height $(m)^2$.

8.2.4 PBC-40 Quality of Life Assessment

The PBC-40 Quality of Life Assessment (PBC-40 QoL) is a study of health-related quality of life (HRQOL). It is a survey containing domains of PBC-40 relate to fatigue, emotional, social, and cognitive function, general symptoms, and itch. This measure has been validated for PBC and the survey will be provided to sites by Enanta. The PBC-40 QoL will be performed as indicated in the SoA (Appendix 1).

8.2.5 Assessment of Pruritus

Pruritus will be monitored in this study. As listed below, two separate scales will be used to assess pruritus in subjects.

- An itch visual analog scale (VAS) will be used to record the intensity of the event (*Furue et al., 2013*). Site personnel should instruct the subject to draw a line on the scale corresponding to the maximum intensity of itch.
- The 5-D itch scale is a multidimensional questionnaire completed by subjects assessing pruritus. The 5D-itch scale includes a range of 0 (no itch) to 10 (worst imaginable itch) covering five dimensions: degree, duration, direction, disability and distribution.

The scales should be completed by the subject as indicated in the SoA (Appendix 1).

8.2.6 Adverse Events

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in Section 8.1 of this protocol. All AEs and SAEs must be recorded in the source documents and eCRF as described below (Section 9.2). At all visits, the PI or designee should inquire about the occurrence of AEs. The following are examples of open-ended questions that may be used to obtain this information: *"How are you feeling?"*; *"Have you had any medical problems recently?"*; *"Have you taken any new medicines since your last visit/assessment?"*

It is the Investigator's responsibility to ensure any necessary additional therapeutic measures and follow-up procedures are performed and documented in the subject source notes and eCRF. Any medication taken during the course of the study through the end of the study will be recorded with indication, dosage, route of administration, and start and stop dates of administration. All subjects will be questioned about concomitant medication at each clinic visit as indicated in the SoA (Appendix 1).

8.3 Clinical Laboratory and Diagnostic Procedures

All laboratory samples will be analyzed by a centralized laboratory. A laboratory reference manual will be provided to the site detailing kit contents, reordering supplies, sample collection (see below), handling, storage and shipment instructions. All unblinded laboratory values will be reviewed by the Investigator, documented, and the results maintained in the source documents. All out-of-range lab findings require an interpretation as to whether or not they are clinically significant. Clinically significant laboratory findings in the opinion of the Investigator should be recorded as an AE (or SAE as appropriate).

At all visits blood samples should be collected before the first dose of the study drug. Additional clinical laboratory evaluations will be performed at other times if judged clinically appropriate by the Investigator, or if the safety review of the data suggests a more detailed assessment of clinical laboratory safety evaluations. Any changes to the scheduled times of the clinical laboratory determination will be agreed to by Enanta and the Investigator, and documented in the study trial master file (TMF).

For Biomarker analysis, fasting serum or plasma samples should be collected before the daily dose of study drug for analysis of FGF19, bile acids, C4, and at visits indicated in the SoA (Appendix 1). Samples should be collected after an overnight fast of a minimum of 8 hours.

8.3.1 Safety Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected according to the SoA (refer to Table 14). Subjects should be instructed to fast for at least 8 hours prior to the

blood draw for the laboratory testing for all visits. Samples will be collected and processed according to the procedures provided by the clinical laboratory in the Laboratory Manual. Creatinine clearance will be calculated using the Cockcroft Gault equation as indicated in the Laboratory Manual.

Table 14: Laboratory Evaluations

CHEMISTRY PANEL Alanine Aminotransferase (ALT/SGPT) Albumin, Serum Albumin/Globulin (A/G) Ratio (calculation) Alkaline Phosphatase, Serum Amylase Aspartate Aminotransferase (AST/SGOT) Bilirubin, Total and Direct BUN BUN/Creatinine Ratio (calculation) Calcium, (Serum) Creatine Kinase Creatinine, Serum (creatinine clearance) Uric Acid Electrolyte Panel (Na^+, K^+, Cl^-, Bicarb.) Phosphorus Gamma Glutamyl Transferase (GGT) Globulin, Total Glucose, Serum Cholesterol, serum Lactate Dehydrogenase (LDH) Lipase Protein, Total, Serum TG (triglycerides)	**HEMATOLOGY PANEL** Hemoglobin Hematocrit Differential WBC Count (percentage and absolute): Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils MCH MCHC MCV Platelets Red Blood Count RBC Morphology White Blood Count
Coagulation tests INR – PT/PTT	**SCREENING TESTS** Viral serology: HIV-1, HIV-2, HBV (HBsAg), anti-HCV antibodies and HCV RNA PBC diagnostic (if needed): AMA/M2/PBC-ANAb
	MARKERS OF CV RISKS AND LIPIDS hs-CRP HDL and LDL-P (high and low-density lipoprotein particles using a lipoprotein subfractions test; eg, LIPOPROFILE) lipoprotein (a) [Lp(a)] assay apoA-I, apoB, apoB/A Ratio, apoC3, apoE isoforms (E2, E3, E4) Total Cholesterol (TC) High Density Lipoprotein – Cholesterol (HDL-C) Low-Density-Lipoprotein – Cholesterol (LDL-C) TG (triglycerides) Total/HDL Cholesterol (CT) Ratio Adiponectin
URINALYSIS Routine urinalysis to include: Color and appearance, pH, SG, Bilirubin, Glucose, Ketones, Leukocytes, Nitrite, Occult blood, Protein, Urobilinogen, Microscopic (including RBCs and WBCs)	**MARKERS OF FIBROSIS AND INFLAMMATION** *ENHANCED LIVER FIBROSIS (ELF) PANEL* - Hyaluronic acid (HA), - Procollagen III amino terminal peptide (PIIINP) - Tissue inhibitor of metalloproteinase 1 (TIMP-1) *PRO-C3* Fibrinogen, CRP, alpha2 macroglobulin and haptoglobin Tumor necrosis factor alpha and beta (TNF-α, β) IL-6. IL1β AST to Platelet Ratio Index (APRI) Fibrosis 4 (FIB-4) Index
PREGNANCY AND MENOPAUSE TESTS Serum pregnancy test Follicle-Stimulating Hormone (FSH)	
BIOMARKERS FGF19 (fasting plasma) Total bile acids (fasting serum) C4 (7α-OH-4-cholesten-3-one)	

8.3.2 Pregnancy and Menopausal Laboratory Testing

All female subjects will undergo a serum pregnancy test at Screening and Baseline, and a urine pregnancy test at Baseline and all other visits according to the SoA. If the results of the urine pregnancy test are positive, a serum pregnancy test should be conducted as soon as possible. A urine pregnancy test must be conducted and confirmed negative on Day 1 prior to the first dose of study drug.

To confirm childbearing status for women claiming that they are postmenopausal, follicle stimulating hormone (FSH) will be measured at Screening. Additionally, a serum pregnancy test should also be drawn in the event the woman is found to be of childbearing potential based on the FSH results.

8.3.3 Noninvasive Evaluations of Fibrosis

The ELF panel combines 3 biomarkers that have been shown to be correlated with the level of liver fibrosis assessed by a liver biopsy. These biomarkers include HA, PIIINP, and TIMP 1. These parameters along with PRO-C3 will be assessed as outlined in Appendix 1.

Fibrosis will be estimated using the APRI and the fibrosis 4 (FIB-4) formulae. The APRI will be calculated by the central laboratory using the following formula:

$$([\text{AST IU/L} / \text{AST ULN}] / [\text{Platelet count } 10^9/\text{L}]) \times 100 = \text{APRI}$$

An online calculator can be found at:
https://www.hepatitisc.uw.edu/page/clinical-calculators/apri

The FIB-4 score will be calculated using the following formula:

$$(\text{Age [years]} \times \text{AST [IU/L]}) / (\text{Platelet count } [10^9/\text{L}] \times (\sqrt{\ } \text{ALT [IU/L]}))$$

An online calculator can be found at:
http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

Refer to the SoA (Appendix 1) for the timing of these tests.

8.3.4 Biomarkers

See Table 14 for full list of biomarkers to be collected in this study.

Fasting serum or plasma samples should be collected before the daily dose of study drug for analysis of FGF19, bile acids, and C4 at visits indicated in the SoA (Appendix 1) at Day 1, and Week 2, 4, 8 and 12 after a fast of a minimum of 8 hours.

For all subjects, samples for FGF19, bile acids, and C4 will be collected predose at the noted visits as indicated in the SoA (Appendix 1).

PK/PD Substudy (select subjects to consent to participate): Additional samples will be collected from subjects at a subset of sites that have the technical capability to collect and process intensive (longer duration) sampling (those also collecting intensive PK) at Day 1 and Day 84 (Week 12). Biomarker samples will be collected at predose and 2, 6, and 8 hours postdose. Additionally, an ALP sample will be collected at the same time points for subjects

participating in the PK/PD substudy (ie, predose and at 2, 6, and 8 hours postdose). On scheduled visits on Week 2, 4 and 8, samples (FGF19, bile acids, C4 and ALP) will be collected at three timepoints: predose and at two timepoints postdose; the first samples collected 1 to 3 hours postdose and the second postdose samples collected at least 1 hour later. Where possible, the samples at each visit should be obtained at different times postdose relative to each other.

[redacted]

8.3.6 Liver Imaging

To exclude cirrhosis and/or advanced fibrosis, a liver Fibroscan will be conducted prior to Baseline in subjects for whom documented fibrosis stage on a recent liver biopsy (<2 years) result is not available and once a subject is considered eligible based on Screening laboratory values.

8.4 Pharmacokinetic Samples

8.4.1 Collection of Pharmacokinetic Samples

Plasma samples will be collected and processed to define the PK parameters according to the procedures provided and/or approved by Enanta Pharmaceuticals, Inc. Plasma PK samples will be collected as shown in the SoA (Appendix 1). More detailed information will be given in the Laboratory Manual.

Population PK(all Subjects): On scheduled visits at Day 1, and Weeks 2, 4, 8 and 12, PK samples will be collected at three timepoints: predose and at two timepoints postdose; the first postdose sample collected 1 to 3 hours postdose and the second postdose sample collected at least one hour later. Where possible, the samples at each visit should be obtained at different times postdose relative to each other.

PK/PD Substudy (select subjects to consent to participate): Additional samples will be collected from subjects at a subset of sites that have the technical capability to collect and process intensive (longer duration) PK samples. At Day 1 and Day 84 (Week 12) PK samples will be collected at predose and 2, 6, and 8 hours postdose. On scheduled visits on Week 2, 4 and 8, PK samples will be collected at three timepoints: predose and at two timepoints postdose; the first samples collected 1 to 3 hours postdose and the second postdose samples collected at least 1 hour later. Where possible, the samples at each visit should be obtained at different times postdose relative to each other.

More detailed information will be provided in the Study Manual. It is important that the date and time of collection of each of the PK blood samples are accurately recorded in the source document. Within 8 hours postdose, an acceptable window around each PK draw is ± 10 minutes. Predose PK samples should be drawn within 30 minutes of the next scheduled dosing time. Actual date and time of PK sample collection will be recorded in the eCRF. In addition, the site should record the time of last dose taken at home prior to the visit.

PK samples may be stored and used for future metabolite identification and/or further evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical study report.

8.4.2 Handling and Bioanalysis of Pharmacokinetic Samples

EDP-305 and its major metabolites (EP-022571, EP-022572, and EP-022679) in human plasma will be quantified by high performance liquid chromatography (HPLC) with tandem mass spectrometric (LC-MS/MS) detection. The method will be fully validated by assessment of precision, accuracy, sensitivity, and specificity of EDP-305 and its major metabolites by a laboratory selected by Enanta Pharmaceuticals, Inc.

Detailed procedures for the collection of blood samples and further procedures for processing, handling and shipping of samples for PK analysis will be provided in the Laboratory Manual.

The lab performing bioanalytical analysis will be provided the randomization scheme and will generally analyze all samples for subjects randomized to EDP-305 plus a few samples for subjects randomized to placebo as a control.

9. SAFETY MONITORING AND REPORTING

9.1 Definitions

9.1.1 Pretreatment Events

A pretreatment event is any event that meets the criteria for an AE/SAE and occurs after the subject signs the ICF but before receiving the first administration of study drug.

9.1.2 Adverse Events

An AE is any event, side effect, or untoward medical occurrence in a subject enrolled in a clinical trial whether or not it is considered to have a causal relationship to the study drug. An AE can therefore be any unfavorable and unintended sign, symptom, laboratory finding outside of normal range with associated clinical symptoms or suspected latent clinical symptoms in the opinion of the Investigator, physical examination finding, or disease temporally associated with the use of the study drug, whether or not the event is considered related to the study drug.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier than planned).

9.1.3 Serious Adverse Events (SAEs)

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

- Results in death: This includes deaths that appear to be completely unrelated to study medication (eg, a car accident).
- Is a life-threatening event: An event that places the subject at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolonged hospitalization of an existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF

  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
- Results in permanent or prolonged (at least 28 days in duration) disability or incapacity.
- Is a congenital anomaly or birth defect in the offspring of a study subject.
- Medically important event: An event that may not be immediately life-threatening, or result in death or hospitalization, or require intervention to prevent one of the outcomes listed above, but is considered medically significant for other reasons. An opportunistic or otherwise unusual infection for the PI's practice, such as tuberculosis, will be considered medically significant.

The term severe is used to describe the intensity of a specific event (as in mild, moderate, or severe); the event itself, however, may be of minor medical significance (such as severe headache). This is not the same as serious, which is based on outcome of the event, as described above. Seriousness, not intensity, serves as a guide for defining regulatory reporting obligations.

9.2 Documenting and Reporting of Adverse Events (Including Serious Adverse Events)

Adverse Events will be evaluated and documented using the grading scales contained in the National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 4.03).

9.2.1 Documenting and Reporting Adverse Events

All AEs reported from the time of informed consent to the end-of-study for each subject will be recorded in the subject's source documents. For subjects who do not receive study drug (ie, screen failures), AEs will only be recorded in the source documents. For subjects enrolled into the study (ie, randomized), record all AEs in the subject's AE eCRF and Clinical Trials SAE Form (if applicable). The AE CRF will indicate if the event occurred prior to the first dose of study drug, during treatment, or during the post-dosing follow-up period. Record all AEs regardless of the intensity, seriousness, or relationship to study drug.

Grade AEs (serious and non-serious) in accordance with the NCI/CTCAE scale (available at *https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)* as presented below:

- **Mild** (Grade 1) asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Moderate** (Grade 2) minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

- **Severe** (Grade 3) Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living
- **Life-threatening** (Grade 4) Life-threatening consequences; urgent intervention indicated
- **Death** (Grade 5) Death related to the AE.

Any recurrence of an AE with similar causality to study drug will be reported as recurrence or exacerbation of the initial event, and not as a new event. Whenever possible, report AEs as a specific diagnosis or syndrome (eg, flu syndrome) rather than as individual signs or symptoms. If no specific diagnosis or syndrome is identified, AEs should be reported as separate and individual events.

An AE includes the following:

- Progression or exacerbation of the subject's underlying disease. Clinical sequelae that result from disease progression, such as pleural effusion or small bowel obstruction, are reportable as AEs.
- Pre-existing event that increases in frequency or intensity.
- Condition detected or diagnosed during the study period, even though it may have been present, in retrospect, prior to the first dose of study drug.
- Laboratory abnormalities outside of normal limits and requiring therapeutic intervention.
- An overdose of the study drug without any signs or symptoms will be considered an AE. A calculated dose that exceeds its correct dose by 10% or more and is administered to the subject will be considered an overdose and documented as an AE.

The following events **will not** be identified as AEs in this study:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, etc); however, the condition (the "triggering event") that leads to the procedure may be an AE.
- Pre-existing conditions present or detected prior to the first dose of study drug that do not worsen.

9.2.2 Assigning Attribution of Adverse Events

The Investigator must attempt to determine the cause of each event. Every effort will be made by the Investigator to assess the relationship of each AE to study drug. To ensure consistency of AE/SAE causality assessments, Investigator(s) should apply the following guideline:

Related: There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and causes other than the study drug have been ruled out, and/or the event re-appeared on re-exposure to the study drug.

Possibly Related: There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug, but there may

also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.

Unlikely Related: The event is unlikely to be related to the study drug and likely to be related to factors other than study drug.

Not Related: The event is related to an etiology other than the study drug (the alternative etiology must be documented in the study subject's medical record).

9.2.3 Classifying Action Taken with Study Drug

In the case of an AE, the actions that can be taken with study drug are defined below in Table 15.

Table 15: Options for Action Taken with Study Drug

Classification	Definition
Dose Not Changed	Study drug dose not changed in response to the AE
Dose Reduced	Study drug dose reduced in response to an AE
Drug Interrupted	Study drug administration interrupted in response to an AE
Drug Withdrawn	Study drug administration permanently discontinued in response to an AE
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances when no opportunity to decide whether to continue, interrupt or withdraw treatment was possible such as when the investigational treatment had been completed before the adverse event began.

9.2.4 Classifying Adverse Event Outcome

For every AE/SAE, the possible outcomes of the event and the definition of the outcome are shown below in Table 16. One outcome must be entered into the appropriate field on the AE and (if appropriate) SAE form for each event as discussed in the eCRF instructions.

Table 16: Classification and Definition of AE Outcomes

Classification	Definition
Recovered / Resolved	Resolution of an AE with no residual signs or symptoms
Recovered / Resolved with sequelae	Resolution of an AE with residual signs or symptoms
Is Recovering / Is Resolving	Incomplete improvement to date but AE continues to improve/resolve and complete resolution is expected over time
Not Recovered / Not Resolved	Either incomplete improvement or no improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. "Fatal" should be used when death is at least possibly related to the adverse event.
Unknown	Outcome of an AE is not known (eg, a subject lost to follow up)

9.2.5 Documenting and Reporting Serious Pretreatment Events and Serious Adverse Events

All SAEs that occur after obtaining informed consent through the EOS visit, regardless of causality, must be reported by the Investigator to [redacted] and Enanta Pharmaceuticals, Inc. In addition, all SAEs, including those that result in death, that occur after the EOS visit and that are considered related to study drug(s) must be reported to [redacted] and Enanta within 24 hours of learning of its occurrence. Additional details are provided in the Safety Management Plan.

The electronic SAE Form should be sent to the Study SAE e-mail address to be distributed to all recipients:

- [redacted]
- [redacted]

SAEs will be recorded on the Clinical Trials SAE Form using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the Investigator for severity, relationship to the investigational study drug(s) and possible etiologies. On the Clinical Trials SAE Form, relationship to study drug(s) will be assessed only as related or not related. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the Investigator is required to follow the event to resolution and report the outcome of the event to [redacted] using the SAE Form.

The Investigator is responsible for notifying the Sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The SAE Form should be completed for new/initial events as well as to report follow-up information on previously reported events. The Investigator is asked to report follow-up information as it becomes available.

Enanta Pharmaceuticals, Inc. or its designees, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, and participating PIs, in accordance with FDA, ICH Guidelines, and/or local regional or country regulatory requirements, as applicable.

9.2.6 Documenting and Reporting of Pregnancy

While females of childbearing potential are allowed in the study, they must agree to use two effective methods of contraception from Screening until 90 days after the last dose of study drug. However, as a precaution, subjects will be counseled to inform the Investigator of any pregnancy that occurs during study treatment and for 90 days after the last dose of study drug/s.

If a female subject or the female partner of a male subject becomes pregnant while participating in the study, study treatment must be permanently discontinued immediately. The Investigator must notify the Sponsor's Medical Monitor and [redacted] within one business day of the sites' knowledge of the subject's (or partner's) pregnancy, by utilizing the study-specified pregnancy report form. If confirmed to be on active drug, the subject or partner will be followed until end of pregnancy and the infant will be followed for one year after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

9.3 Follow-up of Adverse Events and Serious Adverse Events

Follow all AEs (serious and non-serious) until resolution or otherwise explained (see Table 16), the subject dies, the event stabilizes and is not expected to further resolve with the maximum time limit for stabilization defined as 30 days after the occurrence of the event, or when alternative therapy is instituted, whichever occurs first. If alternative therapy is instituted, it should be documented (see Section 8.2.4). Enanta Pharmaceuticals, Inc. may request that the Investigator perform or arrange for supplemental measurements or evaluations to further clarify the nature of the event.

9.4 Sponsor's Review of Adverse Events and Serious Adverse Events

Enanta Pharmaceuticals, Inc. will maintain an ongoing review of all AEs and SAEs.

9.5 Data Safety Monitoring Board

Safety data from this study will be reviewed by a Data Safety Monitoring Board (DSMB) throughout the study. The DSMB will be headed by a DSMB Chair and will include physicians with expertise in diseases of the liver including PBC. Procedures for data review including timing and potential outcomes will be governed by the DSMB charter.

10. SUBJECT SAFETY MANAGEMENT

In the event that two or more subjects experience a similar drug-related Grade 3 or 4 AE or SAE or Grade 3 or 4 laboratory abnormality, a DSMB meeting will be immediately convened by the Sponsor. Based on the data presented, a decision will be made as to whether or not enrollment should be halted, the study should be halted, or if dosing and enrollment into the study should continue.

10.1 Individual Subject Stopping Rules

Study drug will be discontinued in subjects with elevated ALT or AST (see below) and thorough evaluation and follow-up will be performed:

- If ALT or AST increases to >5 × Baseline.
- If ALT or AST increase >2 × Baseline AND the increase is accompanied by a concomitant TB increase to >2 × Baseline OR the INR concomitantly increases by >0.2
- If elevations of ALT/AST are accompanied by signs or symptoms of right upper quadrant abdominal pain, anorexia, nausea, vomiting, fever, eosinophilia, and/or rash.

10.2 Management of Liver Enzyme Elevations

The FDA Guidance for Industry for Drug Induced Liver Injury (FDA, 2009) will provide guidance for the management of changes in liver transaminases (ALT/AST) and TB.

The protocol also includes an algorithm to respond to changes in liver enzymes and functions as follow:

- To establish a baseline utilizing at least 2 lab values at least several weeks apart.
- For subjects with elevated baseline liver chemistry that develop AST or ALT elevations 2 × baseline, subjects will be reassessed promptly (eg, 48-72 hours) with full liver biochemistry and physical exam and if the repeat assessment shows persistent elevations in transaminases, subjects should be followed according to the "close observation" guidelines:
    - Repeat liver enzyme and serum bilirubin tests two or three times weekly. Frequency of repeat testing can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
    - Collect additional PK samples at the same visits as safety labs
    - Obtain a more detailed history of symptoms and prior or concurrent diseases.

- Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtain a history of exposure to environmental chemical agents.
- Obtain additional tests to evaluate liver function, as appropriate (eg, INR, direct bilirubin).
- Consider gastroenterology or hepatology consultations.
- Consider liver biopsy for any patient with persistent evidence of liver injury.

- If a subject lives in a remote area, they can be tested locally with the results promptly communicated to the Investigator site.

10.3 Management of Pruritus

If an event of pruritus is reported by subjects in this study, the location and intensity of the event must be captured on the eCRF as an AE. In addition, as listed below, two separate scales will be used to assess pruritus in subjects who report itching.

- An itch visual analog scale (VAS) will be used to record the intensity of the event (*Furue et al., 2013*). Site personnel should instruct the subject to draw a line on the scale corresponding to the maximum intensity of itch.
- The 5-D itch scale is a multidimensional questionnaire completed by subjects assessing pruritus. The 5D-itch scale includes a range of 0 (no itch) to 10 (worst imaginable itch) covering five dimensions: degree, duration, direction, disability and distribution.

If reported, pruritus should be assessed at each visit until resolution of the event. The scales should be completed by the subject/site personnel during each assessment/visit where pruritus is reported.

[redacted]

11. STATISTICAL CONSIDERATIONS

11.1 General Considerations

All data will be mapped into the appropriate SDTM domains per version 3.2. All analysis datasets will be in the appropriate ADaM data structure. Pinnacle21 will be used to ensure compliance of the SDTM domains and ADaM datasets to CDISC standards.

All quantitative endpoints will be summarized using an 8-number summary (n, mean, standard deviation, median, 25^{th} quartile, 75^{th} quartile, minimum and maximum values). All qualitative endpoints will be summarized by the number of subjects meeting the endpoint and the percentage of subjects out of the appropriate population. The denominator will be displayed when needed.

Statistical inference will be performed as appropriate. Only two-sided test with an α=0.05 will be used.

11.2 Sample Size Considerations

The planned sample size is approximately 105 subjects. Group sample sizes of 45 in each active arm and 15 in the placebo arm achieve 83.552% power to detect a ratio of the group proportions of 40%. The proportion in the smallest active arm is assumed to be 0.4000 under the null hypothesis and 0.0400 under the alternative hypothesis. The proportion in the placebo arm is 10%. The test statistic used is the two-sided Mantel-Haenszel test. The significance level of the test is 0.05. To account for a 10% discontinuation rate, 14 additional subjects will be enrolled to attempt to have 105 who complete treatment, bringing the total number of subjects enrolled to 119.

11.3 Analysis Populations

The following analysis populations are planned:

- *Safety Population:* All subjects who receive at least one dose of study medication. Subjects will be included in the treatment group that corresponds to the study medication received during the study.
- *Efficacy Population:* All subjects who receive at least one dose of study medication. Subjects will be included in the randomized treatment group.
- *Pharmacokinetic Population:* All subjects receiving active study medication and having any measurable plasma concentration of study medication at any timepoint.

11.4 Subject Disposition and Demographic Data

The number of subjects screened, randomized, randomized and treated, randomized and not treated, in the safety population, in the efficacy population, and in the PK population will be summarized. The denominator for the calculation of percentages will be from the number of subjects randomized.

The following categories will also be summarized for subject disposition:

- Completed study drug per protocol
- Discontinued study drug early and the reason for discontinuation
- Completed the study
- Discontinued from the study early and the reason for discontinuation

Subject demographics will be summarized by randomized treatment group for all subjects in the safety population. Appropriate baseline characteristics will be included in addition to demographic characteristics. No statistical testing will be performed. Additional details will be provided in the Statistical Analysis Plan.

11.5 Efficacy Endpoints

11.5.1 Primary Efficacy Endpoints

The primary efficacy endpoint of the study is the proportion of subjects with at least 20% reduction in ALP from pre-treatment values or normalization of ALP at Week 12. The denominator will be the number of subjects in the efficacy population (missing=failure). Treatment comparisons will be made using a Mantel-Haenszel test comparing each of the active treatment arms to placebo, separately.

11.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Bilirubin (Total, Conjugated, Unconjugated) decline from Baseline at Week 12
- Change from Baseline in Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and Gamma-Glutamyl transferase (GGT) at Week 12
- Change from Baseline of noninvasive liver fibrosis markers (Enhanced Liver Fibrosis [ELF] panel, PRO C3, AST to Platelet Ratio Index [APRI] and fibrosis-4 [FIB-4]) at Week 12
- Change from Baseline in fibrinogen, CRP, IL6, IL1β, TNF-α, TNF-β , alpha2 macroglobulin and haptoglobin levels at Week 12

- Change from Baseline in Triglycerides (TG), Total Cholesterol (TC), High Density Lipoprotein Cholesterol (HDL-C), Low Density Lipoprotein Cholesterol (LDL-C) at Week 12
- Change from Baseline in 5D-itch scale and Visual Analog Score (VAS) at Week 12
- Change from Baseline in PBC-40 Quality of Life (QoL) at Week 12
- Pharmacodynamic parameters of EDP-305: FGF19, C4 and Bile Acid (BA) at week 12

Each endpoint will be summarized using an 8-number summary. Subjects in the efficacy population will be included. Comparisons of treatment arms will be performed using an analysis of covariance (ANCOVA) model with treatment and baseline values included in the model where appropriate.

11.6 Safety Endpoints

11.6.1 Adverse Events

Adverse events will be summarized by MedDRA system organ class and preferred term by treatment group. All subjects in the safety analysis set will be included in the summaries. No statistical testing will be performed.

Summaries of Adverse Events will include the following:

- An overall summary of AEs with a line for each of the categories provided below.
- Treatment-emergent adverse events
- Treatment-emergent treatment-related adverse events
- Treatment-emergent adverse events leading to study drug discontinuation
- Serious adverse events
- Serious treatment-related adverse events
- Adverse events leading to death

11.6.2 Clinical Laboratory Data

Summaries of clinical laboratory results will be performed using an 8-number summary by visit and treatment. All subjects in the safety population will be included in these summaries.

The number and percentage of subjects with treatment-emergent laboratory abnormalities will be summarized by treatment group. In addition, shift from baseline tables will be generated by visit and treatment group.

Change from Baseline will be included in summary tables for laboratory parameters. Shift tables will also be generated for safety laboratory parameters by visit and treatment group. All

laboratory data will be included in the data listings and all test values outside the normal range will be flagged.

11.6.3 Electrocardiogram (ECG) Data

ECG data will be summarized using an 8-number summary by visit and treatment. Change from Baseline will be included in summary tables for ECG parameters. In addition, the number and percentage of subjects with significant changes in ECG parameters will be summarized by treatment. No statistical testing will be performed.

11.6.4 Vital Signs

Vital signs data will be summarized using an 8-number summary by visit and treatment. In addition, the number and percentage of subjects with significant changes in vital signs will be summarized by treatment. Change from Baseline will be included in summary tables for vital signs. No statistical testing will be performed.

11.6.5 Concomitant Medications

The number and percentage of subjects taking concomitant medications will be summarized by drug class and drug name. Subjects in the safety population will be summarized by treatment group. No statistical testing will be performed.

11.6.6 Physical Examinations

Physical examination data will be provided in data listings.

11.7 Pharmacokinetic Analyses

The following PK parameters (Table 17) will be calculated as indicated for plasma EDP-305 and its major metabolites as applicable:

Table 17: PK Parameters

PK Parameter	Description
AUC_{last}:	The area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration.
C_{max}:	Maximum observed concentration.
T_{max}:	Time to reach C_{max}. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.

For each EDP-305 dose level, descriptive statistics (sample size, arithmetic means, geometric means, standard deviation, % coefficient of variation, minimum, median, and maximum) will be presented. Figures will be created to display mean and individual subject EDP-305 concentration time curves in plasma on both a linear and logarithmic scale.

11.8 Interim Analyses

An interim analysis may be conducted after 25% of the planned total number of subjects have been enrolled and completed 12 weeks of treatment. Additional information will be provided in the Statistical Analysis Plan (SAP).

12. STUDY ADMINISTRATION

12.1 Ethical Considerations

12.1.1 Ethical Conduct of the Study

The study will be conducted in compliance with this protocol, principles of E6 Good Clinical Practice: Consolidated Guidance (ICH-GCP), Declaration of Helsinki, and all applicable local laws and national regulations governing clinical trials.

12.1.2 Ethical Review

It is the PI's responsibility to ensure that this protocol is reviewed and approved by an appropriate IRB/EC which conforms to the regulations set forth in 21CFR, Part 56 and other national, country, and regional regulations as applicable. The Investigator must also submit the ICF, any other written documentation provided to the subject, and all advertisements that may be used for study-specific recruitment to the IRB/EC for review and approval before commencing study-specific activities. If it is necessary to amend the protocol during the study, then it is the responsibility of the Investigator to ensure that IRB/EC approval is obtained before implementation of the amended procedures. It is also the responsibility of the Investigator to provide the IRB/EC with any SAE or IND safety reports. A copy of the ICF approved by the IRB/EC must be forwarded to Enanta Pharmaceuticals, Inc. for regulatory purposes.

12.1.3 Written Informed Consent

The Investigator or designee must explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in §21CFR Part 5, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated ICF prior to enrollment into this study. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time. In accordance with individual local and national or country-specific subject privacy regulations, the Investigator or designee must explain to each subject prior to Screening that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Enanta Pharmaceuticals, Inc. and its designees, regulatory agencies, and IRBs/ECs. As the study sponsor, Enanta Pharmaceuticals, Inc. will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the PI's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the PI's responsibility to obtain the withdrawal request in writing from the subject and to ensure that no further data will be collected from the subject. Any data collected on the subject prior to withdrawal will be used in the analysis of study results.

12.1.4 Investigator Compliance

No modifications to the protocol should be made without the approval of both the Investigator and Enanta. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (ie, efficacy assessments) will require IRB/IEC notification prior to implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects.

If circumstances require an immediate departure from protocol procedures, the Investigator will contact Enanta to discuss the planned course of action. Contact should be made prior to the implementation of any changes when possible. Any departures from protocol must be fully documented in the source documentation and in a protocol deviation log.

12.2 Data Collection

Study data for each randomized subject will be entered into an eCRF by site personnel. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, other observations, and subject status. The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected. An explanation should be provided for all missing data.

After the subject has completed the study, the Investigator must review and sign the signature page of the eCRF indicating that he has reviewed the completed eCRF and pertinent clinical data for that subject and that, to the best of his knowledge, all data recorded in the eCRF accurately reflects the subject's clinical performance in the study.

Sites are responsible for abiding by the rules and regulations of their IRB/EC for recording and reporting protocol deviations. All deviations reported to the IRB/EC must be reported to Enanta Pharmaceuticals, Inc. and/or their designee and recorded as deviations as appropriate in the eCRF.

12.3 Study Monitoring

Representatives of Enanta Pharmaceuticals, Inc. or its designee will monitor this study until completion. Monitoring will be conducted through on-site visits with the Investigator and site staff as well as any appropriate communications by mail, fax, e-mail, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. The study monitor will insure that the investigation is conducted according to protocol and regulatory requirements, and as described in the Study Monitoring Plan.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the Investigator agrees to allow the IRB/EC, representatives of Enanta Pharmaceuticals, Inc., its designated agent, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the ICF authorizing the use of protected health information.

12.4 Quality Assurance

At its discretion, Enanta Pharmaceuticals, Inc. or its designee may conduct a quality assurance audit of this study. If such an audit occurs, the Investigator will give the auditor direct access to all relevant documents, and will allocate his time and the time of his staff to the auditor as required. In addition, regulatory agencies may conduct an inspection of this study. If such an inspection occurs, the Investigator will allow the inspector direct access to all source documents, eCRFs, and other study documentation for source data check and/or on-site audit inspection.

12.5 Records Retention

The site will retain a copy of all study records in a safe, secure and accessible location for a minimum of 2 years after notification by Enanta Pharmaceuticals, Inc. that the investigations of EDP-305 have been discontinued or for 2 years following marketing approval of the drug, after which time Enanta Pharmaceuticals, Inc. will be contacted for instructions on the disposition of study materials. Study records will contain all of the appropriate documents as detailed in Section 8.0 of the E6 Good Clinical Practice: Consolidated Guidance (ICH-GCP).

12.6 Information Disclosure

12.6.1 Confidentiality

Subject names will remain confidential and will not be supplied to Enanta Pharmaceuticals, Inc. or its designee. Only subject number, subject initials, and birth date will be recorded on the eCRF. If the subject name appears on any other document collected (eg, unit discharge summary), it must be obliterated before the document is transmitted to Enanta Pharmaceuticals, Inc. or its designee. All study findings will be stored in electronic databases. As indicated in the ICF, subjects will give permission for representatives of the Sponsor, regulatory authorities, and the IRB/EC to inspect their medical records to verify the information collected. Subjects will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with local data protection/privacy laws.

Individual subject medical information obtained during this study is confidential and its disclosure to third parties other than those mentioned in the preceding paragraph is prohibited. Medical information obtained during this study may be provided to the subject's personal physician or other appropriate medical personnel when required in connection with the subject's continued health and welfare and with the subject's prior knowledge and permission.

12.6.2 Publication Policy

It is the intention of Enanta Pharmaceuticals, Inc. to publish the results of this study in their entirety within a reasonable period of time following conclusion of the trial. The Sponsor will determine when and where data will be first disclosed.

All information generated from this study is the proprietary property of Enanta Pharmaceuticals, Inc. Enanta Pharmaceuticals, Inc. reserves the right, among other things, to:

- Modify or amend study material to ensure that no confidential or proprietary information is disclosed.
- Ensure that the reported data are factually correct.
- Utilize the information generated from or as a result of this study in any manner it deems appropriate, including but not limited to regulatory submissions, annual reports, and other scientific or business affairs of the company.
- Modify the publication or disclosure or delay it a sufficient time to allow Enanta Pharmaceuticals, Inc.to seek patent protection of any invention contained therein.

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14. APPENDICES

Appendix 1: Schedule of Assessments (SoA)

Study Event	Scr.[1]	Study Assessments per Planned Study Day						EOS
Visit Day	(D-28	D1[2]	D3	D14±2	D28±2	D56±2	D84[3]±2	D112±2
Treatment Week[4]	to -1)			W2	W4	W8	EOT[5]/W12	W16
ICF[6]; Demography; Medical History	x							
Inclusion/Exclusion	x							
FSH[7]; HIV/HCV/HBV	x							
AMA/M2/PBC-ANAb[8]	x							
Pregnancy Test[9]	x	x			x	x	x	x
Height[10], Weight, BMI	x							x
PT/PTT and INR	x							x
Oral Temperature	x	x						x
Physical Exam[11]	x	x	x	x	x	x	x	x
Vital Signs[12]	x	x	x	x	x	x	x	x
ECG	x	x	x		x		x	
Safety Lab. Tests[13]	x	x	x	x	x	x	x	x
PBC-40 QoL		x			x	x	x	x
VAS and 5-D Itch		x			x	x	x	x
Biomarkers (FGF19, C4, BA)[14]		x		x	x	x	x	
CV Markers[15]		x		x	x	x	x	x
Fibroscan	x							
ELF panel, PRO-C3, Inflammatory Markers[16]	x	x					x	
APRI, FIB-4		x					x	
PK/PD Substudy (PK, C4, FGF19, BA, ALP)[17]		x		x	x	x	x	
Population PK Samples[18]		x		x	x	x	x	
Dispense Study Drug		x			x	x		
Study Drug Dosing[19]		daily dosing						
Drug Accountability			x	x	x	x	x	
AEs & Con Meds[20]	x	x	x	x	x	x	x	x
[redacted]		[redacted]			[redacted]	[redacted]	[redacted]	

[1] Screening assessments should be conducted within 28 days prior to the first dose of study drug (ie, Study Days -28 to -1)
[2] On Day 1, all samples are to be collected predose with the exception of respective post-dose PK and PD samples
[3] Subjects should discontinue drug on Day 84. Subjects who return for their EOT Visit after Day 84, should stop dosing on Day 84.
[4] For the treatment phase, indicates number of completed weeks of treatment
[5] Subjects who discontinue treatment early should complete the EOT procedures as soon as possible and return 4 weeks later for the EOS visit
[6] Informed consent must be obtained prior to conducting any study-specific procedures or assessments
[7] For post-menopausal women only
[8] Only if historical values are not available; one test must be positive for study entry to confirm PBC diagnosis (see Inclusion Criterion #3)
[9] Serum pregnancy test at Screening and Baseline, and urine pregnancy testing at Baseline and all other visits. If the urine pregnancy test is positive, a serum pregnancy test should be obtained as soon as possible to confirm.
[10] Height should only be measured at Screening
[11] Full PE at Screening and EOS; all other exams should be targeted to review of new signs and symptoms
[12] Vital Signs include HR, respiratory rate, and BP and will be measured once in the morning before the morning dose of study drug
[13] Safety laboratory tests include chemistry (including liver function tests), hematology, and urinalysis and should be collected predose at all visits; See Table 14 for details

[14] Biomarkers include fasting plasma FGF19, fasting serum bile acids, fasting C4 (7α-OH-4-cholesten-3-one). Samples should be collected after a minimum 8 hr fast and before the subject takes the daily dose of study drug
[15] Lipids and CV risk markers to be collected are detailed in Table 14
[16] Markers of inflammation include fibrinogen, CRP, IL6, IL1β, TNF-α, TNF-β, alpha2 macroglobulin and haptoglobin (see Table 14)
[17] Collect PK/PD samples after a minimum 8 hr fast and before the daily dose of study drug. PK/PD samples on Days 1 and 84 (Week12) collected predose and 2, 6, and 8 hr postdose; Weeks 2, 4 and 8 at predose and two samples postdose; the first sample collected 1 to 3 hours postdose and the second sample at least 1 hour later.
[18] PK predose samples should be collected after a minimum 8 hr fast before the daily dose of study drug. PK samples collected Day 1, Weeks 2, 4, 8 and 12 at predose and two samples postdose; the first sample collected 1 to 3 hours postdose and the second sample at least 1 hour later.
[19] Study drug given in the clinic on days where subject is seen in the clinic
[20] Additional samples may be collected to further assess safety events e.g. pruritus
[redacted]