ENANTA Pharmaceuticals

CLINICAL STUDY PROTOCOL

A PHASE 2 DOSE RANGING, RANDOMIZED, DOUBLE BLIND, AND PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND EFFICACY OF EDP-305 IN SUBJECTS WITH NON-ALCOHOLIC STEATOHEPATITIS (NASH)

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Study Sponsor:	Enanta Pharmaceuticals, Inc. 500 Arsenal St. Watertown, MA 02472
Sponsor Medical Monitor:	[redacted] Enanta Pharmaceuticals, Inc. 500 Arsenal St. Watertown, MA 02472 Phone: [redacted]

CONFIDENTIAL

CONTACT INFORMATION

Role in Study	Name	Address and Telephone
Enanta Medical Monitor	[redacted]	Enanta Pharmaceuticals, Inc. 500 Arsenal St. Watertown, MA 02472 Phone: [redacted]
CRO 24-Hour Emergency Line	[redacted]	[redacted] Investigative sites will be provided country-specific toll-free telephone numbers.
SAE and Pregnancy Reporting	[redacted]	European Union email: [redacted] North America: email: [redacted] Fax: [redacted]

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study 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

AE, AR	adverse event(s), adverse reaction(s)
ALT	alanine aminotransferase
ANOVA	analysis of variance
ANCOVA	analysis of covariance
apo	apolipoproteins
APRI	AST to Platelet Ratio Index
AST	aspartate aminotransferase
AUC	area under the curve
BA	bile acid
BCRP	breast cancer resistance protein
BMI	body mass index
BSEP	bile salt export pump
C4	complement component 4
CK18	cytokeratin 18
C_{max}	maximum concentration
CRO	contract research organization
CV	cardiovascular
CYP	cytochrome P450
CYP7A1	cholesterol 7α-hydroxylase
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EFD	embryo-fetal development
ELF	enhanced liver fibrosis
EOS	end-of-study
EOT	End-of-treatment
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FIH	first-in-human
FE	food effect
FIB-4	Fibrosis-4
FSH	follicle stimulating hormone
FXR	farnesoid X receptor
GCP	good clinical practice
GLP	good laboratory practice
GLP-1	glucagon-like peptide-1
HbA1c	glycated hemoglobin
HDL-C	high density lipoprotein cholesterol

HEK293	human embryonic kidney 293 cells
HOMA	homeostasis model assessment
HV	healthy volunteers
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
IWRS	interactive web response system
LDL-C	low density lipoprotein cholesterol
MAD	multiple ascending dose
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging - proton density fat fraction
mRNA	messenger ribonucleic acid
NAFLD	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
PBO	placebo
PD	pharmacodynamics
P-gp	P-glycoprotein
PI	Principal Investigator
PIIINP	procollagen III amino terminal peptide
PK	pharmacokinetics
PN	presumptive NAFLD; defined as obese with or without prediabetes or type 2 diabetes mellitus
PR	electrocardiographic interval occurring between the onset of the P wave and the QRS complex, representing time for atrial and ventricular depolarization, respectively
PRO C3	type 3 procollagen
PSC	primary sclerosing cholangitis
QD	once daily
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing the time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur

QTcF	QT interval corrected by Fridericia's formula
RR	interval between successive heart beats using the R-wave peaks
SAD	single ascending dose
SAD/FE	single ascending dose / food effect
SAE	serious adverse event(s)
SAP	statistical analysis plan
SHP	small heterodimer partner
SoA	Schedule of Assessments
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TEAE	treatment emergent adverse event
TG	triglyceride(s)
TIMP-1	tissue inhibitor of metalloproteinase 1
TNF	tumor necrosis factor
TGR5	Takeda G-protein-coupled receptor 5/ also known as M-BAR
T_{max}	time to maximum concentration
ULN	upper limit of normal
US	United States
WBC	white blood cell
WTH	waist to hip ratio

PROTOCOL SYNOPSIS

Name of Sponsor/Company: Enanta Pharmaceuticals, Inc.

Name of Investigational Product: EDP-305

Study Title: A Phase 2 Dose Ranging, Randomized, Double Blind, and Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of EDP-305 in Subjects with Non-Alcoholic Steatohepatitis (NASH)

Protocol Number: EDP 305-101

Phase of Development: 2

Study Center: The study will be conducted at approximately 65 US and ex-US sites

Number of Subjects Planned: Approximately 125 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 1mg, 2.5mg or placebo taken once daily (QD) for 12 weeks.

Duration of Treatment: 12 weeks

Study Objectives:

Primary Objectives:

- To evaluate change in alanine aminotransferase (ALT) levels
- To evaluate the safety and tolerability of EDP-305

Secondary Objectives:

- To evaluate the effect of EDP-305 on liver fat
- To evaluate the effect of EDP-305 on fibrosis (liver stiffness)
- To evaluate the effect of EDP-305 on noninvasive liver fibrosis markers
- To evaluate the effects of EDP-305 on lipids
- To evaluate the effects of EDP-305 on glucose metabolism
- To evaluate the effects of EDP-305 on inflammatory markers
- To evaluate the pharmacokinetics (PK) of EDP-305 and its metabolites in plasma
- To evaluate the effect of EDP-305 on body weight
- To evaluate the effect of EDP-305 on waist to hip (WTH) ratio
- To evaluate the pharmacodynamics of EDP-305

Criteria for Evaluation:

Primary Endpoint:

- Change from baseline in ALT levels at Week 12
- Frequency of adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation through Week 12

Secondary Endpoints:

- Change from Baseline in percentage of fat in the liver as assessed by magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) at Week 12
- Change from Baseline in liver stiffness as assessed by magnetic resonance elastography (MRE) at Week 12
- Change from Baseline of noninvasive liver fibrosis markers (Enhanced Liver Fibrosis [ELF] panel) and PRO C3 at Week 12
- Change from Baseline in non-alcoholic fatty liver disease (NAFLD) Fibrosis Score (NFS), AST to Platelet Ratio Index (APRI), and fibrosis 4 (FIB-4) at Week 12
- Change form Baseline in triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), adiponectin and apolipoproteins (Apo)A1, B, C3 at Week 12
- Change from Baseline in fasting glucose and insulin, homeostasis model assessment (HOMA) index (in nondiabetic subjects) and glycated hemoglobin (HbA1c) in subjects with Type 2 diabetes mellitus (T2DM) at Week 12
- Change from Baseline in fibrinogen, CRP, IL6, IL1β, TNF-α, TNF-β , alpha2 macroglobulin and haptoglobin levels at Week 12
- Pharmacokinetic parameters of EDP-305 (and metabolites): C_{max}, t_{max}, and AUC_{last}
- Change from Baseline in body weight at Week 12
- Change in WTH ratio at Week 12
- Pharmacodynamic parameters of EDP-305: FGF19, C4, and bile acid (BA) at Week 12

Study Design:

This is a Phase 2 dose-ranging, randomized, double blind, and placebo-controlled study evaluating the safety, tolerability, PK and efficacy of EDP-305 in subjects with NASH.

The duration of the study will be approximately 20 weeks. The study will consist of a Screening Period, Treatment Period, and a Safety Follow-up Period.

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

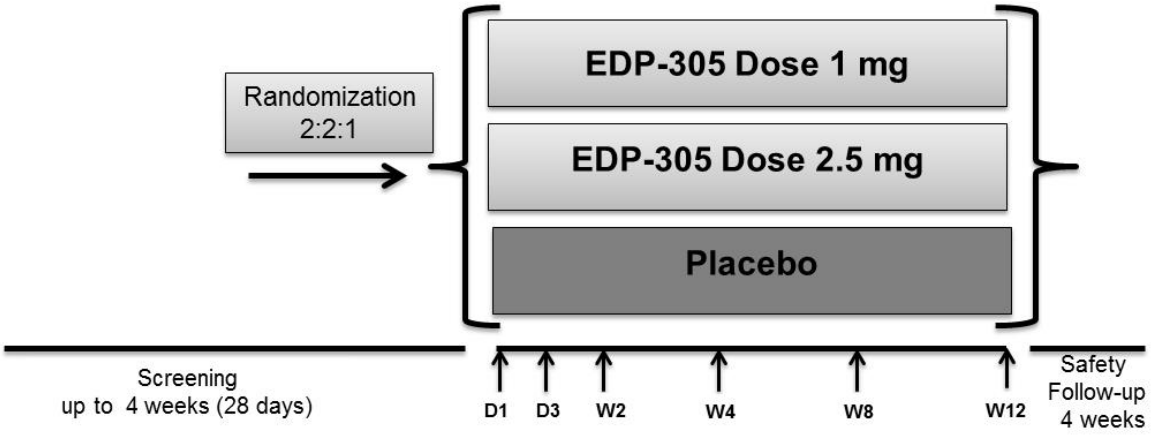
Screening Period: Subjects must review and sign the informed consent form (ICF) prior to completing any study-specific procedures. After signing the ICF, subjects will be screened and must meet all entry criteria for entry into the study. All screening assessments must occur within the -28 to -1 Day 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 2:2:1 to receive one of two oral doses of EDP-305 or placebo in tablet form once daily. Procedures performed are specified in the Schedule of Assessments (Table 19). 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. Subjects will be dispensed study drug and instructed to take study drug once daily for a total of 12 weeks returning to the clinic for assessments on Day 3, and at Weeks 2, 4, 8, and 12. On study days when there is a clinic visit, subjects will be administered their daily dose at the clinic. [redacted]

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 End-of-Treatment (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

A subject must meet all of the following criteria in order to participate in the 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 presence of NASH by:

   - Histologic evidence on a historical liver biopsy within 24 months of Screening consistent with NASH with fibrosis (no cirrhosis), and elevated ALT at Screening

   NOTE: Vitamin E should not have been initiated after the date the biopsy was performed and subjects should have a stable weight since the liver biopsy was performed defined by no more than a 5% change of initial body weight

   OR

   - Phenotypic diagnosis of NASH based on elevated ALT and diagnosis of T2DM or pre-diabetes

   NOTE: Elevated ALT must be ≥50 IU/L and ≤200 IU/L; Known T2DM or pre-diabetes with one of the following criteria: : random plasma glucose concentration >200 mg/dL (11.1 mmol/L) OR fasting plasma glucose >126 mg/dL (7.0 mmol/L) OR 2-hour post-load glucose >200 mg/dL (11.1 mmol/L) during a 75 g oral glucose tolerance test (OGTT) OR HbA1c of at least 6% with or without concomitant treatment with metformin

   AND

   - Screening MRI-PDFF with >8% steatosis

4. Body mass index (BMI) >25 kg/m^2. NOTE: for Asian-Americans, BMI >23 kg/m^2
5. Subjects must have Screening laboratory values for Hepatitis B surface antigen (HBsAg), anti-HCV antibodies and HCV RNA, 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.
6. 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 nonchildbearing 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 post-menopausal (a demonstration of a total cessation of menses for ≥1 year with a follicle stimulating hormone (FSH) level of >35 mIU/mL).
7. 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
8. Male subjects must agree to refrain from sperm donation from the date of Screening until 90 days after their last dose of study drug
9. Subject must be willing and able to adhere to the assessments, visit schedules, prohibitions and restrictions, as described in this protocol

Exclusion Criteria

Subjects will not be eligible to participate in the study if they meet any of the following criteria:

1. Laboratory Screening Results:
   - Total bilirubin >ULN (normal range 0.2–1.2 mg/dL)

   NOTE: Patients with Gilbert's syndrome will be allowed if they have a known history of

Gilbert's syndrome with a normal direct bilirubin value and normal reticulocyte count, and upon review by the medical monitor

- Total white blood cells (WBC) <3,000 cells/mm^3
- Absolute neutrophil count (ANC) <1,500 cells/mm^3
- Platelet count <140,000/mm^3
- Prothrombin time (international normalized ratio, INR)>1.2
- Creatine kinase above the upper limit of normal (ULN) except when in relation with intense exercise
- Serum creatinine >2 mg/dL or clearance creatinine <60 ml/min (based on Cockroft-Gault method)

2. Known history of alpha-1-antitrypsin deficiency
3. Use of an experimental treatment for NASH within the past 6 months
4. Prior use and/or concurrent treatment with obeticholic acid (OCA)
5. Use of immunosuppressant (eg, corticosteroids) for more than 2 weeks in duration within 1 year prior to Screening and during the course of the study
6. Use of experimental or unapproved drugs within a year of Screening
7. Any other condition(s) (including cardiovascular diseases) that would compromise the safety of the subject or compromise the quality of the clinical study, as judged by the Principal Investigator (PI)
8. Pregnant or nursing females
9. 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
10. Clinical suspicion of advanced liver disease or cirrhosis
11. Coexisting liver or biliary diseases, such as primary sclerosing cholangitis (PSC), choledocholithiasis, acute or chronic hepatitis, autoimmune hepatitis, alcoholic liver disease, acute infection of bile duct system or gall bladder, history of gastrointestinal bleeding (secondary to portal hypertension), cirrhosis
12. Suspicion of cancer (eg, liver cancer) with the exception of basal cell carcinoma that has been resected
13. Cirrhosis with or without complications, including history or presence of: spontaneous bacterial peritonitis, hepatocellular carcinoma, bilirubin >2 × ULN
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. Any condition possibly affecting drug absorption (eg, gastrectomy <3 years prior to Screening)
17. 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
18. Subject has received an investigational agent or 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. NOTE: Flu vaccine will be allowed upon Medical Monitor's approval
19. 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
20. Use of cytochrome P450 (CYP)3A4 and P-glycoprotein (P-gp) inducers and inhibitors within 14 days prior to the first dose of study medication and throughout study duration
21. Use of a new statin regimen from Screening and throughout study duration. NOTE: Subjects on a stable dose of statins for at least three months prior to Screening are allowed. No dose modification during the study will be allowed.
22. Current use of fibrates. NOTE: Subjects who discontinued fibrates for at least 3 months before Screening can participate
23. Clinically significant history of drug sensitivity or allergy, as determined by the PI
24. Uncontrolled diabetes mellitus (ie, HbA1c ≥9% or higher) 60 days prior to Day 1
25. Use of a new antidiabetic regimen from Screening and throughout study duration, including metformin, GLP-1 agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors, sulfonylureas, or dipeptidyl peptidase-4 (DPP4) inhibitors, insulin or peroxisome proliferator-activated receptor (PPAR)γ agonists (pioglitazone or rosiglitazone). **For pre-existing antidiabetic treatment**, subjects should be on a stable dose of antidiabetic drugs: (1) for at least 2 months (for metformin and/or sulfonylureas), (2) 3 months (for SGLT2 or DPP4 inhibitors), or (3) 6 months (for GLP-1 receptor agonists and thiazolidinediones) prior to Screening. NOTE: Sulfonylureas and insulin are only permitted if glycemia is self-monitored by the subject; subjects treated with insulin are eligible if clinically stable on insulin treatment (ie, no recurrent acute hypo- or hyperglycemic episodes diagnosed clinically with serum glucose levels of <50 mg/dL or >200 mg/dL) for at least two months prior to Screening.
26. Subjects with contraindications to MRI imaging, or not being able to have the MRI performed

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 (eg, close monitoring, additional PK samples, 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 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).

Analyses Population

- *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 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 each safety laboratory parameter. All laboratory data will be included in the data listings and all test values outside the normal range will be flagged. Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term by treatment group.

Efficacy Analyses: Change in ALT levels at Week 12 from pretreatment value will be calculated. All 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.

Pharmacokinetic Analyses: Plasma PK parameters for each dose level will be calculated from the concentrations of EDP-305 and its major metabolites measured in predose and postdose plasma samples. For each EDP-305 dose level, descriptive statistics (sample size, arithmetic means, geometric means, standard deviation (SD), % 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 PK

parameters AUC_{0-t}, C_{max}, and T_{max} will be calculated as indicated for plasma EDP-305 and its major metabolites.

Sample Size Consideration: Group sample sizes of 44 (in each dose group) and 22 placebo subjects achieves 80.438% power to reject the null hypothesis of equal means when the population mean difference in ALT is (−40.0)–(−10.0) =−30.0 with a standard deviation for both groups of 40.0 and with a significance level (alpha) of 0.050 using a two-sided two-sample equal-variance t-test. To account for a 20% discontinuation rate, 15 additional subjects will be enrolled to attempt to have at least 110 subjects who complete treatment bringing the total number of subjects enrolled to 125.

1. INTRODUCTION

1.1. Overview

EDP-305 [redacted] is a farnesoid X receptor (FXR) agonist being investigated as a potential treatment for Nonalcoholic Steatohepatitis (NASH) with liver fibrosis. This study, EDP 305-101, is a randomized, double-blind, placebo-controlled, Phase 2 study designed to assess the safety, tolerability, and effectiveness of EDP-305 in subjects with NASH.

1.2. Background

1.2.1. NASH and Farnesoid X Receptor (FXR)

Non-alcoholic fatty liver disease (NAFLD) is defined by excess accumulation of lipids in the liver which develops in the absence of other causes for secondary hepatic fat accumulation. Historically, NAFLD encompasses a wide spectrum of conditions from nonalcoholic fatty liver (NAFL) characterized by simple steatosis with minimal or no inflammation to NASH which is characterized by hepatic steatosis and inflammation with hepatocyte damage (ballooning) and with or without fibrosis *(Bertot & Adams, 2016; Chalasani et al., 2012*).

Bile acids (BA) 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. FXR is a member of the nuclear hormone receptor superfamily and is considered a master regulator of many BA activities including feedback regulation of BA synthesis, gluconeogenesis and glycogenolysis in the liver, and peripheral insulin sensitivity in adipose tissue (*McMahan et al., 2013*). Given the critical role BAs play in liver homeostasis and the role of FXR in regulating BA biosynthesis, FXR has become a target for therapeutic intervention in NASH.

1.2.2. Rationale for Development of EDP-305 for NASH

NASH is considered a serious disease with unmet medical need and if not treated, it can progress to life-threatening conditions such as cirrhosis and hepatocellular carcinoma. Recently, NASH has been associated with an approximate 10-fold increase in liver-related mortality when compared to an identical age and sex-matched population (*Ratziu, 2013*). Over the past decade the frequency of NASH as the primary indication for liver transplant has increased dramatically, and is continuing to rise (*Agopian et al., 2012*). Based on the United Network for Organ Sharing and Organ Procurement and Transplantation Network (UNOS/OPTN) registry, from 2004 to 2013, the number of registrants diagnosed with NASH demonstrated the greatest change, increasing 170% (from 804 to >2000 registrants) to become the second leading etiology of chronic liver disease among new waitlist registrants in 2013 (*Wong et al., 2015*). Data showed that patients with NASH were less likely to undergo liver transplantation and less likely to survive for 90 days on the waitlist than patients with hepatitis C virus (HCV) infection, alcoholic liver disease (ALD), or combination of HCV and ALD. In addition, by 2012 NASH had become the second leading etiology of hepatocellular carcinoma (HCC) leading to liver transplantation in the United States (US) (*Wong et al., 2015*).

Farnesoid X receptors are nuclear hormone receptors expressed in high amounts in body tissues that participate in BA metabolism including the liver, intestines, and kidneys. Bile acids (BAs) are the natural ligands of the FXRs. Farnesoid X receptors regulate the expression of the gene encoding for cholesterol 7 alpha-hydroxylase, which is the rate-limiting enzyme in BA synthesis. Additionally, FXRs play a critical role in carbohydrate and lipid metabolism and in the regulation of insulin sensitivity. These receptors also modulate liver growth and regeneration during liver injury.

Data has shown that hepatic expression of FXR is decreased in NAFLD patients, which is associated with hepatic triglyceride (TG) accumulation and hepatic steatosis. Effects observed in FXR deficiency animal models include hepatic steatosis, hyperlipidaemia, hyperglycemia, BA overload, inflammation and fibrosis (*Xu, Li, Zhang, & Ji, 2014*). Moreover, studies have shown that these metabolic dysfunctions can be improved by FXR activation, indicating that FXR agonism may represent a new modality for NASH treatment.

In line with these findings, and to address the unmet medical need of NASH, Enanta Pharmaceuticals is developing EDP-305 as a FXR agonist that selectively activates FXRs. Nonclinical studies have shown that EDP-305 can decrease the expression of genes that encode lipogenic enzymes, as well as inflammation and fibrosis-related genes. In models of NASH and dyslipidemia, EDP-305 has demonstrated the potential for reduction in NASH and improvement in insulin sensitivity. Due to its promising early nonclinical safety and pharmacological profile, In a First-in-Human (FIH) clinical study in a limited number of subjects, EDP-305 appeared to positively affect levels of biomarkers associated with FXR activity. Thus, due to its promising nonclinical safety and pharmacological profile, and early clinical safety results, the Sponsor plans to continue investigation of EDP-305 as a potential treatment for NASH. [redacted]

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 its close synthetic analog obeticholic acid (OCA), were used as controls. Obeticholic acid has recently been approved for the treatment of primary biliary cholangitis (PBC) and is being evaluated for the treatment of NASH.

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 BA 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 affected a dose-dependent increase in small heterodimer partner (SHP) gene expression and decrease in cytochrome P450 (CYP)7A1 messenger ribonucleic acid (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 BA and lipid metabolism, inflammation, fibrosis, and glucose metabolism was evaluated using *in vitro* systems. Obeticholic acid 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 BA (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 BA metabolism was assessed in C57BL/6 mice treated with EDP-305 or OCA orally for 5 days. EDP-305 induced a dose-dependent increase in fibroblast growth factor (FGF)-15 and SHP gene expression in the ileum, and dose-dependent increases in SHP and bile salt export pump (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 nonfasted 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 homeostasis model assessment – insulin resistance (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 primary sclerosing cholangitis (PSC), PBC, cystic fibrosis liver disease (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 alanine aminotransferase (ALT) and aspartate

aminotransferase (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
[redacted]			

1.3.3. Pharmacokinetics

A series of nonclinical studies were conducted to assess the pharmacokinetics (PK) 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 to 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 to 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).

[redacted]

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 Good Laboratory Practice (GLP) studies (mouse and monkey) and in nonpivotal studies (rat, mouse, and monkey). [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 3: [redacted]

[redacted]

in urea concentration (+23% to +48%) consistent with subclinical dehydration; reversible minimal increases in [redacted]

[redacted]

1.3.4.2. Reproductive and Developmental Toxicity Studies

[redacted]

Table 4: Embryo-Fetal Development Studies

Study Type	Title	Duration	Dose Level[a,b]	AUC_{0-24} (µg·hr/mL)	Study Number
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					

[redacted]

[redacted]

1.3.4.3. Genetic Toxicity/Carcinogenesis

[redacted]

1.4. Clinical Studies

Five Phase 1 clinical studies have been conducted and/or are ongoing with EDP-305 [redacted].

Table 5: Clinical Studies with EDP-305

Study ID	Phase / Type	Population Planned/Actual (N)	Title
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

1.4.1. [redacted]

[redacted]

[redacted]

[redacted]

1.4.2.1. [redacted]

[redacted]

Table 7:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

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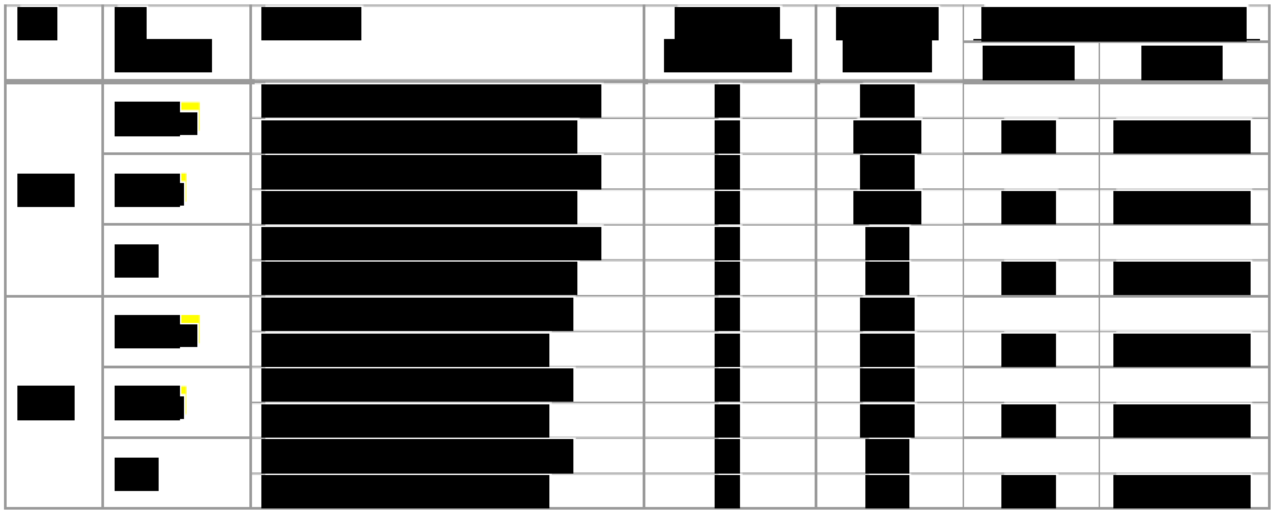
[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

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]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of the study is as follows:

- To evaluate change in ALT levels
- To evaluate the safety and tolerability of EDP-305

2.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the effect of EDP-305 on liver fat
- To evaluate the effect of EDP-305 on fibrosis (liver stiffness)
- To evaluate the effect of EDP-305 on non-invasive liver fibrosis markers
- To evaluate the effects of EDP-305 on lipids
- To evaluate the effects of EDP-305 on glucose metabolism
- To evaluate the effects of EDP-305 on inflammatory markers
- To evaluate the PK of EDP-305 and its metabolites in plasma
- To evaluate the effect of EDP-305 on body weight
- To evaluate the effect of EDP-305 on waist to hip (WTH) ratio
- To evaluate the pharmacodynamics of EDP-305

2.2. Endpoints

2.2.1. Primary Endpoints

The primary endpoints of the study are:

- Change from Baseline in ALT levels at Week 12
- Frequency of AEs, SAEs, and AEs leading to discontinuation through Week 12

2.2.2. Secondary Endpoints

The secondary endpoints of the study are as follows:

- Change from Baseline in percentage of fat in the liver as assessed by magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) at Week 12
- Change from Baseline in liver stiffness as assessed by magnetic resonance elastography (MRE) at Week 12

- Change from Baseline of noninvasive liver fibrosis markers (Enhanced Liver Fibrosis [ELF] panel) and PRO C3 at Week 12
- Change from Baseline in NAFLD Fibrosis Score (NFS), AST to Platelet Ratio Index (APRI), and fibrosis 4 (FIB-4) at Week 12
- Change form baseline in TG, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), adiponectin and apolipoproteins (Apo)A1, B, C3 at Week 12
- Change from Baseline in fasting glucose and insulin, HOMA index (in nondiabetic subjects) and glycated hemoglobin (HbA1c) in subjects with Type 2 diabetes mellitus (T2DM) at Week 12
- Change from Baseline in fibrinogen, CRP, IL6, IL1β, TNF-α, TNF-β, alpha2 macroglobulin, and haptoglobin levels at Week 12
- Pharmacokinetic parameters of EDP-305 (and metabolites): C_{max}, t_{max}, and AUC_{last}
- Change from Baseline in body weight at Week 12
- Change in WTH ratio at Week 12
- Pharmacodynamic parameters of EDP-305: FGF19, C4, and bile acid (BA) at Week 12

3. SELECTION OF SUBJECTS

A total of approximately 125 subjects with a diagnosis of NASH 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 presence of NASH by:
   - Histologic evidence on a historical liver biopsy within 24 months of Screening consistent with NASH with fibrosis (no cirrhosis), and elevated ALT at Screening

   NOTE: Vitamin E should not have been initiated after the date the biopsy was performed and subjects should have a stable weight since the liver biopsy was performed defined by no more than a 5% change of initial body weight

   OR

   - Phenotypic diagnosis of NASH based on elevated ALT and diagnosis of T2DM or pre-diabetes

   NOTE: Elevated ALT must be ≥ 50 IU/L and ≤ 200 IU/L; Known T2DM or pre-diabetes with one of the following criteria: random plasma glucose concentration >200 mg/dL (11.1 mmol/L) OR fasting plasma glucose >126 mg/dL (7.0 mmol/L) OR 2-hour post-load glucose >200 mg/dL (11.1 mmol/L) during a 75 g oral glucose tolerance test (OGTT) OR HbA1c of at least 6% with or without concomitant treatment with Metformin

   AND

   - Screening MRI-PDFF with >8% steatosis
4. Body mass index (BMI) >25 kg/m^2. NOTE: for Asian-Americans, BMI >23 kg/m^2
5. Subjects must have Screening laboratory values for Hepatitis B surface antigen (HBsAg) anti-HCV antibodies and HCV RNA 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
6. 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 nonchildbearing 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 post-menopausal (a demonstration of a total cessation of menses for ≥1 year with a follicle stimulating hormone (FSH) level of >35 mIU/mL)

7. 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
8. Male subjects must agree to refrain from sperm donation from the date of Screening until 90 days after their last dose of study drug
9. Subject must be willing and able to adhere to the assessments, visit schedules, prohibitions and restrictions, as described in this protocol

3.2. Subject Exclusion Criteria

Subjects will not be eligible to participate in the study if they meet any of the following criteria:

1. Laboratory Screening Results:
   - Total bilirubin >ULN (normal range 0.2–1.2 mg/dL)
   NOTE: Patients with Gilbert's syndrome will be allowed if they have a known history of Gilbert's syndrome with a normal direct bilirubin value and normal reticulocyte count, and upon review by the medical monitor.
   - Total white blood cells (WBC) <3,000 cells/mm^3
   - Absolute neutrophil count (ANC) <1,500 cells/mm^3
   - Platelet count <140,000/mm^3
   - Prothrombin time (international normalized ratio, INR) >1.2
   - Creatine kinase above the upper limit of normal (ULN) except when in relation with intense exercise
   - Serum creatinine >2 mg/dL or clearance creatinine <60 mL/min (based on Cockroft-Gault method)
2. Known history of alpha-1-Antitrypsin deficiency
3. Use of an experimental treatment for NASH within the past 6 months
4. Prior use and/or concurrent treatment with obeticholic acid (OCA)
5. Use of immunosuppressant (eg, corticosteroids) for more than 2 weeks in duration within 1 year prior to Screening and during the course of the study
6. Use of experimental or unapproved drugs within a year of Screening
7. Any other condition(s) (including cardiovascular diseases) that would compromise the safety of the subject or compromise the quality of the clinical study, as judged by the Principal Investigator (PI)

8. Pregnant or nursing females
9. 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
10. Clinical suspicion of advanced liver disease or cirrhosis
11. Coexisting liver or biliary diseases, such as PSC, choledocholithiasis, acute or chronic hepatitis, autoimmune hepatitis, alcoholic liver disease, acute infection of bile duct system or gall bladder, history of gastrointestinal bleeding (secondary to portal hypertension), cirrhosis
12. Suspicion of cancer (eg, liver cancer) with the exception of basal cell carcinoma that has been resected
13. Cirrhosis with or without complications, including history or presence of: spontaneous bacterial peritonitis, hepatocellular carcinoma, bilirubin >2 × ULN
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. Any condition possibly affecting drug absorption (eg, gastrectomy <3 years prior to Screening)
17. 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
18. Subject has received an investigational agent or 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. NOTE: Flu vaccine will be allowed upon Medical Monitor's approval
19. 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
20. Use cytochrome P450 (CYP)3A4 and P-glycoprotein (P-gp) inducers and inhibitors within 14 days prior to the first dose of study medication and throughout study duration
21. Use of a new statin regimen from Screening and throughout study duration. NOTE: Subjects on a stable dose of statins for at least three months prior to Screening are allowed. No dose modification during the study will be allowed.
22. Current use of fibrates. NOTE: Subjects who discontinued fibrates for at least 3 months before Screening can participate
23. Clinically significant history of drug sensitivity or allergy, as determined by the PI.
24. Uncontrolled diabetes mellitus (ie, HbA1c ≥9% or higher) 60 days prior to Day 1
25. Use of a new antidiabetic regimen from Screening and throughout study duration, including metformin, GLP-1 agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors, sulfonylureas, or dipeptidyl peptidase-4 (DPP4) inhibitors, insulin or peroxisome proliferator-activated receptor (PPAR)γ agonists (pioglitazone or rosiglitazone). **For pre-existing antidiabetic treatment**, subjects should be on a stable dose of antidiabetic drugs: (1) for at least 2 months (for metformin and/or sulfonylureas), (2) 3 months (for SGLT2 or DPP4 inhibitors), or (3) 6 months (for GLP-1 receptor

agonists and thiazolidinediones) prior to Screening. NOTE: Sulfonylureas and insulin are only permitted if glycemia is self-monitored by the subject; subjects treated with insulin are eligible if clinically stable on insulin treatment (ie, no recurrent acute hypo- or hyperglycemic episodes diagnosed clinically with serum glucose levels of <50 mg/dL or >200 mg/dL) for at least two months prior to Screening.

26. Subjects with contraindications to MRI imaging, or not being able to have the MRI performed

4. STUDY DESIGN

This is a Phase 2 dose-ranging, randomized, double blind, and placebo-controlled study evaluating the safety, tolerability, PK and efficacy of EDP-305 in subjects with NASH.

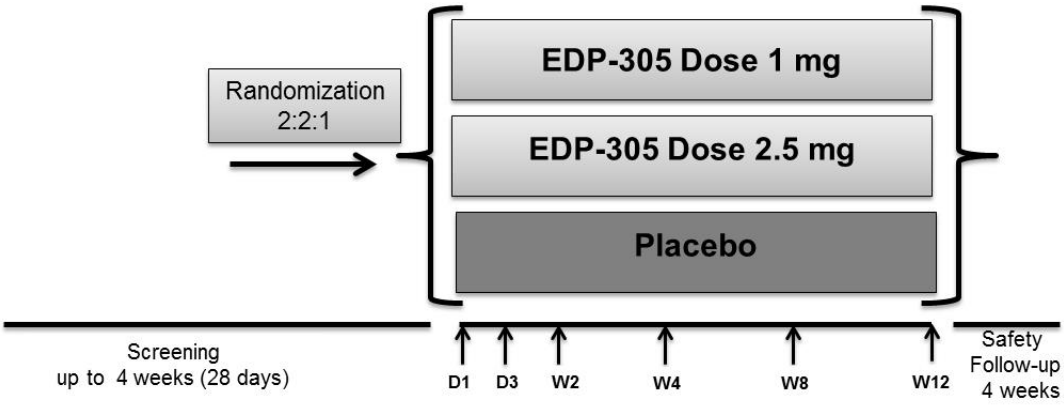
The study is composed of 3 phases or periods:

- 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 2:2:1 to receive one of two doses of EDP-305 or 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 Assessments (SoA) (Table 19).

Figure 1. Study Design



Abbreviations: D=Day; W=Week

4.2. Rationale for Study Design

This proposed study will evaluate EDP-305 in patients with NASH 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 2:2:1 ratio.

4.2.1. Justification of Design and Control Group

Currently, there are no approved pharmacologic therapies for this disease. The recommended first-line nonpharmacologic therapy is lifestyle modification through dietary modification and increased physical activity (*Ratziu, 2013*).

Based on nonclinical and *in vitro* data, EDP-305 is an FXR agonist which plays an essential role in the feedback regulation of BA biosynthesis and given the critical role BAs play in liver homeostasis, FXR has become a target for therapeutic intervention in NASH.

[redacted]

This Phase 2 study aims to evaluate safety, tolerability, and PK/PD (ie, dose selection) of the investigational novel FXR agonist, EDP-305 in a targeted patient population with presumptive presence of NASH by either a prior liver biopsy or phenotypic characteristics but no liver biopsy at entry. Subjects will have confirmed presence of NASH by histologic evidence on a prior liver biopsy within 24 months and elevated ALT, OR phenotypic diagnosis of NASH based on elevated ALT, BMI (>25 kg/m^2 or >23 kg/m^2 for Asian-Americans), and diagnosis of T2DM or pre-diabetes. These subjects at high risk for NASH will be assessed based on evidence of fatty liver, two components of the metabolic syndrome, and evidence of liver fat and stiffness by imaging.

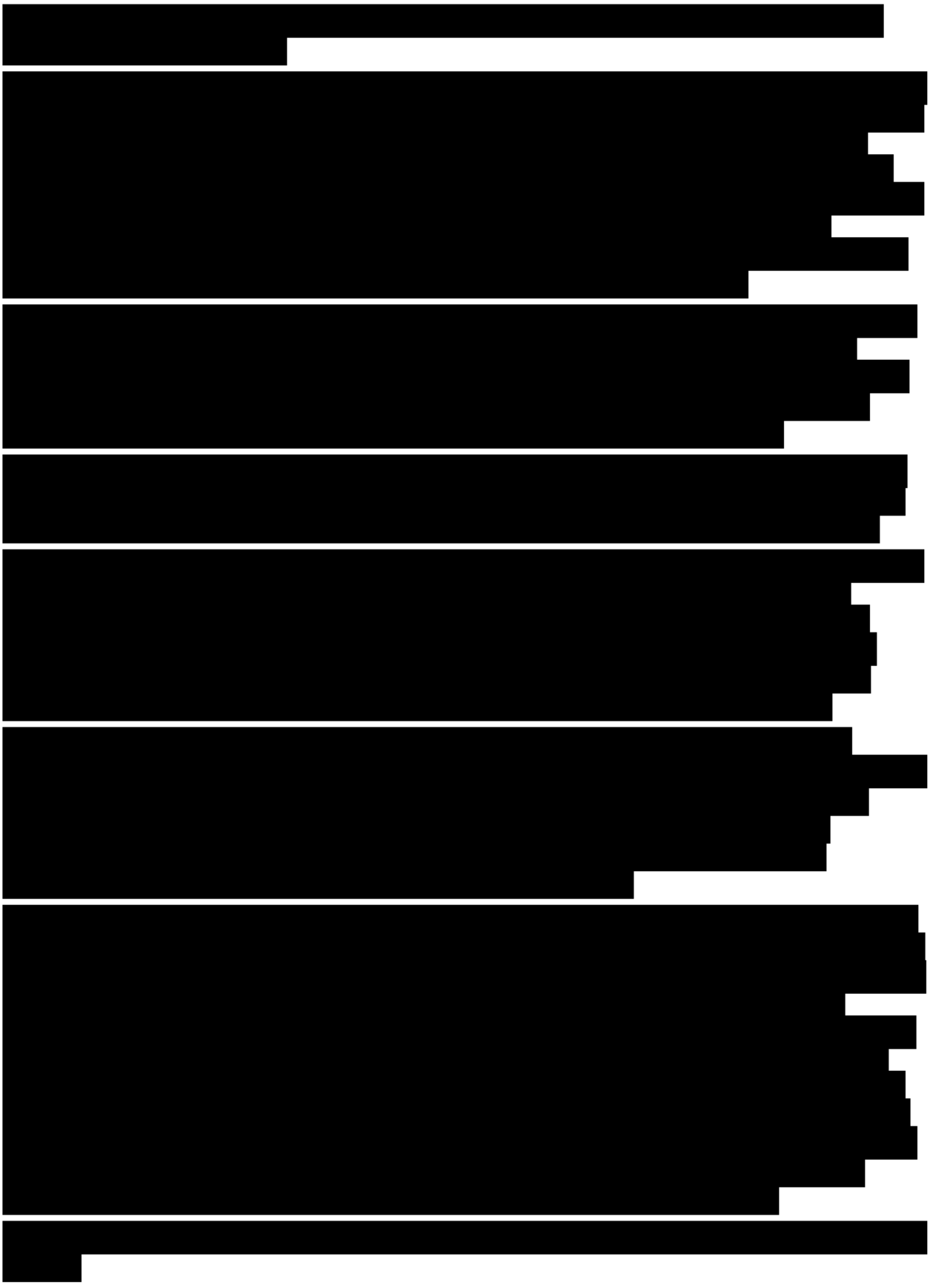
This double-blind phase of this study is being conducted for 12 weeks. Based on the mechanism of EDP-305 and, on observed data in other short-term treatment Phase 2 studies that were published with similar therapies *(Neuschwander-Tetri et al., 2015),* the Sponsor believes that liver enzyme reductions and change in noninvasive biomarkers (imaging and metabolic/mechanistic markers) will be seen after >1 month of therapy.

[redacted]

The purpose of the double-blind design is to obtain the most unbiased assessment of clinical safety and efficacy with the doses being studied. To assess changes in liver fat and fibrosis an MRI and MRE will be conducted during the screening period and at the end of treatment. Additionally, markers for liver fibrosis and inflammation, cardiovascular markers, and biomarkers for NASH will be evaluated throughout the study and changes from baseline evaluated. [redacted]

4.2.2. Justification of EDP-305 Dose

This phase 2 study 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 NASH [redacted]



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 [redacted]

[redacted] Matching placebos for the two strengths will also be supplied [redacted] Study drug and matching placebo tablets will be supplied by Enanta.

[redacted]

Additional information will be provided in the Pharmacy Manual.

5.2. Packaging and Labeling

EDP-305 tablets and matching placebo will be supplied in high density polyethylene bottles [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]

5.3. Storage

[redacted]

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 patients 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/ Randomization

Subjects will be randomized to study treatment using an Interactive Web Response System (IWRS). [redacted] Subjects will be randomized to the treatment groups shown below:

- Treatment Group 1 (N=50); EDP-305 1 mg orally for 12 weeks
- Treatment Group 2 (N=50); EDP-305 2.5 mg orally for 12 weeks
- Treatment Group 3 (N=25); Placebo (PBO) orally for 12 weeks

[redacted] 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.

[redacted]

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.

[redacted] The bottle number dispensed to the subject and the number of tablets dispensed will be recorded in the site source documents. [redacted]

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 (Table 19). 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

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

Subjects taking Vitamin E and antidiabetic medications should be on a stable dose for at least 3 months prior to screening.

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 (Table 19).

5.8.1 [redacted]

[redacted]

5.9. Prohibited Medications

Inhibitors and inducers of CYP3A4 and P-gp are prohibited within 14 days prior to the first dose of study medication and throughout study duration.

A comprehensive list of CYP3A4 inducers and inhibitors can be found at: *http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx*

Additionally, medications that inhibit or induce the transporter proteins P-gp are also prohibited during study participation. A list of these medications can be found at *http://bts.ucsf.edu/fdatransportal/index/*.

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.

Use of a new antidiabetic regimen from Screening and throughout study duration, including metformin, GLP-1 agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors, sulfonylureas, or dipeptidyl peptidase-4 (DPP4) inhibitors, insulin or peroxisome proliferator-activated receptor (PPAR)γ agonists (pioglitazone or rosiglitazone). **For pre-existing antidiabetic treatment**, subjects should be on a stable dose of antidiabetic drugs: (1) for at least 2 months (for metformin and/or sulfonylureas), (2) 3 months (for SGLT2 or DPP4 inhibitors), or (3) 6 months (for GLP-1 receptor agonists and thiazolidinediones) prior to Screening. NOTE: Sulfonylureas and insulin are only permitted if glycemia is self-monitored by the subject; subjects treated with insulin are eligible if clinically stable on insulin treatment (ie, no recurrent acute hypo- or hyperglycemic episodes diagnosed clinically with serum glucose levels of <50 mg/dL or >200 mg/dL) for at least two months prior to Screening.

5.10. Other Restrictions

Table 14 outlines protocol restrictions other than prohibited medications outlined above and the timing of those restrictions.

Table 14: Protocol Restrictions

Restricted Medication/Food/Activity	Timing of Restriction	
	From (minimum)	To
Experimental treatment for NASH	6 months prior to Screening	End of Study Visit
OCA	Any prior or concurrent use	End of Study Visit
Immunosuppressants (eg, corticosteroids) for more than 2 weeks	1 year prior to Screening	End of Study Visit
New statin regimen	3 months prior to Screening	End of Study Visit
Experimental or unapproved drugs	Within 1 year of Screening	End of Study Visit
Investigational agent or vaccine*	30 days prior to first dose of study drug	End of Study Visit
Biologic Product	3 months (or 5 elimination half-lives) prior to first dose of study drug	End of Study Visit
New antidiabetic regimen of metformin and/or sulfonylureas	2 months prior to Screening	End of Study Visit
New antidiabetic regimen of insulin	2 months prior to Screening	End of Study Visit

Restricted Medication/Food/Activity	Timing of Restriction	
	From (minimum)	**To**
New antidiabetic regimen of SGLT2 inhibitors	3 months prior to Screening	End of Study Visit
New antidiabetic regimen of DPP4 inhibitors	3 months prior to Screening	End of Study Visit
New antidiabetic regimen of GLP-1 receptor agonists or thiazolidinediones	6 months prior to Screening	End of Study Visit

*Flu vaccine will be allowed upon Medical Monitor's approval

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/Clinical Research Organization (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 NASH Biomarkers, Fibrosis and Inflammatory Markers, MRI/MRE, and Laboratory Liver Test Results

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

- Biomarker laboratory data
    - FGF-19, total BAs
    - C4 [7α-OH-4-cholesten-3-one]
    - CK18
    - GLP-1
- 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
    - APRI
    - NFS
    - FIB-4
- Liver Tests
    - ALT

- AST
- GGT

However, abnormal liver test results will be flagged if the lab results are ≥2 × baseline and these flagged results will be shared with the Investigator and the Medical Monitor (and/or designee) for safety monitoring purposes.

MRI and MRE results postbaseline will be blinded to the Investigators, site personnel, and Sponsor. Additionally, the MRI facility and radiologist will be blinded to the subject's study treatment and the MRI and MRE readings will be read centrally.

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 investigator have attempted and failed to contact the medical monitor, and/or the urgency of the case required immediate action, investigators should use their best judgment, based on the nature and urgency of the clinical situation, and proceed with unblinding.

- For unblinding, in the event the local [redacted] medical monitor cannot be reached, sites at all locations should call the following 24/7 global medical coverage hotline: [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 (eg, the reason, date) 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.

The Safety and Risk Management group 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.

NOTE: Investigative sites will be provided country-specific toll-free telephone numbers.

7. STUDY CONDUCT AND VISIT SCHEDULE

7.1. Study Visits

Details of assessments at each visit are presented in the SoA (Table 19).

7.1.1. Screening

Screening procedures will occur after the subject signs and dates an Institutional Review Board (IRB) or Ethics Committee (EC) approved informed consent form (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 (Table 19). 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 rescreened under the following circumstances 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.
- Subjects who have abnormal laboratory results, which may potentially reflect erroneous results, based on Investigator judgement.

7.1.3. Baseline (Day 1)

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 and exclusion criteria, subjects who continue to satisfy eligibility

requirements will be randomized in a 2:2:1 ratio to their treatment group. Predose assessments and procedures will be conducted as noted in the SoA (Table 19) and considered Baseline values.

After predose 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. [redacted] K and PD samples will be collected as described in SoA (Table 19).

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)

All subjects will be requested to return to the clinic on Days 3, and Weeks 2, 4, and 8 for on-treatment study visits. Subjects will be instructed to fast overnight for a minimum of 8 hours prior to each visit. Except for days when there is a clinic visit, subjects will take their daily dose of study drug at home. Treatment period assessments are listed in Table 19.

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 (Week 12) visit. 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 (Table 19).

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 EOS visit 4 weeks after the last dose of study drug for follow-up safety assessments (Table 19). For subjects who complete the study, the EOS visit would be scheduled on Day 112.

Any subject with ongoing AEs/SAEs 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 may withdraw from the study at any time at their own request, or subjects may be withdrawn at any time at the discretion of the investigator or Enanta for safety, behavioral, or administrative reasons. However, the Investigator should consult with the Sponsor's Medical Monitor where possible 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 (Table 19). 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 scheduled 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.

7.2.1. Withdrawal Criteria

Subjects may 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. Reasons for discontinuation include:

- 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.
- Principal Investigator 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

8.1. Timing of Assessments

The timing of assessments is shown in Table 19.

8.2. 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 NASH should be recorded.

8.3. Clinical Evaluations

8.3.1. Vital Sign Measurements and Electrocardiograms

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 after the subject has been supine for 5 minutes and before dosing. Oral 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 and before dosing. 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). The clinical interpretation by the PI or designee of the ECGs should be recorded on a hard copy of the ECGs (ie, clinically significant [CS] or nonclinically significant [NCS]).

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.

8.3.2. 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 (Table 19) and will include a review 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).

8.3.3. Weight, Body Mass Index, and Waist to Hip Ratio

Height and body weight should be obtained with the subject in light clothes and no shoes. Body mass index should be calculated at Screening (to assess eligibility) according to the following equation:

$$BMI=\text{weight (kg)}/\text{height (m)}^2$$

The waist to hip measurements should be obtained with the subject in light cloths or undergarments only. The waist circumference measurement should be obtained level with the belly button and upon exhale. The hip measurement should be obtained with the measuring tape across the largest part of the buttocks. The ratio is calculated by dividing the measurement of the waist circumference by the measurement of the hip circumference.

These measurements will be obtained as specified in the SoA (Table 19).

8.3.4. 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 Investigator 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 (Table 19).

8.4. Clinical Laboratory and Diagnostic Procedures

All laboratory samples will be analyzed by a centralized laboratory (ie, Covance 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 of clinically significance. Clinically significant laboratory findings in the opinion of the Investigator should be recorded as an AE (or SAE as appropriate) (Section 9.1).

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 selected biomarker analysis, fasting serum or plasma samples should be collected before the daily dose of study drug for analysis of FGF-19, BAs, and C4 at visits indicated in the SoA (Table 19).Samples should be collected after an overnight fast of a minimum of 8 hours.

8.4.1. Safety Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected according to the SoA (Table 19). Subjects should be instructed to fast overnight 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. Laboratory parameters to be collected are outlined in Table 15.

Creatinine clearance will be calculated by the central laboratory using the Cockcroft Gault equation and actual body weight:

CL_{Cr} (mL/min) = {((l40−age [years])×weight)/(72×S_{Cr})}×0.85 (if female).

On line calculator can be found at:
https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc.

S_{Cr} =serum creatinine

8.4.2. Noninvasive Evaluations of Fibrosis

The ELF panel combines 3 biomarkers that have been shown to 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 Table 19.

Fibrosis will be estimated using the APRI, the fibrosis 4 (FIB-4) formulae, and the NAFLD fibrosis score (NFS).

The APRI will be calculated by the central laboratory using the following formula:

([AST IU/L / AST ULN] / [Platelet count 10^9/L]) × 100 = APRI

On line calculator can be found at: *http://www.hepatitisc.uw.edu/page/clinical-calculators/apri*

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

(Age [years] × AST [IU/L]) / (Platelet count [10^9/L] × (√ ALT [IU/L]))

On line calculator can be found at: *http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4*

The NFS will be calculated by the central laboratory using the following formula:

-1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×10^9/L) – 0.66 × albumin (g/dl)

On line calculator can be found at:

https://www.mdcalc.com/nafld-non-alcoholic-fatty-liver-disease-fibrosis-score

Refer to the SoA (Table 19) for the timing of these tests.

Table 15: Laboratory Evaluations

<table>
<tr>
<td rowspan="3">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
Blood urea nitrogen (BUN)
BUN/Creatinine Ratio (calculation)
Calcium, (Serum)
Creatine Kinase
Creatinine, Serum (and creatinine clearance [Cockroft Gault])
Uric Acid
Electrolyte Panel (Na^+, K^+, Cl^-, Bicarb.)
Phosphorus
Gamma Glutamyl Transferase (GGT)
Globulin, Total
Glucose, Serum
Lactate Dehydrogenase (LDH)
Lipase
Protein, Total, Serum
HbA1c
HOMA indices
Fasting Insulinemia
Fasting Glucose
Total Cholesterol (TC)
Triglycerides (TG)</td>
<td>HEMATOLOGY PANEL
Hemoglobin
Hematocrit
Differential WBC Count (percentage and absolute):
Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Mean corpuscular volume (MCV)
Platelets
Red Blood Count (RBC)
White Blood Cell (Count) (WBC)</td>
</tr>
<tr>
<td>VIRAL DETECTION FOR ENTRY CRITERIA
Human immunodeficiency virus (HIV)-1, HIV-2, Hepatitis B virus (HBV) (Hepatitis B surface antigen [HBsAg]), hepatitis C virus (HCV)</td>
</tr>
<tr>
<td>MARKERS OF CV RISKS AND LIPIDS
Triglycerides (TG)
HDL and LDL-P (high and low-density lipoprotein particles using a lipoprotein subfractions test; e.g., LIPOPROFILE)
lipoprotein (a) [Lp(a)] assay
apoA-I, apoB, apoC3, apoB/A Ratio, apoE isoforms (E2, E3, E4)
Total Cholesterol (TC)
High Density Lipoprotein – Cholesterol (HDL-C)
Low-Density-Lipoprotein – Cholesterol (LDL-C)
Total/HDL Cholesterol (CT) Ratio
Adiponectin
hs-CRP</td>
</tr>
<tr>
<td>URINALYSIS
Routine urinalysis to include: Color and appearance, pH, SG, Bilirubin, Glucose, Ketones, Leukocytes, Nitrite, Occult blood, Protein, Urobilinogen, Microscopic (including RBCs and WBCs)</td>
<td>BIOMARKERS FOR NASH
Cytokeratin (CK)18
GLP-1 (glucagon-like peptide-1)

PD Markers for FXR Activity:
Fibroblast growth factor (FGF)19 (fasting plasma)
Total bile acids (BAs) (fasting serum)
C4 (7α-OH-4-cholesten-3-one)</td>
</tr>
<tr>
<td>PREGNANCY
Serum pregnancy test
Follicle-Stimulating Hormone (FSH)</td>
<td rowspan="2">FIBROSIS AND INFLAMMATORY MARKERS
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, and β)
IL-6. IL1β
AST to Platelet Ratio Index (APRI)
Fibrosis 4 (FIB-4)
NAFLD fibrosis score (NFS score)</td>
</tr>
<tr>
<td>COAGULATION TEST
International Normalized Ratio (INR)
Prothrombin Time (PT)
Partial thromboplastin time (PTT)</td>
</tr>
</table>

8.4.3. 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 (Table 19). More detailed information will be given in the Laboratory Manual.

Population PK (for subjects not participating in PK/PD Substudy): 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 Sampling for Subjects with Transaminase or ALP Elevations: Subjects with persistent transaminase or ALP elevations, and have evidence of liver injury, additional PK samples will be collected at each visit where safety labs are obtained (see Section 10.2).

More detailed information will be given in the Study Manual. It is important that the date and time 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.

8.4.3.1. 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 with tandem mass spectroscopy (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 and as a control a few samples for subjects randomized to placebo.

8.4.4. Pregnancy and Menopausal LaboratoryTesting

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, FSH levels 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.

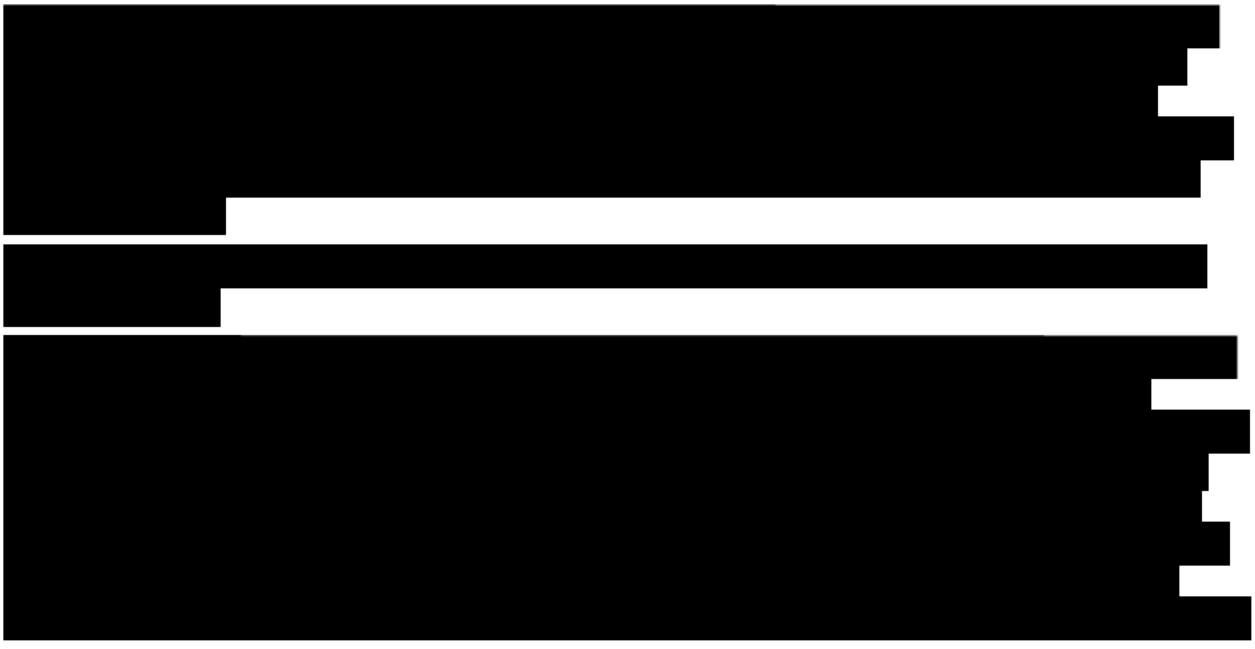
8.4.5. Liver Magnetic Resonance Imaging

All eligible subjects must undergo a liver MRI-PDFF and liver MRE during the screening period and at the end of treatment. Once a subject is considered eligible based on screening laboratory values, a liver MRI-PDFF and MRE will be conducted prior to Baseline. For subjects who complete treatment, a final liver MRI and MRE will also occur at the end of treatment (ie, Week 12). For subjects who discontinue treatment early but have received at least 14 days of study drug, the MRI and MRE should be conducted as soon as possible after discontinuing treatment.

Details for the scheduling and conduct of the MRI-PDFF and MRE will be provided in the study manual.

8.4.6. PD biomarkers for FXR activity

See Table 15 and SOA (Table 19) for full list of biomarkers to be collected in this study.



[redacted]

8.4.7. [redacted]

[redacted]

[redacted]

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 study 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 preplanned 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 (i.e., randomized), record all AEs in the subject's AE eCRF and Clinical Trials SAE Form (if applicable). The AE eCRF 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 – 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 16.

Table 16: 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 17. 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 17: 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 (e.g., 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/Follow–up visit, regardless of causality, must be reported by the Investigator to [redacted] and Enanta Pharmaceuticals, Inc., within 24 hours of learning of its occurrence. In addition, all SAEs that occur after the EOS Visit and that are considered related to study drug(s) and all deaths must also be reported within 24 hours of learning of its occurrence. Additional details are provided in the Safety Management Plan. The eCRF should be completed for new/initial events as well as to report follow-up information on previously reported events in the same way as for AEs. Upon stating the seriousness, further details should be provided in the eCRF. Investigators are asked report follow up information as soon as it becomes available, to ensure timely reporting to Health Authorities.

The SAE Form should be sent to the [redacted] group via fax or email in case the eCRF is not available:

[redacted]
Email (back up): [redacted] (US)
Email (back up): [redacted] (non-US)
Fax (back up): [redacted]
Fax (back up): [redacted]

SAEs will be recorded on the 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. Relationship to study drug(s) will be recorded as related or not related on the SAE form. 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 the [redacted] using the SAE Form.

The Investigator is responsible for notifying [redacted]/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, International Conference on Harmonization (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 nonserious) until resolution or otherwise explained (see Table 17), 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. 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 NASH. 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 total bilirubin 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

For subjects who meet the discontinuation criteria and have evidence of liver injury, additional PK samples will be obtained at the same visits as safety labs.

Please refer to Section 10.2 for the close monitoring for subjects who meet criteria for drug discontinuation due to elevated ALT/AST.

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 total bilirubin.

The following close observation guidelines will apply to subjects for whom the repeat assessment shows persistent elevations of transaminases, but who do not meet drug discontinuation criteria, and for subjects who discontinue study drug due to ALT/AST elevations.

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.

- For subjects with alkaline phosphatase (ALP) elevations of 2 × ULN, subjects will be reassessed promptly (eg, 48–72 hours) with full liver biochemistry and physical exam. Labs should be repeated until resolution. Above guidelines for close monitoring should also apply.
- If a subject lives in a remote area, they can be tested locally with the results promptly communicated to the Investigator site

11. STATISTICAL CONSIDERATIONS

11.1. General Considerations

All data will be mapped into the appropriate Study Data Tabulation Model (SDTM) domains per version 3.2. All analysis datasets will be in the appropriate Analysis Data Model (ADaM) data structure. Pinnacle21 will be used to ensure compliance of the SDTM domains and ADaM datasets to Clinical Data Interchange Standards Consortium (CDISC) standards.

All quantitative endpoints will be summarized using an 8-number summary (n, mean, standard deviation, median, 25th quartile, 75th 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 $\alpha = 0.05$ will be used.

11.2. Sample Size Considerations

Group sample sizes of 44 (in each dose group) and 22 placebo subjects achieves 80.438% power to reject the null hypothesis of equal means when the population mean difference in ALT is (−40.0)–(−10.0) =−30.0 with a standard deviation for both groups of 40.0 and with a significance level (alpha) of 0.050 using a two-sided two-sample equal-variance t-test. To account for a 20% discontinuation rate, 15 additional subjects will be enrolled to attempt to have at least 110 subjects who complete treatment bringing the total number of subjects enrolled to 125.

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 (SAP).

11.5. Efficacy Endpoints

11.6. Primary Efficacy Endpoints

The primary efficacy endpoint of the study is the change from baseline in ALT at Week 12. All 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. Multiple Imputation (MI) will be used to impute missing data. Details will be provided in the SAP.

11.6.1. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Change from Baseline in percentage of fat in the liver as assessed by MRI-PDFF at Week 12
- Change from Baseline in liver stiffness as assessed by magnetic resonance elastography (MRE) at Week 12
- Change from Baseline of noninvasive liver fibrosis markers (ELF panel) and PRO C3 at Week 12
- Change from Baseline in NFS, APRI, and FIB-4 at Week 12
- Change form Baseline in TG, TC, HDL-C, LDL-C, adiponectin, and ApoA1, B, C3 at Week 12
- Change from Baseline in fasting glucose and insulin, HOMA index (in nondiabetic subjects) and HbA1c in subjects with T2DM 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 body weight at Week 12
- Change in waist to hip WTH ratio 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 ANCOVA model with treatment and baseline values included in the model where appropriate.

11.7. Safety Endpoints

11.7.1. Adverse Events

The primary safety endpoint of the study is the frequency of AEs, SAEs, and AEs leading to discontinuation through Week 12.

Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (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 AEs will include the following:

- An overall summary of AEs with a line for each of the categories provided below:
- Treatment-emergent AEs
- Treatment-emergent treatment-related AEs
- Treatment-emergent AEs leading to study drug discontinuation
- SAEs
- Treatment-related SAEs
- AEs leading to death

11.7.2. 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.

11.7.3. Electrocardiogram Data

Electrocardiogram 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 ECG parameters will be summarized by treatment. No statistical testing will be performed.

11.7.4. 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. No statistical testing will be performed.

11.7.5. 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.

11.7.6. Physical Examinations

Physical examination data will be provided in data listings.

11.8. Pharmacokinetic Endpoints

The PK parameters listed in Table 18 will be calculated as indicated for plasma EDP-305 and its major metabolites as applicable.

Table 18: 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 Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.

Plasma PK parameters for each dose level will be calculated from the concentrations of EDP-305 and its major metabolites measured in predose and postdose plasma samples. For each EDP-305 dose level, descriptive statistics (sample size, arithmetic means, geometric means, standard deviation (SD), % 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 PK parameters AUC_{0-t}, C_{max}, and T_{max} will be calculated as indicated for plasma EDP-305 and its major metabolites.

11.9. [redacted]

[redacted]

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 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 21Code of Federal Regulations (CFR), 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 Investigational New Drug 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, CRFs, and other study documentation for source data check and/or on-site audit inspection.

12.5. Retention of Records

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 study. 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

Table 19: Schedule of Assessments

Study Event	**Screening[1]**	**Study Assessments per Planned Study Day**						**EOS**
Visit Day	**D-28 to -1**	**D1[2]**	**D3**	**D14±2**	**D28±2**	**D56±2**	**D84±3[3]**	**D112±2**
Treatment Week[4]				**W2**	**W4**	**W8**	**W12/EOT[5]**	**W16**
ICF[6]; Demography ;Medical History	x							
Inclusion/Exclusion	x							
FSH[7]; HIV,HCV, and HBV	x							
Pregnancy Test[8]	x	x			x	x	x	x
Height, Weight and BMI[9]	x	x					x	x
Physical Exam[10]	x	x	x	x	x	x	x	x
Vital Signs[11]	x	x	x	x	x	x	x	x
Oral Temperature	x	x						x
ECG	x	x	x		x		x	
Waist to Hip Ratio		x					x	
Safety Lab. Tests[12]	x	x	x	x	x	x	x	x
PT/PTT and INR	x							x
CV Markers[13]		x		x	x	x	x	x
MRI-PDFF, MRE	x						x	
ELF Panel, PRO C3, Inflammatory Markers[14, 15]		x					x	
APRI, FIB-4, and NFS		x					x	
FGF-19, C4, BA, and ALT[16]		x		x	x	x	x	
PK/PD sub study (PK, C4, FGF-19, BA, and ALT)[17]		x		x	x	x	x	
Population PK samples[18]		x		x	x	x	x	
CK-18 and GLP-1[15]		x		x	x	x	x	
Study Drug Dosing[19]		Daily Dosing						
Drug Accountability			x	x	x	x	x	
AE/SAE & Con Meds	x	x	x	x	x	x	x	x
Exploratory research samples[15]		x			x	x	x	

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 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. For the EOT visit for subjects who discontinue early, all procedures for the Week 12 visit will be conducted; however, an MRI /MRE will not be performed if the subject has discontinued study drug prior to Day 14 and only 1 PK sample will be obtained. Subjects who discontinue the study early should complete the EOT procedures as soon as possible and return 4 weeks later for the EOS visit. For subjects with persistent transaminase elevations and who discontinue study drug with evidence of liver injury, additional PK samples will be collected at each visit where safety labs are obtained
6. Informed consent must be obtained prior to conducting any study-specific procedures or assessments
7. For post-menopausal women only
8. 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.
9. Height to be assessed at Screening only
10. Full physical exam (PE) at screening and EOS Visit; subsequent PE should be targeted to review new signs and symptoms
11. Vital Signs include heart rate, respiratory rate, blood pressure, and will be measured once in the morning before the morning dose of study drug
12. Safety laboratory tests include chemistry (including liver function tests), hematology, and urinalysis and should be collected predose at all visits; See Table 15 for details. Creatinine clearance will be calculated based on serum creatinine value performed all visits.. HbA1c will be obtained at Screening, Baseline, and Week 12 only
13. Lipids and CV risk markers to be collected are detailed in Table 15
14. Markers of inflammation include fibrinogen, CRP, IL6, IL1β, TNF-α, TNF-β , alpha2 macroglobulin and haptoglobin (See Table 15)
15. Samples will be collected from all subjects predose. Additional samples may be collected to further assess safety events.
16. Samples should be collected after a minimum 8 hr fast and before the subject takes the daily dose of study drug. All samples collected Day 1, Weeks 2, 4, 8 and 12 at predose and two samples postdose; with the first sample collected 1 to 3 hours postdose and the second sample collected at least 1 hour later
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 with the first sample collected 1 to 3 hours postdose and the second sample collected at least 1 hr later
18. PK predose samples should be collected after a minimum 8 hour 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. For subjects with persistent transaminase or ALP elevations, and have evidence of liver injury and who remain on study drug, [redacted].
19. Study drug given in the clinic on days where subject is seen in the clinic