ENANTA
Pharmaceuticals

# CLINICAL STUDY PROTOCOL

# A PHASE 2b RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING SAFETY AND EFFICACY OF EDP-305 IN SUBJECTS WITH LIVER-BIOPSY PROVEN NON-ALCOHOLIC STEATOHEPATITIS (NASH) (ARGON-2)

## PROTOCOL NUMBER: EDP 305-102

## EUDRACT NUMBER: 2019-003876-38

| | |
|---|---|
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| | |
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| | |
| **Study Sponsor:** | Enanta Pharmaceuticals, Inc.<br>500 Arsenal St.<br>Watertown, MA 02472 |
| | |
| **Sponsor Medical Monitor:** | [redacted] |

CONFIDENTIAL

# Contact Information

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| CRO 24-Hour Emergency Line | [redacted] | [redacted] |
| SAE and Pregnancy Reporting | [redacted] | [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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| | |
|---|---|
| AE, AR | adverse event(s), adverse reaction(s) |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| apo | apolipoproteins |
| APRI | AST to Platelet Ratio Index |
| ASCVD | atherosclerotic cardiovascular disease |
| 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 | 7-alpha-Hydroxy-4-cholesten-3-one |
| CK18 | cytokeratin 18 |
| $C_{max}$ | maximum concentration |
| CRO | contract research organization |
| CRP | C-reactive protein |
| CV | cardiovascular |
| CYP | cytochrome P450 |
| CYP7A1 | cholesterol 7α-hydroxylase |
| DLQI | dermatology life quality index |
| EC | ethics Committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| 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 |
| FIB-4 | fibrosis-4 score |
| FSH | follicle stimulating hormone |
| FXR | farnesoid X receptor |
| GCP | good clinical practice |
| GGT | Gamma-Glutamyl Transferase |
| 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 |
| IA | interim analysis |
| 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 |
| MATE1, MATE2-K | multidrug and toxin extrusion proteins |
| MRGPR | Mas-related G-protein coupled receptor |
| 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 |
| NAS | NAFLD activity score |
| NFS | NAFLD fibrosis score |
| NOAEL/NOEL | no observed adverse effect level / no observed effect level |
| OCA | obeticholic acid |
| OCT2 | organic cation transporter 2 |
| PBC | primary biliary cholangitis |
| PD | pharmacodynamics |
| P-gp | P-glycoprotein |
| PI | principal investigator |
| PIIINP | procollagen III amino terminal peptide |
| PK | pharmacokinetics |
| PD | pharmacodynamics |
| PN | presumptive NAFLD |
| 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 |
| QoL | quality of life |

| | |
|---|---|
| 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 |
| SAE | serious adverse event(s) |
| SAP | statistical analysis plan |
| SHP | small heterodimer partner |
| 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 |
| VAS | visual analog score |
| WBC | white blood cell |

# PROTOCOL SYNOPSIS

| |
|---|
| **Name of Sponsor/Company:** Enanta Pharmaceuticals, Inc. |
| **Name of Investigational Product:** EDP-305 |
| **Study Title:** A Phase 2b Randomized, Double Blind, Placebo-Controlled, Multicenter Study Evaluating Safety and Efficacy of EDP-305 in Subjects with Liver Biopsy Proven Non-Alcoholic Steatohepatitis (NASH) (ARGON-2) |
| **Protocol Number:** EDP 305-102 |
| **Phase of Development:** 2b |
| **Study Center:** This will be a multicenter global study (including for example, North America, Europe, Asia-Pacific (APAC) and Latin America (LATAM)) |
| **Number of Subjects Planned:** [redacted] |
| **Investigational Product, Dosage, Duration and Mode of Administration:** EDP-305 will be supplied as 0.5 mg and 1 mg tablets for oral administration; doses administered will be EDP-305 1.5 mg, EDP-305 2 mg, or matching placebo taken once daily (QD) for 72 weeks. |
| **Duration of Treatment:** 72 weeks |
| **Study Objectives:**<br>**Primary Objective:**<br>To evaluate the effect of EDP-305 compared to placebo on liver histology in non-cirrhotic NASH subjects with stage 2 or 3 fibrosis<br>**Secondary Objectives:**<br>• To evaluate the effect of EDP-305 on liver histology by assessing:<br>➢ Improvement of fibrosis by at least 1 stage and/or resolution of NASH, without worsening of either<br>➢ No worsening of fibrosis and no worsening of NASH<br>➢ Resolution of fibrosis<br>➢ Improvement in each histological feature of NASH by at least 1 point<br>➢ Improvement of fibrosis by ≥ 2 stages<br>➢ Improvement in NAS by at least 2 points with no worsening of fibrosis<br>➢ Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject<br>➢ Resolution of NASH and no worsening of liver fibrosis<br>➢ Histological progression to cirrhosis based on the overall assessment made<br>• To evaluate the safety of EDP-305<br>• To evaluate the effect of EDP-305 on pruritus |

- To evaluate the effect of EDP-305 on hepatic steatosis
- To evaluate the effect of EDP-305 on liver stiffness
- To evaluate the effect of EDP-305 on lipid profile
- To evaluate the pharmacokinetics (PK) of EDP-305 and its metabolites in plasma

[redacted]

**Criteria for Evaluation:**

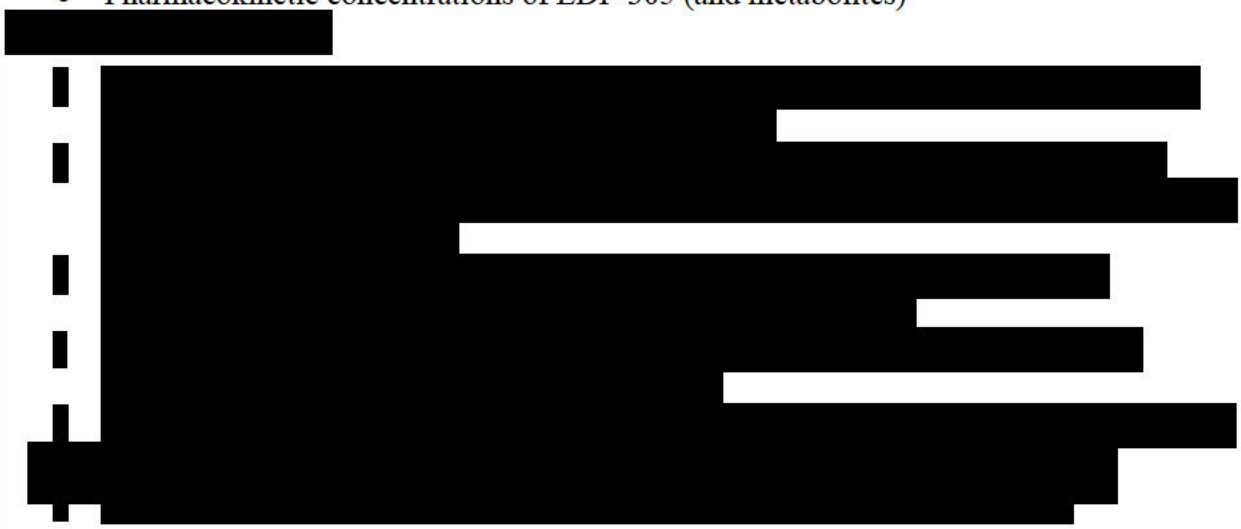
**Primary Endpoint:**

- Proportion of subjects who achieve ≥1 stage improvement in fibrosis without worsening of steatohepatitis and/or resolution of steatohepatitis and no worsening of liver fibrosis as determined by liver biopsy at 72 weeks *[Note: No worsening of steatohepatitis is defined as no increase in NAS for ballooning, inflammation, or steatosis. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis]*

**Secondary Endpoints:**

- Proportion of subjects with improvement of fibrosis by at least 1 stage and/or resolution of NASH without worsening of either as determined by liver biopsy at Week 72
- Proportion of subjects with no worsening of fibrosis combined with no worsening of NASH as determined by liver biopsy at Week 72
- Proportion of subjects with resolution of fibrosis as determined by liver biopsy at Week 72
- Proportion of subjects with improvement in each histologic feature of NASH, by at least 1 point as determined by liver biopsy at Week 72
- Proportion of subjects with improvement of fibrosis by ≥ 2 stages by liver biopsy at Week 72
- Proportion of subjects with improvement in NAS by at least 2 points with no worsening of fibrosis as determined by liver biopsy at Week 72
- Proportion of subjects with improvement of fibrosis and resolution of NASH as a composite endpoint as defined by both endpoints being met in the same subject
- Proportion of subjects with resolution of NASH and no worsening of liver fibrosis
- Proportion of subjects with histological progression to cirrhosis as determined by liver biopsy at Week 72
- Frequency of adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation through Week 72 and 4-week follow-up period
- Change from Baseline in 5D-itch scale and Visual Analog Score (VAS) through Week 72

- Change from Baseline in percentage of fat in the liver as assessed by magnetic resonance imaging proton density fat fraction (MRI-PDFF) at Week 12 and Week 72
- Change from Baseline in liver stiffness as assessed by magnetic resonance elastography (MRE) at Week 12 and Week 72
- Change from Baseline in triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and adiponectin through Week 72
- Pharmacokinetic concentrations of EDP-305 (and metabolites)



**Study Design:**

This is a phase 2b randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of EDP-305 in subjects with liver biopsy proven NASH.

The duration of the study will be approximately up to 86 weeks. The study will consist of a Screening, Treatment, and Safety Follow-up Period.

| Study Period | Duration |
|---|---|
| ***Screening*** | Up to 10 weeks (70 Days) |
| ***Treatment*** | 72 weeks |
| ***Safety Follow-up Period*** | 4 weeks |
| ***Total approximate duration of participation*** | up to 86 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 -70 to -1 Day window. Screening assessments must be performed and confirmed sequentially as follows: a) medical history and other non-invasive assessments, b) laboratory assessments, c) MRI-PDFF and MRE and, lastly, d) liver biopsy.

*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 collection of safety laboratory samples. Subjects will be randomized 1:1:1 to receive one of two oral doses of EDP-305 or placebo in tablet form once daily. Predose assessments will be conducted (including

laboratory sample collection) before the subject receives the first dose of study drug in the clinic. Following dosing, laboratory samples will be collected. Subjects will be dispensed study drug and instructed to take study drug once daily, preferably in the morning, for a total of 72 weeks returning to the clinic for assessments on Week 2, Week 4, every 4 weeks from Week 4 to 48 and every 8 weeks from Week 48 to 72 (EOT visit). On Day 7, safety and drug accountability and compliance will be monitored over the phone. On scheduled clinic visit days, the visit should be scheduled close to the time that the subject normally takes the study drug so that dosing can occur at the site. Subjects should bring their study drug with them.

If the clinic visit occurs within 4 hours of the time the subject normally takes their daily dose of study drug, subjects will be administered their daily dose of study drug at the clinic. If the clinic visit is scheduled to occur more than 4 hours after the time the subject normally takes their daily dose of study drug at home, then the subject should not wait until the clinic visit but should proceed to take the daily dose of study drug at home per their normal dosing routine. Details on procedures and study assessments to be performed are outlined in the Schedule of Assessments (SoA) and respective sections of the protocol.

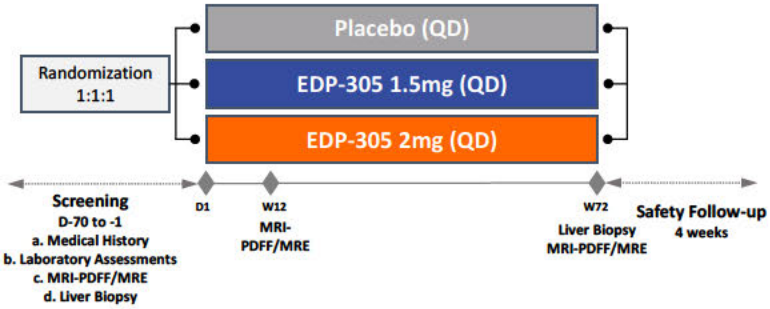
*Safety Follow-up:* The Safety Follow up visit (EOS: end-of-Study visit) will occur 4 weeks after the last dose of study drug for all subjects including those who discontinue treatment early (i.e. prior to completing 72 weeks of dosing). Final study assessments will be completed at that visit.

*Early Termination:* Subjects who discontinue treatment early should return to the clinic within one week following the last dose of study drug for an End-of-Treatment (EOT) visit. They should then return to the clinic for the EOS visit four weeks following the last dose of study drug.

For subjects who discontinue study treatment early, only those who complete at least 36 weeks of treatment should have the EOT biopsy within two weeks of treatment discontinuation; subjects who discontinue prior to receiving 36 weeks of study drug should forgo the EOT biopsy.

For subjects who discontinue between Weeks 10 and 12, the MRI and MRE must be conducted within 1 week of the final dose of study drug. If the MRI/MRE cannot be conducted within the 7-day timeframe, then it should not be conducted and the reason noted in the source documents. For subjects who had the MRI and MRE conducted at the Week 12 visit but discontinue treatment prior to Week 36, no additional MRI and MRE will be conducted. For subjects who discontinue treatment at Week 36 or later, the MRI and MRE should be conducted within 2 weeks after discontinuing treatment.

**Study Design:**



**Eligibility Criteria:**

***Subject Inclusion Criteria***

*A subject must meet all the following criteria in order to participate in the study:*

1. Informed consent documentation signed and dated by the subject.
2. Male and female subjects, of all ethnic origins, between the ages of 18 and 75 years, inclusive.
3. Subjects of all ethnic origins should have a Body Mass Index (BMI) > 25 kg/$m^2$ and ≤45 except for Asian subjects who qualify for the study with BMI > 23kg/$m^2$.
4. Histological evidence of definite NASH based on NASH Clinical Research Network (CRN) criteria obtained from assessment of a liver biopsy by the central histopathologist. The biopsy may be obtained either 1) during the Screening window or 2) within 26 weeks prior to the Screening visit. *[Note: if the liver biopsy needs to be performed as part of the Screening assessments, it may be scheduled following informed consent, but must not be performed until the subject has qualified for study entry based on completion of all other Screening assessments and procedures.]*
5. NAFLD Activity Score (NAS) of 4 or greater with a score of at least 1 in each component of the NAS (steatosis scored 0-3, lobular inflammation scored 0-3, ballooning scored 0-2).
6. Fibrosis stage 2 or 3 using the NASH CRN Histologic Scoring System.
7. For subjects taking Vitamin E or pioglitazone, the following three criteria apply:
   - subjects must have been on a stable dose for at least 12 weeks prior to the qualifying biopsy, and
   - treatment with Vitamin E or pioglitazone cannot have started after the qualifying biopsy, and
   - it is expected that subjects will continue on the same dosing regimen throughout study participation unless required to adjust doses due to safety reasons.
8. Subjects who had previously been taking Vitamin E or pioglitazone (but are no longer taking either one), must have discontinued Vitamin E or pioglitazone a minimum of 12 weeks prior to the qualifying biopsy.
9. Weight change <5% after the qualifying biopsy.
10. 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.]*
11. For hypertensive patients, blood pressure should be controlled by stable dose of anti-hypertensive medication for at least 8 weeks prior to Screening with the intention to keep the regimen stable during the study.
12. A woman of childbearing potential who is sexually active (see Section 3.3 for clarification) with a male must agree to use two effective methods of contraception from the date of Screening until 30 days after the last dose of study drug. Effective methods of contraception are defined as:
    A condom with or without spermicide for the male partner and at least one of the following for the female subject:

a. Intrauterine device
b. Occlusive cap (diaphragm or cervical/vault caps)
c. Established oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive (started a minimum of 2 weeks prior to Screening)
d. Bilateral tubal ligation or fallopian tube inserts

The above does not apply to a female subject who has a vasectomized male as the sole partner or who is of nonchildbearing potential (i.e., physiologically incapable of becoming pregnant) as defined below:

a. Has had a hysterectomy ≥12 weeks prior to dosing or
b. Has had a bilateral oophorectomy (ovariectomy), or bilateral salpingectomy, or
c. Is postmenopausal, defined as
   - Having a total cessation of menses for at least 2 years, or
   - Having a cessation of menses between 1 to 2 years together with a follicle stimulating hormone [FSH] level of >35 mIU/mL

13. A male subject who has not had a vasectomy and is sexually active with a woman of childbearing potential must agree to use effective contraception from the date of Screening to 90 days after the last dose of study drug (*Note: For a male subject who has had a vasectomy, use of a condom with or without spermicide will still be required)*. Effective contraception is defined as a condom and spermicide and at least one of the following for a female partner:
    a. Intrauterine device
    b. Occlusive cap (diaphragm or cervical/vault caps)
    c. Established oral, injectable, implantable, transdermal, or intravaginal contraceptive (started a minimum of 2 weeks prior to Screening)
    d. Bilateral tubal ligation or fallopian tube inserts
14. Male subjects must agree to refrain from sperm donation from the date of Screening until 90 days after the last dose of study drug.
15. Subject must be willing and able to adhere to the assessments, visit schedules, prohibitions and restrictions, as described in this protocol.
16. AST > 30 IU/L.
17. Magnetic resonance imaging - proton density fat fraction (MRI-PDFF) ≥8%.

***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 as indicated below:
   - Total white blood cells (WBC) <3000 cells/$mm^3$
   - Absolute neutrophil count (ANC) <1500 cells/$mm^3$
   - Platelet count <140,000/$mm^3$
   - International Normalized Ratio, INR >1.2 (unless due to use of anticoagulants)
   - Estimated glomerular filtration rate (eGFR) < 60 mL/min according to the Modification of Diet in Renal Disease (MDRD) equation
   - AST ≥5× ULN
   - ALT ≥5× ULN
   - ALP ≥ 2x ULN

- Total bilirubin > 1.5 times ULN during Screening.

  *[Note: Patients with Gilbert's syndrome will be allowed following review by the Medical Monitor if they have a known history of Gilbert's syndrome with a normal direct bilirubin value and normal reticulocyte count.]*

2. Pregnant or nursing females.
3. MELD: Model for End-stage Liver Disease score >12.
4. Clinical or laboratory evidence of known chronic liver disease such as alcoholic liver disease, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis, Wilson disease, iron overload, alpha-1-antitrypsin deficiency, drug-induced liver injury, known or suspected hepatocellular carcinoma (HCC).
5. History of acute liver complications due to gallstones (e.g., acute cholecystitis or acute biliary obstruction), unless the subject has had a cholecystectomy (more than 12 weeks prior to Screening).
6. History of liver transplant, or current placement on a liver transplant list.
7. Hepatorenal syndrome (type I or II).
8. Prior variceal hemorrhage, uncontrolled encephalopathy, liver cirrhosis Child-Pugh Class A, B, and C, esophageal varices, or refractory ascites within the previous 26 weeks of Screening and/or histological presence of liver cirrhosis.
9. Prior or planned ileal resection, or prior or planned bariatric surgery. *[Note: Subjects who have undergone gastric surgeries that do not affect drug absorption (e.g., gastric band or gastric sleeve procedures) will be allowed if they are stable for at least 1 year prior to Screening. Gastrectomy or Roux-en-Y bypass will be allowed if stable for at least 3 years prior to Screening.]*
10. Subjects with clinically or otherwise documented cardiovascular or cerebrovascular disease including clinically significant anomalies of rhythm or pattern of ECG, that in the judgement of the Principal Investigator (PI) could affect the safety of the subject or their ability to comply with the study requirements.
11. HbA1c ≥ 9.5% within 60 days prior to Day 1.
12. Use of a new antidiabetic regimen in the months prior to Screening 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 (e.g. pioglitazone or rosiglitazone). For pre-existing antidiabetic treatment, subjects should be on a stable dose of antidiabetic drugs: (1) for at least 8 weeks (for metformin and/or sulfonylureas), (2) 12 weeks (for SGLT2 or DPP4 inhibitors), or (3) 12 weeks (for GLP-1 receptor agonists and thiazolidinediones) prior to Screening with the intention to keep the regimen stable during the study. *[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 (i.e., no recurrent acute hypo- or hyperglycemic episodes diagnosed clinically with serum glucose levels of <50 mg/dL or >200 mg/dL) for at least 8 weeks prior to Screening.]*
13. Use of a new statin regimen or other lipid lowering agents from 12 weeks prior to Screening. *[Note: Subjects on a stable dose of statins or other lipid lowering agents for at least 12 weeks prior to Screening are allowed with the intention to keep the regimen stable during the study.]*

14. Use of a new fibrate regimen from 12 weeks prior to Screening. *[Note: Subjects on a stable dose of fibrates for at least 12 weeks prior to Screening are allowed with the intention to keep the regimen stable during the study.]*
15. Subjects with contraindications to MRI imaging, or not being able to have the MRI performed. *[Note: Contraindications to MRI include insurmountable claustrophobia, implantable, metal devices, girth, etc. Stents or other devices allowed at PI's discretion, if they do not interfere with functioning MRI.]*
16. Subject has received any investigational agent (including investigational vaccine) or biological product within 30 days or 5 times the half-life (whichever is longer) prior to the planned first dose of study drug. *[Note: This includes agents administered during clinical trial participation; See Section 5.9.5.]*
17. Use of an experimental or approved treatment for NASH within 26 weeks of Screening. *[Note: Subjects enrolled in a previous clinical trial for EDP-305 who discontinued due to safety reasons within any time window are not eligible for enrollment.]*
18. Prior use of obeticholic acid (OCA) within 26 weeks of Screening and/or concurrent treatment with OCA (or any other FXR agonists). *[Note: Subjects who have previously received OCA and who discontinued due to safety reasons within any time window are not eligible for enrollment.]*
19. Use of systemic immunosuppressant (e.g., corticosteroids) for more than 4 weeks in duration within 1 year prior to Screening with the intention to continue during the study (chronic use of inhaled, topical, ophthalmological, nasal corticosteroids is allowed).
20. Use of any prohibited concomitant medications, including systemic CYP3A4 inhibitors and inducers, within 14 days prior to the first dose of study drug and for the duration of the study.
21. Clinically significant history of drug sensitivity or drug allergy, as determined by the PI.
22. Current or history of significant alcohol consumption defined as: >14 standard drinks per week and/or ≥4 standard drinks per occasion for males and >7 standard drinks per week and/or ≥3 standard drinks per occasion for females. [*Note: A standard drink is 12 oz of beer (5% alcohol), 5 oz table wine (12% alcohol), or 1.5 oz of spirits (40% alcohol).]*
23. History of substance (including alcohol) abuse and in the judgment of the PI, the subject would not be suitable for participation in the study.
24. Any other condition(s) that would compromise the safety of the subject or compromise the quality of the clinical study, as judged by the PI.
25. Use of medication for weight loss or appetite reduction (e.g. orlistat, bupropion/naltrexone, phentermine-topiramate, phentermine, lorcaserin, non-prescription supplements) at Screening. [*Note: Subjects on a stable dose for at least 12 weeks prior to Screening or time of pre-treatment liver biopsy are allowed if intended to be continued at the same dose during the study. However start of new medications during the study is not allowed.*]
26. History of malignancy of any organ system (other than localized and considered cured cutaneous basal or squamous cell carcinoma, or in situ cervical cancer), treated or untreated, within 5 years of Screening.

**Subject Withdrawal:**

Subjects may be discontinued from the study at any time if the subject, PI, or Sponsor determines that it is not in the best interest of the subject to continue participation. Reasons for discontinuation include:

- Adverse Event
- Lack of efficacy
- Lost to Follow-up
- Withdrawal by subject
- Protocol Deviation (including non-compliance with study drug dosing or study procedures)
- Pregnancy
- Study terminated by Sponsor
- Other

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 within one week to complete the EOT Visit and for the Safety Follow up Visit, 4 weeks after their last dose.

**Statistical Methods:**

Detailed statistical analysis will be outlined in the Statistical Analysis Plan (SAP).

*Analyses Populations*

- *Safety Population (SAF)*: All subjects who receive at least one dose of study drug. Subjects will be included in the treatment group that corresponds to the study drug received during the study.
- *Intent-to-treat (ITT) Population:* ITT subjects will be considered those randomized to treatment. ITT subjects will be analyzed according to the treatment to which they were randomized. In the event the SAF is the same as ITT only the ITT will be reported. This will be the primary efficacy population.
- *Per Protocol (PP) Population:* All randomized and treated subjects that do not have major protocol deviations which could unduly influence the efficacy analysis.
- *Pharmacokinetic Population***:** All subjects receiving active study drug and having any measurable plasma concentration of study drug at any time point.

*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.

*Pruritus Analyses:* Descriptive statistics will be provided for patient reported outcomes such as the 5D-itch scale, VAS and other assessments. Observed, change from baseline, and percent change from baseline results will be presented by visit and treatment group. Additional modeling may be performed if data permits. Further analysis of all pruritus assessment tools will be described in detail in the SAP.

*Efficacy Analyses:* Logistic regression models will analyze the co-primary endpoints of (1) proportion of subjects who achieve ≥1 stage improvement in fibrosis without worsening of steatohepatitis (2) resolution of steatohepatitis without worsening of liver fibrosis as determined by liver biopsy at 72 weeks. Treatment groups will be compared for each endpoint at a 0.025 significance level. A responder will be considered any subject achieving either endpoint. The proportion of responders for each endpoint will be compared using a logistic regression model with treatment group, diabetes status and use of Vitamin E and/or pioglitazone and baseline covariate NAS as effects. The odds ratio and 97.5% confidence interval will be reported as well.

*Non-invasive Tests (NITs):* Descriptive statistics will be provided, including observed, change from baseline, and percentage change from baseline by visit and treatment group. These tests include imaging (MRI-PDFF, MRE), and non-invasive fibrosis markers. Additional ANCOVA modeling will be performed across timepoints as appropriate. Further analysis of all NITs will be described in detail in the SAP.

*Pharmacokinetic Analyses:* Summary of plasma concentration data will be descriptive in nature. Available plasma concentration-time data in the PK Population will be summarized by treatment group. Mean plasma concentration-time figures may be created for EDP-305 and its metabolites, as allowed by the data.

*Pharmacodynamic Analyses:* A descriptive summary of C4, FGF-19 and BA will be provided, including change from baseline and percentage change from baseline by visit and treatment group. Graphical summaries will be provided.

*Pharmacokinetic/Pharmacodynamic Analyses:* The relationship between PK of EDP-305 and measures of PD activity (e.g. C4, FGF-19, BA) will be summarized, as allowed by the data.

*Quality of Life scales (SF-36 and CLDQ-NASH) and Cardiovascular risk score (ASCVD) analyses:* Each scale will be scored and summarized by author suggested scoring and analysis methods, as appropriate. Descriptive statistics will be provided, including observed and change from baseline by visit and treatment group. Complete detail of how each scale is scored and analyzed will be described in detail in the SAP.

[redacted]

[redacted]

**Study Governance:**

The study will be governed by the data and safety monitoring board (DSMB): A group of 3 experts independent from the Sponsor whose role and responsibility and interactions with the Sponsor and Study CRO will be defined in a DSMB Charter.

# 1. INTRODUCTION

## 1.1. Overview

EDP-305 (also known as EPS-2305, EPC-2305 or EP-022305) is a farnesoid X receptor (FXR) agonist being investigated by Enanta Pharmaceuticals, Inc. (Enanta) as a potential treatment for Nonalcoholic Steatohepatitis (NASH) with liver fibrosis. This study, EDP 305-102, is a randomized, double-blind, placebo-controlled, phase 2b study designed to assess the safety and efficacy of EDP-305 compared to placebo in subjects with liver biopsy proven 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 Takeda G-protein-coupled receptor 5 (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 (*FDA, 2018*) 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*).

FXRs are nuclear hormone receptors expressed in high amounts in body tissues that participate in BA metabolism including the liver, intestines, and kidneys. BAs are the natural ligands of the FXRs. FXRs 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 have 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, hyperlipidemia, hyperglycemia, BA overload, inflammation and fibrosis (*Xu et al., 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 is developing EDP-305 as a selective FXR agonist. 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. In a First-in-Human (FIH) clinical study, EDP-305 was generally safe and well tolerated and appeared to positively affect levels of biomarkers associated with FXR activity (*Ahmad et al., 2018*). In the phase 2 clinical study, EDP 305-101, 12-week therapy with EDP-305 led to statistically significant improvements in liver biochemistry and hepatic steatosis. Pharmacokinetic (PK) exposures were associated with strong target engagement as measured by 7-alpha-Hydroxy-4-cholesten-3-one (C4) and gamma-glutamyl transferase (GGT) reductions and fibroblast growth factor -19 (FGF-19) and alkaline phosphatase (ALP) increases. EDP-305 was generally safe, with the majority of treatment-emergent adverse events (TEAEs) being mild to moderate. Thus, due to its promising nonclinical safety and pharmacological profile, and clinical efficacy and safety results to date, the Sponsor plans to continue investigation of EDP-305 as a potential treatment for NASH with fibrosis.

## 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 is 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 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:

- [redacted]

- [redacted]

### 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.

[redacted]

### 1.3.3. Pharmacokinetics

A series of nonclinical studies were conducted to assess the 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 [redacted]

#### 1.3.3.2. Distribution

[redacted]

#### 1.3.3.3. Metabolism

[redacted]

#### 1.3.3.4. Drug Interactions

Note that results from clinical drug-drug interaction (DDI) studies are presented in Section 1.4.

[redacted]

*In vitro* studies suggest that there is potential for EDP-305 to inhibit organic anion-transporting [redacted]

[redacted]

### 1.3.4. Toxicology

EDP-305 has been administered by oral gavage to mice, rats and monkeys during the toxicology program. Single and repeat dose general toxicology studies for up to 26 weeks in mice and up to 39 weeks in monkeys of once-daily dosing duration was generally well-tolerated. [redacted]

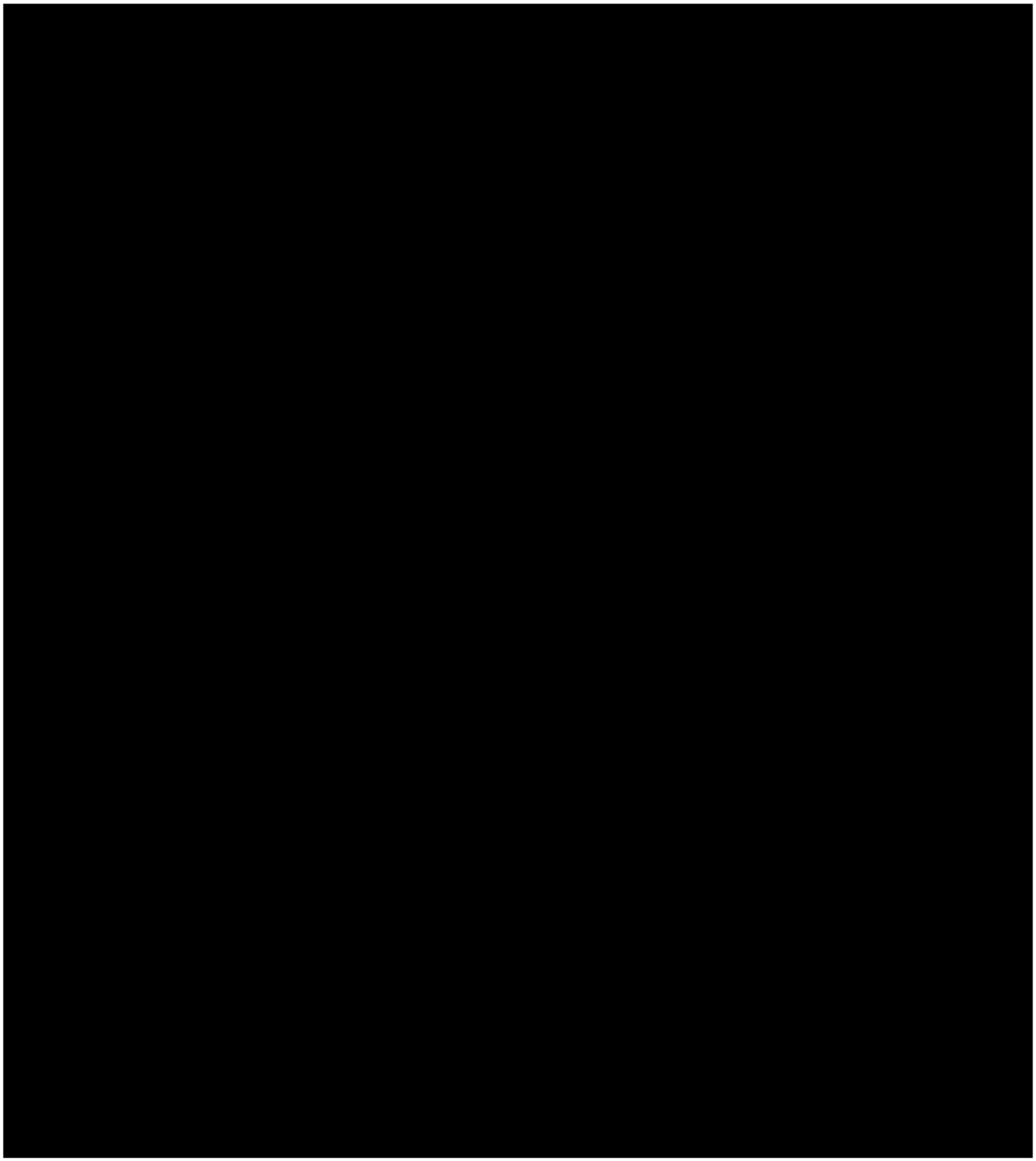
EDP-305 was negative in GLP genetic toxicology assays, including the bacterial mutation [redacted]

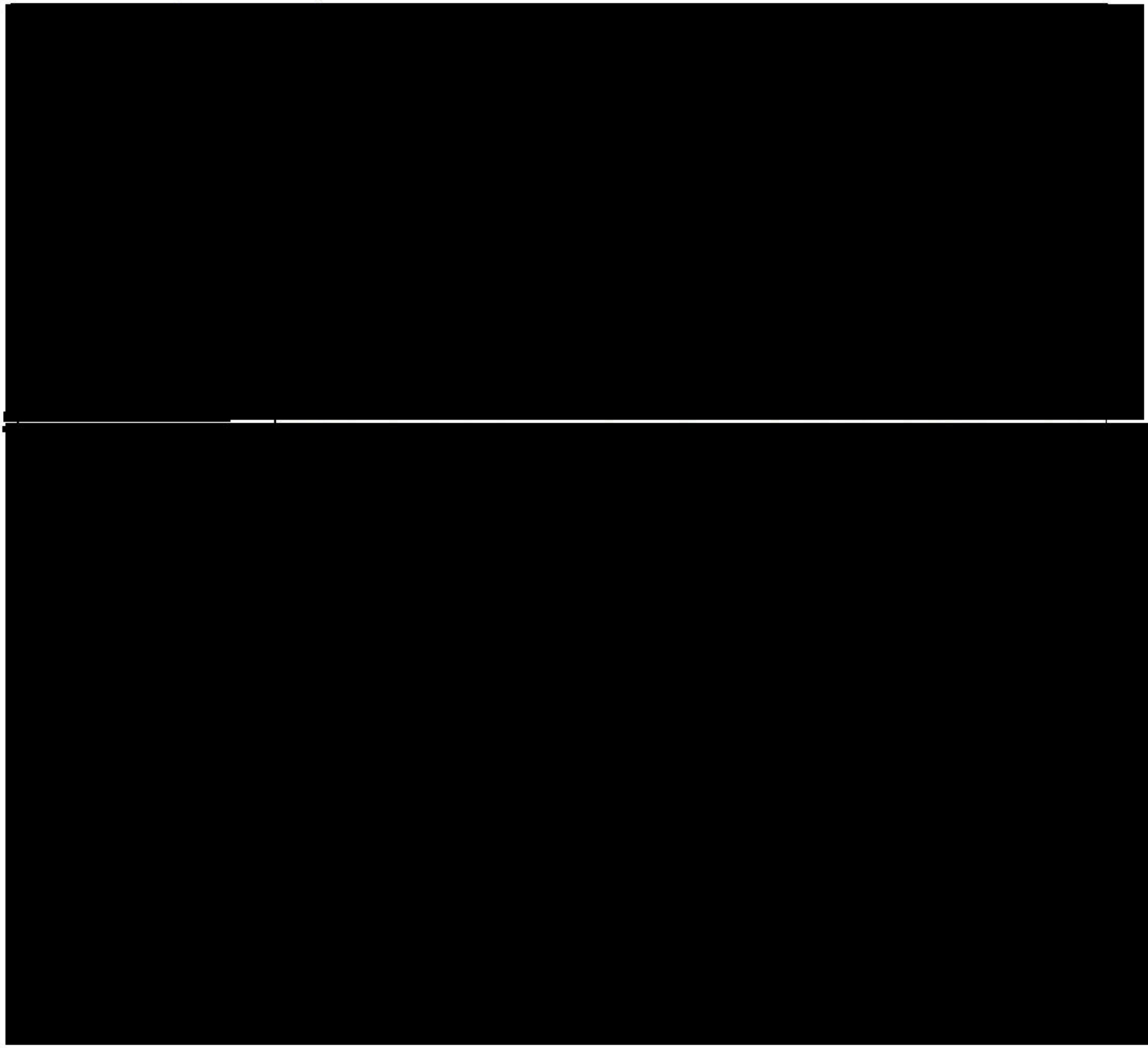
## 1.4. Clinical Studies

### 1.4.1. Phase 1 Clinical Studies

To date, data are available from eight phase 1 studies listed below in Table 2. Detailed information on these studies are available in the IB.

**Table 2: EDP-305 Phase 1 Clinical Studies Conducted under the NASH IND**





### 1.4.2. Phase 2 Clinical Study: EDP 305-101

*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)*

EDP 305-101 (ARGON-1) was 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. A total of 134 subjects with a diagnosis of NASH were enrolled into the study. Presence of NASH was based on either histologic evidence (a historical liver biopsy within 24 months of Screening and consistent with NASH with fibrosis and no cirrhosis) or phenotypic diagnosis of NASH based on elevated ALT and diagnosis of Type 2 diabetes mellitus (T2DM) or pre-diabetes. In both cases, subjects had a Screening magnetic resonance imaging-proton density fat fraction (MRI-PDFF) with >8% steatosis and elevated ALT. This study evaluated two active doses of EDP-305 versus placebo; 1 mg and 2.5mg for 12 weeks. The primary objectives of the study were to evaluate the change in ALT levels at week 12 and to evaluate the safety and tolerability of EDP-305. Key secondary endpoints included change from baseline in percentage of fat in the liver measured by MRI-PDFF, PK, change from baseline in lipids, and target engagement as measured by C4 and FGF-19.

The ALT change from baseline at week 12 was statistically significant ($P$ = .0495) at the 2.5 mg dose compared to placebo. There was a numerically higher value in the 1 mg dose compared to placebo that did not reach statistical significance ($P$ = .3039). The least square (LS) mean change (week 12) were -27.9, -21.7, and -15.5, following doses of 2.5 mg, 1 mg, and placebo, respectively. At week 12, >20 U/L reduction in ALT was observed in 61% of subjects treated with EDP-305 2.5 mg, 52% treated with EDP-305 1 mg, and 35% with placebo, and >30 U/L reduction in ALT was observed in 37% of subjects treated with EDP-305 2.5 mg, 40% treated with EDP-305 1 mg, and 20% with placebo.

Overall, EDP-305 was generally safe, with the majority of TEAEs being mild to moderate. The most common (≥5%) TEAEs with EDP-305 included pruritus, rash, gastro-intestinal (GI) related symptoms (nausea, vomiting, diarrhea), urinary tract infection, dizziness, decreased appetite and cough. As for tolerability of EDP-305 in this 12-week phase 2a study, pruritus was present in approximately 51% of the subjects in the 2.5 mg arm compared to less than 10% in the 1 mg arm and less than 5% in the placebo arm, with the majority being mild or moderate in severity. Among subjects with severe pruritus, there were 2 subjects in the 2.5 mg arm and 2 subjects in the 1 mg arm compared to none in the placebo arm. There were no study discontinuations due to severe pruritus except for one subject in the 1 mg arm. Overall, the incidence of treatment discontinuation due to pruritus was 1.8% for 1 mg and 20.8% for 2.5 mg and none in the placebo arm, with all the discontinuations in the 2.5 mg arm being due to moderate pruritus.

Based on Common Terminology Criteria for Adverse Events (CTCAE) grading, there were very few treatment-emergent laboratory abnormalities in the EDP-305 arms: Grade 3 increase in serum/plasma glucose were observed more frequently in subjects taking EDP-305 with 7% in the 1 mg arm, 21% in the 2.5 mg arm, and 4% in the placebo arm. Likewise, grade 3 uric acid increase were observed more frequently in subjects taking EDP-305 with 18% in 1 mg, 19% in 2.5 mg and 4% in placebo. In addition, one subject with a Grade 3 amylase, and one subject with a Grade 3 ALT were reported in the 2.5 mg arm.

There were no clinically significant changes in ECG or vital signs, and no other clinically significant laboratory abnormalities.

The absolute change from baseline in liver fat content (measured by MRI-PDFF) at week 12 was statistically significant ($P$ = .0009) at the 2.5mg dose compared to placebo but not at the 1mg dose ($P$ = .4946). The LS mean changes (week 12) were -7.1, -3.3, and -2.4 following doses of 2.5 mg, 1 mg, and placebo, respectively. The percentage change from baseline in liver fat (measured by MRI-PDFF) at week 12 was statistically significant ($P$ = .0065) at the 2.5 mg dose compared to placebo but not at the 1 mg dose ($P$ = .6097). The LS mean percentage changes (week 12) were -30.5, -15.3, and -11.9 following doses of 2.5 mg, 1 mg, and placebo, respectively. Approximately 45%, 26% and 25% of subjects were MRI-PDFF responders (i.e. ≥30% fat reduction), following doses of 2.5 mg, 1 mg, and placebo, respectively. Within the MRI-PDFF responders, mean change in ALT reduction was more profound in the EDP-305 arms compared to placebo, with >30 U/L ALT reduction in 2.5 and 1 mg compared to 16 U/L in placebo.

Changes in lipids at 12 weeks were minimal. Across the lipid profile, only reductions in high-density lipoproteins (HDL) following the 2.5mg dose was statistically significant compared to placebo ($P$ < .0001). The reduction was numerically small (LS mean change of -8.3 mg/dL in 2.5 mg compared to -1.9 mg/dL in 1 mg, and -0.15 mg/dL in placebo). Small, numeric increases not statistically significant in low-density lipoproteins (LDL) were observed with EDP-305 compared to placebo (LS mean changes of 6.5 ($P$ = .0897), 4.7 ($P$ = .1411), and -5 mg/dL following doses of 2.5 mg, 1 mg, and placebo, respectively). The small numeric changes in HDL and LDL are not likely to be clinically relevant.

In Study EDP 305-101, mean (range) predose concentrations (week 12) of 6 (1, 15) ng/mL and 18 (1.7, 38) ng/mL at 1 and 2.5 mg, were observed respectively. At comparable suspension doses (2x tablet) in Study EDP 305-001, mean predose concentrations of 1.8-2.6 ng/mL and 6-11 ng/mL following suspension doses of 2.5 and 5 mg, were observed, across healthy volunteers (HV) and subjects with presumptive NAFLD (PN). Mean (range) systemic exposures measured by AUC from time 0 to 8 hours ($AUC_{0-8}$) [week 12] were 119 (17, 436) ng•hr/mL and 208 (24, 469) ng•hr/mL at 1 and 2.5 mg, respectively. At comparable suspension doses (2x tablet) in Study EDP 305-001, mean $AUC_{0-8}$ (Day 14) of 62-64 ng•hr/mL and 108-169 ng•hr/mL following suspension doses of 2.5 and 5 mg, were observed, across HVs and subjects with PN. Overall, higher EDP-305 PK exposures were observed in terms of steady state (predose) and systemic exposures (AUC) compared to previous studies (Study EDP 305-001, (*Ahmad et al., 2018*).

EDP-305 exposures in study EDP 305-101 were associated with strong target engagement as assessed by several biomarkers and generally consistent with previous data from study EDP 305-001 (*Ahmad et al., 2018*). Statistically significant reductions ($P$ < .001) in C4 at week 12 were observed following EDP-305 compared to placebo with mean changes of -72%, -42%, and 17% following doses of 2.5 mg, 1 mg, and placebo, respectively. The C4 reductions were accompanied with increases in FGF-19 with mean changes of 574%, 64%, and 73% following doses of 2.5 mg, 1 mg, and placebo, respectively.

C4 reductions and FGF-19 increase in 2.5 mg were also associated with changes in ALP and GGT that reflect FXR target engagement at week 12. For ALP, statistically significant increases ($P$ < .0001 for 2.5 mg and $P$ < .0128 for 1 mg) were observed following EDP-305 compared to

placebo (LS mean changes of 46.8%, 20.1%, and -0.7% following doses of 2.5 mg, 1 mg, and placebo, respectively). For GGT, statistically significant reductions ($P < 0.0001$ for 2.5 mg and 1 mg) were observed following EDP-305 compared to placebo (LS mean changes of -54.6%, -34.8%, and -5.2% following doses of 2.5 mg, 1 mg, and placebo, respectively).

In summary, the primary and key secondary endpoints, ALT and liver fat content reduction as measured by MRI-PDFF, respectively at week 12, were met in the 2.5 mg dosing group. EDP-305 was generally safe, with the majority of TEAEs being mild to moderate. Higher incidence of moderate pruritus was noted in the 2.5 mg, that led to approximately 20% discontinuations. PK exposures were associated with strong target engagement as measured by C4 and GGT reductions and FGF-19 and ALP increases. These results support further evaluation of EDP-305 in patients with NASH.

## 1.5. Potential Risks and Benefits

### 1.5.1. Potential Risks to Subjects Enrolled in the Study

To date, potential risks to subjects receiving EDP-305 have been estimated based on safety data from 10 clinical studies including one phase 2 study in subjects with PBC.

EDP-305 has been administered in approximately 480 subjects, including approximately 110 subjects with NASH who received 1 mg or 2.5 mg of EDP-305 up to 12 weeks.

EDP-305 has been shown to be generally safe and overall well-tolerated in the 8 completed or ongoing phase 1 studies where healthy subjects or hepatic impaired patients (Child Pugh A and B) received either a single or multiple doses up to 20 mg (suspension) for up to 14 days, and in subjects with NASH in the 12-week phase 2 study who received multiple doses at 1 mg or 2.5 mg (tablet) for up to 12 weeks.

In the 12-week phase 2 study with EDP-305 in subjects with NASH (EDP 305-101; ARGON-1), the following were the most commonly (i.e. in more than ≥5% subjects who received EDP-305) reported TEAEs in subjects who received at least one dose of EDP-305 (1 or 2.5 mg/day) for up to 12 weeks:

- Pruritus generalized or localized
- Rash
- GI related disorder (nausea, vomiting, diarrhea)
- Urinary tract infection
- Dizziness
- Decreased appetite
- Cough

Pruritus was identified as the most frequent TEAE associated with the use of EDP-305 (2.5 mg). Grade 3 increase in serum/plasma glucose and uric acid were observed more frequently in subjects taking EDP-305. In addition, Grade 3 treatment-emergent laboratory abnormalities were observed: one subject with G3 amylase and one subject with G3 ALT.

Other clinically significant laboratory abnormalities that led to drug discontinuation across all studies were:

- One transient, moderate liver enzyme elevation (ALT/AST) in one subject (MAD-HV-20mg) that led to drug discontinuation; the ALT/AST returned to normal (Study EDP 305-001)

### 1.5.2. Potential Benefits to Subjects Enrolled in the Study

Currently, there are no approved drugs for the treatment of NASH. Given the high prevalence of NASH, the associated morbidity, the growing burden of end-stage liver disease, and limited availability of livers for organ transplantation, identifying therapies that will slow the progress of, halt, or reverse NASH and NAFLD will address an unmet medical need (*FDA, 2018*).

As mentioned in Section 1.2.2, FXRs are nuclear hormone receptors expressed in high amounts in body tissues that participate in BA metabolism including the liver, intestines, and kidneys. BAs are the natural ligands of the FXRs. FXRs 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 have shown that hepatic expression of FXR is decreased in NAFLD patients, which is associated with TG accumulation and hepatic steatosis. Effects observed in FXR deficiency animal models include hepatic steatosis, hyperlipidemia, hyperglycemia, BA overload, inflammation and fibrosis (*Xu et al., 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.

EDP-305 is a selective FXR agonist. 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 (Section 1.2.2). In a FIH clinical study, EDP-305 was generally safe and well-tolerated and appeared to positively affect levels of biomarkers associated with FXR activity (*Ahmad et al., 2018*). In the phase 2 clinical study in subjects with NASH, (EDP 305-101), 12-week therapy with EDP-305 led to statistically significant improvements in liver biochemistry and hepatic steatosis. PK exposures were associated with strong target engagement as measured by C4 and GGT reductions and FGF-19 and ALP increases. EDP-305 was generally safe, with the majority of TEAEs being mild to moderate. Thus, due to its promising nonclinical safety, pharmacological, clinical efficacy and safety profile to date, the Sponsor is investigating EDP-305 as a potential treatment for NASH with fibrosis. Recently, OCA, an FXR agonist with a similar mechanism of action to EDP-305, was shown to have positive effects on liver fibrosis in NASH patients *(Younossi et al., 2019)*.

It is not known whether EDP-305 will have similar effects to OCA in this study.

# 2. OBJECTIVES AND ENDPOINTS

## 2.1. Objectives

### 2.1.1. Primary Objective

To evaluate the effect of EDP-305 compared to placebo on liver histology in non-cirrhotic NASH subjects with stage 2 or 3 fibrosis

### 2.1.2. Secondary Objectives

- To evaluate the effect of EDP-305 on liver histology by assessing:
  - Improvement of fibrosis by at least 1 stage and/or resolution of NASH, without worsening of either
  - No worsening of fibrosis and no worsening of NASH
  - Resolution of fibrosis
  - Improvement in each histological feature of NASH by at least 1 point
  - Improvement of fibrosis by $\geq 2$ stages
  - Improvement in NAS by at least 2 points with no worsening of fibrosis
  - Improvement of fibrosis and resolution of NASH as a composite endpoint and as defined by both endpoints being met in the same subject
  - Resolution of NASH and no worsening of liver fibrosis
  - Histological progression to cirrhosis based on the overall assessment made
- To evaluate the safety of EDP-305
- To evaluate the effect of EDP-305 on pruritus
- To evaluate the effect of EDP-305 on hepatic steatosis
- To evaluate the effect of EDP-305 on liver stiffness
- To evaluate the effect of EDP-305 on lipid profile
- To evaluate the PK of EDP-305 and its metabolites in plasma

## 2.2. Endpoints

### 2.2.1. Primary Endpoint

- Proportion of subjects who achieve ≥1 stage improvement in fibrosis without worsening of steatohepatitis and/or resolution of steatohepatitis and no worsening of liver fibrosis as determined by liver biopsy at 72 weeks *[Note: No worsening of steatohepatitis is defined as no increase in NAS for ballooning, inflammation, or steatosis. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis]*

### 2.2.2. Secondary Endpoints:

- Proportion of subjects with improvement of fibrosis by at least 1 stage and/or resolution of NASH without worsening of either as determined by liver biopsy at Week 72
- Proportion of subjects with no worsening of fibrosis combined with no worsening of NASH as determined by liver biopsy at Week 72
- Proportion of subjects with resolution of fibrosis as determined by liver biopsy at Week 72
- Proportion of subjects with improvement in each histologic feature of NASH, by at least 1 point as determined by liver biopsy at Week 72
- Proportion of subjects with improvement of fibrosis by $\geq 2$ stages by liver biopsy at Week 72
- Proportion of subjects with improvement in NAS by at least 2 points with no worsening of fibrosis as determined by liver biopsy at Week 72
- Proportion of subjects with improvement of fibrosis and resolution of NASH as a composite endpoint as defined by both endpoints being met in the same subject
- Proportion of subjects with resolution of NASH and no worsening of liver fibrosis
- Proportion of subjects with histological progression to cirrhosis as determined by liver biopsy at Week 72
- Frequency of adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation through Week 72 and 4-week follow-up period
- Change from Baseline in 5D-itch scale and Visual Analog Score (VAS) through Week 72
- Change from Baseline in percentage of fat in the liver as assessed by magnetic resonance imaging proton density fat fraction (MRI-PDFF) at Week 12 and Week 72
- Change from Baseline in liver stiffness as assessed by magnetic resonance elastography (MRE) at Week 12 and Week 72
- Change from Baseline in TG, total cholesterol (TC), HDL cholesterol, LDL cholesterol and adiponectin through Week 72
- Pharmacokinetic concentrations of EDP-305 (and metabolites)

# 3. SELECTION OF SUBJECTS

A total of approximately 336 subjects with a diagnosis of NASH as proven by liver biopsy are planned for enrollment into this study.

## 3.1. Subject Inclusion Criteria

A subject must meet all the following criteria in order to participate in the study:

1. Informed consent documentation signed and dated by the subject.
2. Male and female subjects, of all ethnic origins, between the ages of 18 and 75 years, inclusive.
3. Subjects of all ethnic origins should have a Body Mass Index (BMI) > 25 kg/$m^2$ and ≤45 except for Asian subjects who qualify for the study with BMI > 23kg/$m^2$.
4. Histological evidence of definite NASH based on NASH Clinical Research Network (CRN) criteria obtained from assessment of a liver biopsy by the central histopathologist. The biopsy may be obtained either 1) during the Screening window or 2) within 26 weeks prior to the Screening visit. *[Note: if the liver biopsy needs to be performed as part of the Screening assessments, it may be scheduled following informed consent, but must not be performed until the subject has qualified for study entry based on completion of all other Screening assessments and procedures.]*
5. NAFLD Activity Score (NAS) of 4 or greater with a score of at least 1 in each component of the NAS (steatosis scored 0-3, lobular inflammation scored 0-3, ballooning scored 0-2).
6. Fibrosis stage 2 or 3 using the NASH CRN Histologic Scoring System.
7. For subjects taking Vitamin E or pioglitazone, the following three criteria apply:
   - subjects must have been on a stable dose for at least 12 weeks prior to the qualifying biopsy, and
   - treatment with Vitamin E or pioglitazone cannot have started after the qualifying biopsy, and
   - it is expected that subjects will continue on the same dosing regimen throughout study participation unless required to adjust doses due to safety reasons.
8. Subjects who had previously been taking Vitamin E or pioglitazone (but are no longer taking either one), must have discontinued Vitamin E or pioglitazone a minimum of 12 weeks prior to the qualifying biopsy.
9. Weight change <5% after the qualifying biopsy.
10. 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.]*
11. For hypertensive patients, blood pressure should be controlled by stable dose of anti-hypertensive medication for at least 8 weeks prior to Screening with the intention to keep the regimen stable during the study.
12. A woman of childbearing potential who is sexually active (see Section 3.3 for clarification) with a male must agree to use two effective methods of contraception from

the date of Screening until 30 days after the last dose of study drug. Effective methods of contraception are defined as:
A condom with or without spermicide for the male partner and at least one of the following for the female subject:

a. Intrauterine device
b. Occlusive cap (diaphragm or cervical/vault caps)
c. Established oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive (started a minimum of 2 weeks prior to Screening)
d. Bilateral tubal ligation or fallopian tube inserts

The above does not apply to a female subject who has a vasectomized male as the sole partner or who is of nonchildbearing potential (i.e., physiologically incapable of becoming pregnant) as defined below:

a. Has had a hysterectomy ≥12 weeks prior to dosing or
b. Has had a bilateral oophorectomy (ovariectomy), or bilateral salpingectomy or
c. Is postmenopausal, defined as
    a. Having a total cessation of menses for at least 2 years, or
    b. Having a cessation of menses between 1 to 2 years together with a follicle stimulating hormone [FSH] level of >35 mIU/mL.

13. A male subject who has not had a vasectomy and is sexually active with a woman of childbearing potential must agree to use effective contraception from the date of Screening to 90 days after the last dose of study drug (*Note: For a male subject who has had a vasectomy, use of a condom with or without spermicide will still be required)*. Effective contraception is defined as a condom and spermicide and at least one of the following for a female partner:
    a. Intrauterine device
    b. Occlusive cap (diaphragm or cervical/vault caps)
    c. Established oral, injectable, implantable, transdermal, or intravaginal contraceptive (started a minimum of 2 weeks prior to Screening)
    d. Bilateral tubal ligation or fallopian tube inserts
14. Male subjects must agree to refrain from sperm donation from the date of Screening until 90 days after the last dose of study drug.
15. Subject must be willing and able to adhere to the assessments, visit schedules, prohibitions and restrictions, as described in this protocol.
16. AST >30 IU/L
17. Magnetic resonance imaging – proton density fat fraction (MRI-PDFF) ≥8%.

## 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 as indicated below:

    - Total white blood cells (WBC) <3000 cells/$mm^3$
    - Absolute neutrophil count (ANC) <1500 cells/$mm^3$
    - Platelet count <140,000/$mm^3$
    - International Normalized Ratio, INR >1.2 (unless due to use of anticoagulants)
    - Estimated glomerular filtration rate (eGFR) < 60 mL/min according to the Modification of Diet in Renal Disease (MDRD) equation

- AST ≥5× ULN
- ALT ≥5× ULN
- ALP ≥ 2x ULN
- Total bilirubin > 1.5 times ULN during Screening.

*[Note: Patients with Gilbert's syndrome will be allowed following review by the Medical Monitor if they have a known history of Gilbert's syndrome with a normal direct bilirubin value and normal reticulocyte count.]*

2. Pregnant or nursing females.
3. MELD: Model for End-stage Liver Disease score >12.
4. Clinical or laboratory evidence of known chronic liver disease such as alcoholic liver disease, PBC, PSC, autoimmune hepatitis, Wilson disease, iron overload, alpha-1-antitrypsin deficiency, drug-induced liver injury, known or suspected hepatocellular carcinoma (HCC).
5. History of acute liver complications due to gallstones (e.g., acute cholecystitis or acute biliary obstruction), unless the subject has had a cholecystectomy (more than 12 weeks prior to Screening).
6. History of liver transplant, or current placement on a liver transplant list.
7. Hepatorenal syndrome (type I or II).
8. Prior variceal hemorrhage, uncontrolled encephalopathy, liver cirrhosis Child-Pugh Class A, B, and C, esophageal varices, or refractory ascites within the previous 26 weeks of Screening and/or histological presence of liver cirrhosis.
9. Prior or planned ileal resection, or prior or planned bariatric surgery. *[Note: Subjects who have undergone gastric surgeries that do not affect drug absorption (e.g., gastric band or gastric sleeve procedures) will be allowed if they are stable for at least 1 year prior to Screening. Gastrectomy or Roux-en-Y bypass will be allowed if stable for at least 3 years prior to Screening.]*
10. Subjects with clinically or otherwise documented cardiovascular or cerebrovascular disease including clinically significant anomalies of rhythm or pattern of ECG, that in the judgement of the Principal Investigator (PI) could affect the safety of the subject or their ability to comply with the study requirements.
11. HbA1c ≥ 9.5% within 60 days prior to Day 1.
12. Use of a new antidiabetic regimen in the months prior to Screening 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 (e.g., pioglitazone or rosiglitazone). For pre-existing antidiabetic treatment, subjects should be on a stable dose of antidiabetic drugs: (1) for at least 8 weeks (for metformin and/or sulfonylureas), (2) 12 weeks (for SGLT2 or DPP4 inhibitors), or (3) 12 weeks (for GLP-1 receptor agonists and thiazolidinediones) prior to Screening with the intention to keep the regimen stable during the study. *[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 (i.e., no*

*recurrent acute hypo- or hyperglycemic episodes diagnosed clinically with serum glucose levels of <50 mg/dL or >200 mg/dL) for at least 8 weeks prior to Screening.]*

13. Use of a new statin regimen or other lipid lowering agents from 12 weeks prior to Screening. *[Note: Subjects on a stable dose of statins or other lipid lowering agents for at least 12 weeks prior to Screening are allowed with the intention to keep the regimen stable during the study.]*
14. Use of a new fibrate regimen from 12 weeks prior to Screening. *[Note: Subjects on a stable dose of fibrates for at least 12 weeks prior to Screening are allowed with the intention to keep the regimen stable during the study.]*
15. Subjects with contraindications to MRI imaging, or not being able to have the MRI performed. *[Note: Contraindications to MRI include insurmountable claustrophobia, implantable, metal devices, girth, etc. Stents or other devices allowed at PI's discretion, if they do not interfere with functioning MRI.]*
16. Subject has received any investigational agent (including investigational vaccine) or biological product within 30 days or 5 times the half-life (whichever is longer) prior to the planned first dose of study drug. *[Note: This includes agents administered during clinical trial participation; See Section 5.9.5.]*
17. Use of an experimental or approved treatment for NASH within 26 weeks of Screening. *[Note: Subjects enrolled in a previous clinical trial for EDP-305 who discontinued due to safety reasons within any time window are not eligible for enrollment.]*
18. Prior use of OCA within 26 weeks of Screening and/or concurrent treatment with OCA (or any other FXR agonists). *[Note: Subjects who have previously received OCA and who discontinued due to safety reasons within any time window are not eligible for enrollment.]*
19. Use of systemic immunosuppressant (e.g., corticosteroids) for more than 4 weeks in duration within 1 year prior to Screening with the intention to continue during the study (chronic use of inhaled, topical, ophthalmological, nasal corticosteroids is allowed).
20. Use of any prohibited concomitant medications, including systemic CYP3A4 inhibitors and inducers, within 14 days prior to the first dose of study drug and for the duration of the study.
21. Clinically significant history of drug sensitivity or drug allergy, as determined by the PI.
22. Current or history of significant alcohol consumption defined as: >14 standard drinks per week and/or ≥4 standard drinks per occasion for males and >7 standard drinks per week and/or ≥3 standard drinks per occasion for females. [*Note: A standard drink is 12 oz of beer (5% alcohol), 5 oz table wine (12% alcohol), or 1.5 oz of spirits (40% alcohol).]*
23. History of substance (including alcohol) abuse and in the judgment of the PI, the subject would not be suitable for participation in the study.
24. Any other condition(s) that would compromise the safety of the subject or compromise the quality of the clinical study, as judged by the PI.
25. Use of medication for weight loss or appetite reduction (e.g. orlistat, bupropion/naltrexone, phentermine-topiramate, phentermine, lorcaserin, non-prescription

supplements) at Screening. [*Note: Subjects on a stable dose for at least 12 weeks prior to Screening or time of pre-treatment liver biopsy are allowed if intended to be continued at the same dose during the study. However start of new medications during the study is not allowed.*]

26. History of malignancy of any organ system (other than localized and considered cured cutaneous basal or squamous cell carcinoma, or *in situ* cervical cancer), treated or untreated, within 5 years of Screening

## 3.3. Additional Contraception Details/Requirements

In the context of this study, sexual abstinence is considered a highly effective method of birth control only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Subjects who practice true abstinence, because of the subject's lifestyle choice (i.e., the subject should not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active, they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Vasectomy

Vasectomized male partner is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of child bearing potential, trial female participant and that the vasectomized partner has received medical assessment of the surgical success.

Birth control methods that are considered unacceptable in clinical trials

- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.
- Female condom and male condom should not be used together.
- Norethindrone is an oral progestin-only pill that is available at a dose that is substantially lower than the dose in any combination estrogen-progestin contraceptive pill. In contrast to estrogen-progestin oral contraceptive pills and other progestin-only pills, ovulation is not consistently suppressed with norethindrone pills. As such, norethindrone progestin-only pills may have a higher typical use failure rate than combination pills or other progestin-only pills.

# 4. STUDY DESIGN

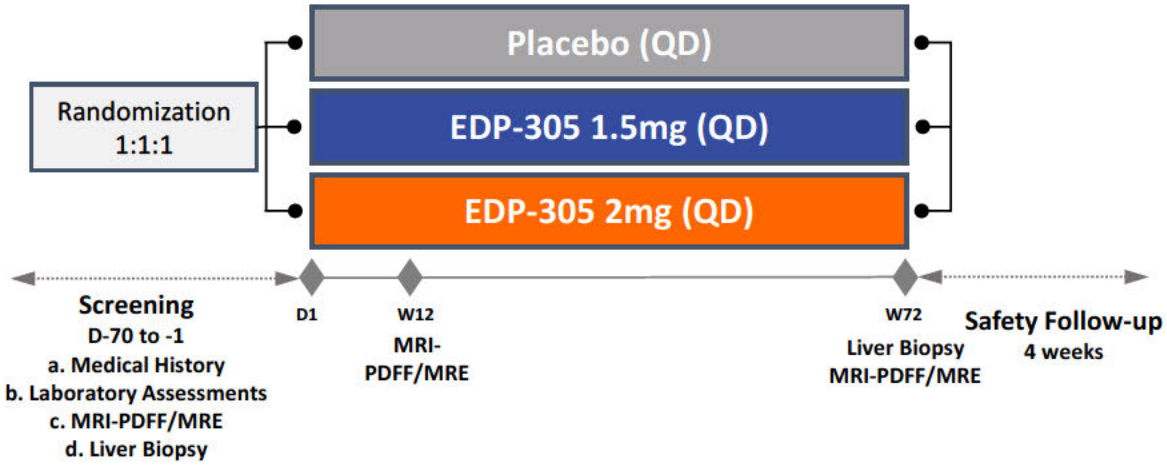
This is a phase 2b randomized, double blind, placebo-controlled multicenter study evaluating the safety and efficacy of two doses of EDP-305 compared to placebo in subjects with liver biopsy proven NASH.

The study is composed of 3 periods:

- Screening period: includes the Screening Visit and may occur over a time period of 70 days (10 weeks) prior to the first dose of study drug.
- Treatment period: begins with the first dose of study drug on Day 1 and concludes with the End of Treatment (EOT) Visit. Subjects who complete dosing will have their EOT visit during Week 72.
- Safety Follow-up period: commences following the last dose of study drug and concludes at the End of Study (EOS) Visit. Subjects who complete the safety follow-up period will have their EOS visit during Week 76.

## 4.1. Dose and Treatment Schedule

**Figure 1: Study Design**




Subjects will be randomized 1:1:1 to receive EDP-305 1.5 mg, EDP-305 2mg or matching placebo. Every subject will receive a single daily dose of blinded study drug for a total of 72 weeks. An overview of the study design is shown in Figure 1. Study visits and assessments are detailed in the Schedule of Assessments.

## 4.2. Rationale for Study Design

This study will evaluate EDP-305 in subjects with NASH who will be randomized in a 1:1:1 ratio to one of three treatment groups: (1) 1.5 mg EDP-305, (2) 2 mg EDP-305, or (3) placebo.

### 4.2.1. Justification of Design, Endpoints and Patient Population

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*).

As summarized in Section 1.4, EDP-305 underwent extensive evaluation in eight phase 1 studies and a proof of concept study in NASH.

A total of 328 subjects received at least one dose of EDP-305 in the phase 1 program. The phase 1 program assessed the PK and PD of EDP-305 over broad range of doses. The PK of EDP-305 was well characterized providing support for once daily dosing. EDP-305 demonstrated target engagement as measured by reduction in C4 and increase in FGF-19 (Study EDP 305-001), which combined with the safety data provided the basis for dose selection in the early phase 2 program. Drug-drug interaction studies provided the needed information to guide dosing recommendation of EDP-305 when administered concomitantly with medications most commonly used by NASH patients, including statins, antidiabetic and antihypertensive drugs. EDP-305 was safe and well tolerated across the phase 1 program.

In Study EDP 305-101 (Section 1.4.2), 12-week therapy with EDP-305 led to statistically significant improvements in liver biochemistry and hepatic steatosis. EDP-305 was generally safe, with the majority of TEAEs being mild to moderate. PK exposures were associated with strong target engagement as measured by C4 and GGT reductions and FGF-19 and ALP increases.

This phase 2b study aims to evaluate the safety and efficacy of two doses of EDP-305 compared to placebo for the treatment of NASH in subjects with liver biopsy proven NASH. As suggested in the Food and Drug Administration (FDA) guidance (*FDA, 2018*), this late stage phase 2 trial will explore the effect of EDP-305/placebo treatment on histological endpoints. The endpoints will include improvement in fibrosis measured using liver biopsy as well as reduction of inflammatory changes.

The patient population selected for inclusion in the trial is designed to represent the target population for treatment. Specifically, in patients with liver disease, there is a significant overlap of NASH and various metabolic conditions including obesity and T2DM. In order to be reflective of the NASH population, these patients will not be excluded from participation in this trial. However, they must be on stable medication regimens prior to study entry so as not to confound study results due to medication changes (dose modifications are allowed for safety reasons). Likewise, many NASH patients take pioglitazone or Vitamin E and these patients will not be excluded from study entry, but the study will be stratified based on whether or not a subject is taking these medications. A liver biopsy proven diagnosis of NASH will be required for study entry. As recommended (*FDA, 2018*), the liver biopsy must be obtained within 6 months of the Screening Visit (or within the Screening period) so as to represent the most accurate status of disease possible. To ensure patients have evidence of steatohepatitis and significant liver fibrosis without cirrhosis, the population with the greatest benefit risk ratio, they must have a NAS $\geq$ 4 and a CRN fibrosis score of 2 or 3.

As suggested in the FDA guidance (*FDA, 2018*), non-invasive markers including imaging and biochemical markers will be assessed in this study. These markers will contribute to the understanding of the correlation between histological changes and non-invasive assessments.

According to the FDA guidance on non-cirrhotic NASH *(FDA, 2018),* the duration of phase 2 trials should be at least 12–18 months, given that histological changes take time. Subjects in this study will take blinded study drug for 72 weeks to allow assessment of improvement in fibrosis and other histological endpoints. Of note, in a recent phase 3 Study, OCA (an FXR agonist)

showed improvement in fibrosis in non-cirrhotic NASH over a study duration of 18 months (*Younossi et al., 2019*).

Finally, to control bias in interpretation of results, the trial will be a double-bind, placebo-controlled design.

### 4.2.2. Justification of EDP-305 Dose

The dose selection was based on comprehensive evaluation of efficacy, safety, tolerability, PK, and target engagement data from a proof-of-concept study EDP 305-101 (ARGON-1), as well as relevant literature data for other FXR agonists. Based on this evaluation, doses of 1.5 mg and 2 mg were selected for the current study. These doses are expected to provide:

- Exposures in the anticipated therapeutic range
- A strong target engagement
- A maximal efficacy in terms of histologic improvement
- A balanced profile in terms of efficacy and tolerability

An exposure-response (clinical utility analysis) of EDP-305 evaluating relationships between PK and efficacy (reduction in ALT and liver fat) and safety (frequency of pruritus) was also conducted, as described below, to further support the dose selection.

To date, the molecular mechanisms underlying the pruritus induced by FXR agonists such as EDP-305 and OCA have not been fully resolved. BAs, including OCA, are reported to activate the bile acid-sensing TGR5 (*D'Amore et al., 2014*; *Maruyama et al., 2002*; *Rizzo et al., 2010*). Subsequently, TGR5 was shown to mediate bile acid-induced itch in mice (*Alemi et al., 2013*; *Lieu et al., 2014*), however, a direct link between activation of TGR5 by OCA or its metabolites and pruritus has not been established and, moreover, EDP-305 does not significantly activate the TGR5 receptor (See IB). Emerging data suggest that Mas-related G-protein coupled receptor (MRGPR) family play a central role in bile acid-induced pruritus but, to date, the relevance of these observations to pruritus observed with EDP-305 and OCA has not been explored (*Meixiong et al., 2019*; *Sanjel et al., 2019*; *Yu et al., 2019*). In the absence of a detailed understanding of the mechanism of EDP-305-induced pruritus and a lack of validated animal models to assess itching, it has not been possible to determine an exposure-effect relationship for pruritus in a preclinical setting. As a result, dose selection for EDP-305 is based exclusively on data derived from clinical observations across the current clinical program and particularly from Study EDP 305-101 (Section 1.4.2).

As mentioned in Section 1.4.2, efficacy as measured by ALT change from baseline at week 12 was statistically significant ($P = .0495$) at the 2.5 mg dose compared to placebo. There was a numerically higher value in the 1 mg dose compared to placebo that did not reach statistical significance ($P = .3039$). The least square (LS) mean changes (week 12) were -27.9, -21.7, and -15.5, following doses of 2.5 mg, 1 mg, and placebo, respectively. At week 12, >20 U/L reduction in ALT was observed in 61% of subjects treated with EDP-305 2.5 mg, 52% treated with EDP-305 1 mg, and 35% with placebo, and >30 U/L reduction in ALT was observed in 37% of subjects treated with EDP-305 2.5 mg, 40% treated with EDP-305 1 mg, and 20% with placebo.

The absolute change from baseline in liver fat content (measured by MRI-PDFF) at week 12 was statistically significant ($P = .0009$) at the 2.5 mg dose compared to placebo but not at the 1 mg dose ($P = .4946$). The LS mean changes (week 12) were -7.1, -3.3, and -2.4, following doses of 2.5 mg, 1 mg, and placebo, respectively. Approximately 45%, 26%, and 25% of subjects were

MRI-PDFF responders (i.e. ≥30% fat reduction) following doses of 2.5 mg, 1 mg, and placebo, respectively. Within the MRI-PDFF responders, mean change in ALT reduction was more profound in the EDP-305 arms compared to placebo, with >30 U/L ALT reduction in the 2.5 arm and the 1 mg arm compared to 16 U/L in the placebo arm.

EDP-305 was generally safe, with the majority of TEAEs being mild to moderate. The most common (≥5%) TEAEs with EDP-305 included pruritus, rash, GI related symptoms (nausea, vomiting, diarrhea), urinary tract infection, dizziness, decreased appetite and cough. As for tolerability of EDP-305 in this 12-week phase 2a study, pruritus was present in approximately 51% of the subjects in the 2.5 mg arm compared to less than 10% in the 1 mg arm and less than 5% in the placebo arm, with the majority being mild or moderate in severity. Among subjects with severe pruritus, there were 2 subjects in the 2.5 mg arm and 2 subjects in the 1 mg arm compared to none in the placebo arm. There were no study discontinuations due to severe pruritus except for one subject in the 1 mg group. Overall, the incidence of treatment discontinuation due to pruritus was 1.8% for 1 mg and 20.8% for 2.5 mg and none in the placebo arm, with all the discontinuations in the 2.5 mg arm being due to moderate pruritus.

In Study EDP 305-101, higher EDP-305 PK exposures observed in terms of steady state (predose) and systemic exposures (AUC) compared to previous studies (Study EDP 305-001). At week 12, mean predose exposures were [redacted] 1 and 2.5 mg doses, respectively, compared to [redacted] across comparable doses in Study EDP 305-001. Mean systemic exposures were [redacted] following 1 and 2.5 mg doses, respectively, compared to [redacted] across comparable doses in Study EDP 305-001.

EDP-305 exposures in study EDP 305-101 were associated with strong target engagement as shown by reductions in C4, and increases in FGF-19 and ALP, and a robust reduction in marker of liver injury, GGT.

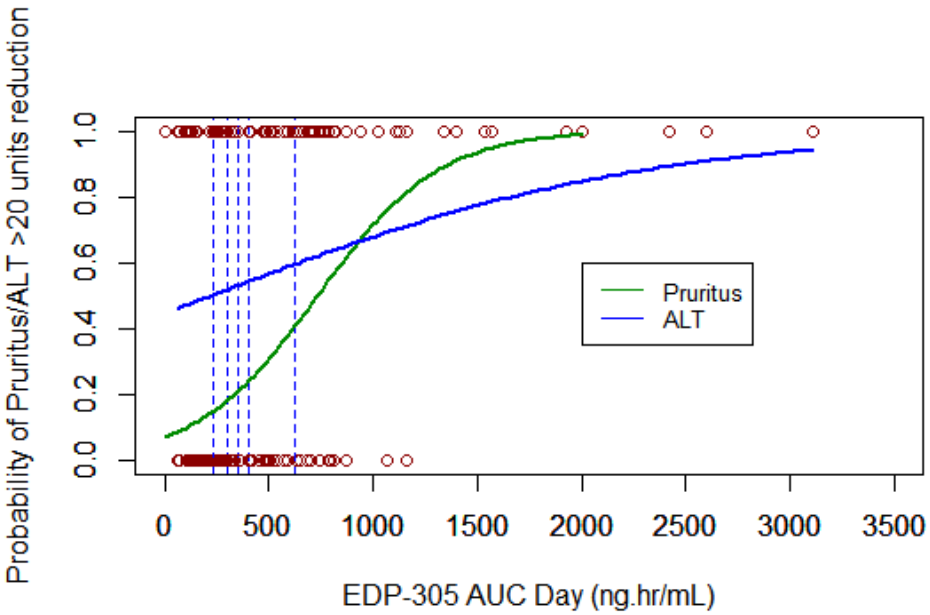
A clinical utility analysis (*Derendorf & Schmidt, 2019*) was conducted to assess exposure-response relationships for EDP-305 in study EDP 305-101 and provide basis for the dose selection for the current study. A threshold of ALT response of 20 U/L reduction was selected as basis for evaluation. The rate of ALT response (defined as reduction of 20 U/L or higher) and rate of pruritus were modeled as a function of EDP-305 exposures. As shown in Figure 2 below, probability of ALT response as a function of EDP-305 exposures was relatively flat, indicating that doses ≥1.5 mg and ≤2 mg might be associated with similar ALT responses (50-60%) and potentially lead to favorable histologic changes (*Loomba & Adams, 2019*). On the other hand, the rate of pruritus increased with increasing EDP-305 exposures. Doses lower than 2.5 mg may be associated with a lower rate of pruritus, and could result in pruritus rates that are at or below the observed rate of pruritus in the placebo arm in the REGENERATE study (19%) (*Younossi et al., 2019*). Changes in lipids are expected to be minimal in this dose range (1.5-2 mg) (Section 1.4.2).

A reduction of approximately 30% in MRI-PDFF has been associated with steatosis improvement (*Patel et al., 2016*). The response in MRI-PDFF at week 12 (≥30% reduction) was assessed as a function of EDP-305 exposures. Based on this analysis, the proportion of liver fat responders based on MRI-PDFF reduction is expected to be similar between doses of 1.5 and 2 mg (data on file).

Based on a comprehensive evaluation of data from Study EDP 305-101, an exposure-response (clinical utility analysis) and, relevant literature, doses of 1.5 mg and 2 mg were selected in the current study. Both doses are expected to:

- Result in PK exposures in the anticipated therapeutic range
- Be associated with optimal target engagement (measured by C4, FGF-19, ALP) and reduction in GGT
- Result in ALT responses (ALT reduction of >20 U/L) in the range of 50-60%, which is expected to translate into favorable histologic improvement (*Loomba & Adams, 2019*)
- Be potentially associated with a lower rate of pruritus compared to 2.5 mg (≤25%)
- Have similar MRI-PDFF (liver fat) responses that may correlate with steatosis improvement (*Patel et al., 2016*)

**Figure 2: Probability of Pruritus and ALT response as a function of EDP-305 exposure**




Dashed lines show median AUCs corresponding to 1, 1.5, 1.75, 2 and 2.5 mg (left to right)

# 5. STUDY DRUG AND TREATMENT OF SUBJECTS

## 5.1. Description of Study Drug

EDP-305 drug product tablets consist of [redacted] and [redacted] strengths supplied as round, white to off-white tablets. The [redacted] tablet is not debossed while the [redacted] tablet is debossed with I to differentiate strength on one side of the tablet. Matching placebos for the two strengths will also be supplied as round, white to off-white tablets with no debossing on the [redacted] placebo tablet and the [redacted] placebo debossed with I. Study drug and matching placebo tablets will be supplied by Enanta.

The matching placebo will contain all the excipients present in the EDP-305 drug product tablets with the exception of the active drug. The tablets contain standard excipients used in the manufacture of tablets that have been previously contained in drug products approved by the FDA. [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 with [redacted] per bottle. All bottles containing clinical trial material will be labeled in compliance with applicable local and national regulations for labeling of investigational products.

EDP-305 tablets will be packaged in a 60-cc white high density polyethylene bottle with a child-resistant polypropylene closure. Each bottle will contain [redacted] and a polyester coil. The bottles will be induction sealed.

## 5.3. Storage

EDP-305 drug product tablets and placebo tablets in bottles will be shipped to the clinical site and stored at controlled room temperature (15 – 30 C; 59 - 86°F).

## 5.4. Accountability

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

## 5.5. Handling and Disposal

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

Enanta will provide instructions for the destruction of any unused study drug. If Enanta authorizes destruction at the study site, the PI 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 IWRS. Subjects will be randomized to the treatment groups shown below:

- Treatment Group 1 (N=112); EDP-305 1.5 mg orally for 72 weeks
- Treatment Group 2 (N=112); EDP-305 2 mg orally for 72 weeks
- Treatment Group 3 (N=112); Placebo orally for 72 weeks

In addition, subjects will be stratified based on 1) use of Vitamin E and/or pioglitazone and 2) type 2 diabetes mellitus (T2DM) status.

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 Pharmacy Manual.

On scheduled clinic visit days, the visit should be scheduled close to the time that the subject normally takes the study drug so that dosing can occur at the site. Subjects should bring their study drug with them. If the clinic visit occurs within 4 hours of the time the subject normally takes their daily dose of study drug, subjects will be administered their daily dose of study drug at the clinic. If the clinic visit is scheduled to occur more than 4 hours after the time the subject normally takes their daily dose of study drug at home, then subjects should not wait until the clinic visit but should proceed to take the daily dose of study drug at home per their normal dosing routine.

If a subject forgets to take study drug at their scheduled time, the dose may be taken later that day; however, the following rules apply:

- no more than 1 dose should be taken on any calendar day and
- there must be a minimum of 16 hours between doses.

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

### 5.7.1. Dispensing of Study Drug

Study drug (EDP-305 and matching placebo) must be dispensed by a qualified pharmacist or an authorized designee with appropriate training and only for administration to the study subjects.

Study drug will be dispensed to subjects by qualified site personnel at all scheduled visits starting on Day 1. Enough study drug will be provided to last the subject to the next clinical visit. Subjects will bring their drug bottles (used and unused) with them to the clinic visit. Subjects will be instructed to store study drug in the original bottle at room temperature.

### 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 Schedule of Assessments. 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 PI 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. 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 Schedule of Assessments.

Generic substitutions of all stable medications for underlying diseases will be allowed during the study. Changing a medication within the same therapeutic class will also be permitted during the study.

### 5.8.1. Coadministration of Vitamin E and Pioglitazone

For subjects taking Vitamin E or pioglitazone, the following three criteria apply:

- subjects must have been on a stable dose for at least 12 weeks prior to the qualifying biopsy, and
- treatment with Vitamin E or pioglitazone cannot have started after the qualifying biopsy, and
- subjects should remain on the same dosing regimen throughout study participation unless required to adjust doses due to safety reasons.

Note that subjects who had previously been taking Vitamin E or pioglitazone (but are no longer taking either one), must have discontinued Vitamin E or pioglitazone a minimum of 12 weeks prior to the qualifying biopsy.

Any subject who initiates a high dose or increases to a higher dose of Vitamin E (≥800 IU/day) during the course of the study must undergo early termination procedures (including liver biopsy and imaging if beyond week 36 (Section 7.2)).

[redacted]

## 5.9. Prohibited Medications

### 5.9.1. Inhibitors and Inducers of CYP34

Systemic inhibitors and inducers of CYP3A4 are prohibited within 14 days prior to the first dose of study drug and throughout study duration.

A comprehensive list of CYP3A4 inducers and inhibitors can be found at:
*https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers*

### 5.9.2. Lipid Lowering Agents

Subjects on a stable dose of statins for at least 12 weeks prior to Screening are allowed. Dose modifications and initiation of new statins are allowed during the study if medically necessary.

Subjects on a stable dose of fibrates for at least 12 weeks prior to Screening are allowed. Dose modifications and initiation of new fibrates are allowed during the study if medically necessary.

The same guidance should be followed for other lipid lowering agents such as niacin and ezetimibe and generic substitutions are allowed.

### 5.9.3. Antidiabetic Treatments

For pre-existing antidiabetic treatment, subjects should be on a stable dose of antidiabetic drugs: (1) for at least 8 weeks (for metformin and/or sulfonylureas), (2) 12 weeks (for SGLT2 or DPP4 inhibitors), or (3) 12 weeks (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 (i.e., no recurrent acute hypo- or hyperglycemic episodes diagnosed clinically with serum glucose levels of <50 mg/dL or >200 mg/dL) for at least 8 weeks prior to Screening. Dose modifications and initiation of new antidiabetic regimen are allowed during the study if medically necessary except for GLP-1 agonists and peroxisome proliferator-activated receptor (PPAR)γ agonists (e.g. pioglitazone or rosiglitazone). Subjects that initiate new regimens of GLP-1 and PPAR agonists must undergo early termination procedures (including liver biopsy and imaging if beyond week 36 (Section 7.2)).

### 5.9.4. Immunosuppressants

Use of systemic or long-acting intravenous immunosuppressants (e.g., corticosteroids) for more than 4 weeks in duration within one year prior to Screening with the intention to continue during the study is an exclusion criterion for the study. Subjects with a disease or condition requiring

chronic use of systemic immunosuppressants should not be enrolled into the study. Intraarticular or intramuscular injection of immunosuppressants is not allowed more than once during the duration of the study.

Note that use (including chronic use) of inhaled, topical, ophthalmological, or nasal corticosteroids is allowed. Short courses of short acting corticosteroids (e.g.. for acute exacerbation of asthma) will be allowed for a maximum period of 2 weeks per treatment course to control the underlying disease. Systemic corticosteroids for the management of pruritus will not be allowed.

A list of immunosuppressants and restrictions will be provided in the study binder.

### 5.9.5. Vaccines, Investigational Products and Treatments for NASH

In accordance with the exclusion criteria, subjects may not receive any investigational vaccine, investigational agent, or biological product within 30 days or 5 times the half-life (whichever is longer) prior to the first dose of study drug. Once enrolled into the study, subjects may not receive any investigational agent (including investigational vaccines) or biological product. However, vaccines administered per local standard of care including those for COVID-19, influenza, tetanus, polio, and pneumonia will be allowed during the study. Administration of these vaccines must be documented in the eCRF.

Use of any medications for the treatment of NASH (other than study drug taken as part of this study) are prohibited during the study. Use of OCA within 26 weeks of Screening is exclusionary for study entry and use of OCA or any FXR agonist during the study is prohibited.

## 5.10. Other Restrictions

Gastrointestinal surgeries (e.g. ileal resection, bariatric surgery including gastric band or gastric sleeve procedures gastrectomy, cholecystectomy) will not be allowed during the study. However, if required for medical /safety reasons, the subject will be terminated from the study and must undergo early termination procedures.

Potential start of new medications for weight loss or appetite reduction during the study is also not allowed.

Refer to the Inclusion / Exclusion criteria listed in Section 3 for other protocol restrictions.

# 6. BLINDING

The study will be double-blinded meaning the subjects, Sponsor, PIs, 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
- Data Safety Monitoring Board (DSMB) members or DSMB meeting attendees (including Enanta representatives not associated with the day-to-day conduct of the study) for the purposes of unblinded data review as outlined in the DSMB charter

## 6.1. Blinding of Study Samples

### 6.1.1. Blinding of MRI/MRE, NASH FibroSure, and Liver Biopsy

The following results will be blinded to the PIs, site personnel, and Sponsor:

- Postbaseline MRI and MRE results
- Week 72/ET liver biopsy results
- Postbaseline NASH FibroSure® results.

Additionally, the MRI/MRE facilities 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 all study personnel involved in study conduct, including the Sponsor, CRO, PIs, 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 PI 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, where possible, the PI should attempt to contact the study Medical Monitor to discuss the need for unblinding. In situations in which the PI has attempted and failed to contact the Medical Monitor, and/or the urgency of the case required immediate action, PIs 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 CRO Medical Monitor cannot be reached, sites at all locations should call the following 24/7 global medical coverage hotline: (+1) 919-674-5468.

Once a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the Medical Monitor should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (e.g., the reason, date) should be clearly recorded in the subject's study file. In addition, the PI 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.

## 6.3. 24/7 Access for Urgent Protocol-Related Medical Issues/Questions

In a study-related health emergency, when the study Medical Monitor(s) cannot be reached by a caller, an on-call physician can be reached 24 hours per day/7 days per week for discussion of urgent protocol medical-related questions. The on-call physician can be reached as follows:

- Telephone: [redacted] (global reachable number) (telephone number allowing a global reach from both landlines and mobile phones – NOT a toll-free number).
- [redacted]- This internet page contains a list of country-specific contact numbers. Countries not listed here need to dial the global reachable number as indicated above. There may be restrictions when dialing a country-specific number from a mobile phone.

# 7. STUDY CONDUCT AND VISIT SCHEDULE

## 7.1. Study Visits

Details of assessments at each visit are presented in the Schedule of Assessments.

### 7.1.1. Screening

#### 7.1.1.1. Initial 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 Schedule of Assessments. Screening will occur over a ten-week period. All Screening assessments must occur no earlier than 70 days before the first dose of study drug at the Day 1 visit unless otherwise approved by the study Medical Monitor. Screening assessments should be performed and confirmed sequentially as follows: a) medical history and other non-invasive assessments, b) laboratory assessments, c) MRI-PDFF and MRE and, lastly, d) liver biopsy.

Histological evidence of definite NASH based on the judgement of the central histopathologist is required for study entry. Tissue samples from a previous biopsy taken within 26 weeks of the Screening visit may be used or a biopsy may be performed during the Screening window. Refer to Section 8.4.8 and the study binder for detailed instructions. If a new liver biopsy is required to satisfy entry criteria, subjects must satisfy all other study entry criteria before the liver biopsy is performed.

Slight extensions to the Screening window for such cases as delayed biopsy or imaging results, or for logistical reasons, may be permitted only with the approval of the Medical Monitor. In such cases, the Medical Monitor will determine if any Screening assessments, e.g., safety labs, may need to be repeated.

#### 7.1.1.2. Retest/Rescreen and Screen Failures

After all Screening assessments are completed, subjects who satisfy all entry criteria (i.e., meet all inclusion criteria but none of the exclusion criteria) should be enrolled into the study.

**Retest:** Subjects with an out-of-range lab value or multiple out of range values, not consistent with the subject's medical history or that may reflect erroneous results based on PI judgement, may retest the respective lab(s). A retest and all remaining assessments must occur within the 8-week Screening window.

**Rescreening:** Subjects who did not qualify for study entry and are, or will be, out of the 10-week Screening window may be rescreened once under the following circumstances with the approval of the Medical Monitor. In each case, the Medical Monitor will determine which, if any, of the Screening assessments may not need to be repeated.

- Subjects who have abnormal laboratory results, which may potentially reflect erroneous results, based on PI judgement, and have exceeded the allowable Screening window for retesting of these parameters
- Subjects who have recently initiated concomitant medications requiring a stable regimen or requiring a medically necessary dose modification, or who have recently discontinued medications and have not yet met the wash out period, but otherwise met all study criteria performed, may rescreen once these respective requirements are met per protocol
- Subjects who are eligible based on completion of all Screening assessments but transiently (for personal reasons) unable to commit to all upcoming study visits and procedures
- Subjects who were impacted by COVID-19 restrictions may rescreen provided the assessments conducted to date meet eligibility and/or retesting criteria.

**Screen Failures:** Subjects who do not satisfy all entry requirements (i.e., meet all inclusion criteria and do not have any of the exclusion criteria) either following Screening or, if appropriate, following retest or rescreen will be considered screen failures.

### 7.1.2. 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. Site personnel will conduct a thorough review of applicable inclusion and exclusion criteria to ensure the subject satisfies all eligibility criteria; subjects who continue to satisfy eligibility requirements will be randomized in a 1:1:1 ratio to their treatment group. Predose assessments and procedures will be conducted as noted in the Schedule of Assessments and considered Baseline values.

After predose study procedures are completed including predose blood collection for PK and biomarker analysis, subjects will receive the first dose of study drug in the clinic. Postdose blood samples for PK and biomarker analysis will be collected as described in Section 8.4 and shown in the Schedule of Assessments.

Before leaving the clinic, subjects will receive study drug and instructions on how to take the drug at home. Subjects will also be given the two pruritus measurement scales (Section 8.3.5) with instruction on how to complete the scales at home.

### 7.1.3. Treatment Period Visits (Day 7 through Week 72/EOT)

**Phone Contact:** On Day 7, sites will contact subjects by phone to assess AEs, inquire about concomitant medications taken during the past week, and confirm subjects are taking study drug appropriately. Site personnel will also remind subjects to complete the pruritus visual analog and 5D-itch scales and to bring the scales back with them to the next clinic visit.

At Weeks 52, 60 and 68, the site will contact the subject by phone to assess drug accountability, concomitant medications, and AE/SAEs. In addition, for females of child-bearing potential, the site will confirm that the at-home pregnancy test was performed and that the results were negative. If the results were positive, the procedures listed in Section 8.4.6 should be followed.

**Clinic Visits:** All subjects will be requested to return to the clinic for on-treatment study visits as follows: Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 56, 64, and 72 following the Day 1 (initial dosing) visit. Note that all treatment visit weeks are determined based on day of initial

dosing. Subjects will be instructed to fast overnight for a minimum of 8 hours prior to each visit so that safety laboratory samples can be drawn fasted. Treatment period assessments per visit are shown in the Schedule of Assessments.

Refer to Section 5.7 for instructions on study drug dosing. Refer to Section 8.4 for instructions on collection of safety laboratory samples.

At the end of the treatment period, subjects will complete the EOT visit. Subjects who complete the full scheduled 72 weeks of treatment will complete the EOT assessments at the Week 72 visit. Subjects who discontinue treatment early should complete EOT assessments at the time of treatment discontinuation (if in the clinic) or within one week following last dose of study drug if the subject discontinues treatment while not in the clinic. Procedures performed are specified in the Schedule of Assessments.

Subjects should take their last dose of study drug in the clinic at the Week 72 visit.

### 7.1.4. 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 (Schedule of Assessments). For subjects who complete the study, the EOS visit will be scheduled during Week 76.

Any subject with ongoing AEs/SAEs at the EOS visit should be followed until resolution of their AE/SAE or until the PI 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 PI or Enanta for safety, behavioral, or administrative reasons. However, the PI 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 PI 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 within one week and undergo the EOT evaluations (Schedule of Assessments). Subjects should then return for the Safety Follow Up assessments (EOS visit) 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 PI 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, PI or Sponsor determines that it is not in the best interest of the subject to continue participation. Reasons for discontinuation include:

- Adverse Event
- Lack of efficacy
- Lost to follow-up
- Withdrawal by subject
- Protocol deviation (including non-compliance with study drug dosing or study procedures)
- 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 PI.

## 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 will promptly notify the PI and will also inform the regulatory authorities of the suspension or termination of the study and the

reasons for the action. The PI is responsible for promptly informing the IRB/EC and providing the reasons for the suspension or termination of the study.

### 7.3.2. Site Termination

A single site may warrant termination under the following conditions:

- Failure of the site to enroll subjects into the study at an acceptable rate
- Failure of the site to comply with pertinent governmental regulations as appropriate
- Submission of knowingly false information from the research facility to the Sponsor, clinical monitor, or governmental authority
- Failure to adhere to the protocol requirements
- Data recording is inaccurate or incomplete
- PI does not adhere to the protocol or applicable regulatory guidelines in conducting the study

### 7.3.3. Study Termination Procedures

If the study is terminated by Enanta 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 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 Schedule of Assessments.

## 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. Whenever possible, the date of diagnosis of NASH should be recorded.

## 8.3. Clinical Evaluations

### 8.3.1. Vital Sign Measurements, Body Temperature and Electrocardiograms

Vital signs will include heart rate (HR), respiratory rate, and blood pressure (BP). Vital signs will be measured at times shown in the Schedule of Assessments after the subject has been supine for 5 minutes and before dosing.

Body temperature should be taken at the Screening, Day 1, and EOS visits according to site standard practices.

Resting 12-lead ECGs will be performed locally and recorded at the times indicated in the Schedule of Assessments after the subject has been supine for 5 minutes and before dosing. A standard bedside 12-lead ECG machine that calculates HR and measures the PR, QRS, QT, RR, and QTc (QTcF) intervals should be utilized. If the site does not have an ECG machine that calculates these values, the site will need to calculate the values.If a blood draw and ECG are scheduled at the same time, then the ECG should be obtained first.

The normal ranges for the ECG are as follows:

- PR: 120 - 220 msec
- QRS: 70 – 120 msec
- QT: ≤ 500 msec
- QTcF: ≤ 450 msec
- Heart Rate: 50 – 100 bpm

The PI 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). Ranges outside of the normal ranges listed above should be recorded as abnormal. The clinical interpretation by the PI or designee of the ECGs should be recorded on a hard copy of the ECGs (i.e., normal, abnormal clinically significant [CS] or abnormal nonclinically significant [NCS]).

The PI or designee must repeat any ECG where the QTcF interval >450 msec, or absolute QT > 500 msec, or with a change from Baseline in QTcF >60 msec. These abnormal ECGs must be repeated once regardless of whether or not the values are considered clinically significant by the PI or designee. Also, ECGs may be repeated at the discretion of the PI 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 PI or designee will perform the physical examination. A full physical examination will be conducted at Screening, Week 12 and EOS as indicated in the Schedule of Assessments 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 (e.g., use of contact lenses does not need to be recorded).

### 8.3.3. Weight and Body Mass Index (BMI)

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:

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

These measurements will be obtained as specified in the Schedule of Assessments.

### 8.3.4. Quality of Life Assessment

Quality of life will be assessed using standardized, validated questionnaires including SF-36 and CLDQ-NASH. In addition, Dermatology Life Quality Index (DLQI) will be completed by subjects who report pruritus. Instructions on administration of the questionnaires by the site and completion of the questionnaires by the subject will be provided in the study binder.

### 8.3.5. Assessment of Pruritus

Pruritus will be monitored in this study at the times indicated in the Schedule of Assessments. As listed below, two separate scales may be used to assess pruritus in subjects:

- First, an itch visual analog scale (VAS) will be used to record the intensity of the event (*Furue et al., 2013*). Site personnel should instruct the subject to draw a line on the scale corresponding to the maximum intensity of itch within the last two weeks.
- If VAS score is greater than zero (i.e. itch), a multidimensional 5D-itch scale developed by Elman (*Elman et al., 2010*) will be used to assess five different dimensions of pruritus within the last two weeks. The five dimensions assessed are duration, degree, direction, disability, and distribution.
- The scales should be administered as indicated in the study binder.

The scales will be completed by the subject in the clinic during the visit for the in-clinic visits as indicated in the Schedule of Assessments. For the Day 7 phone contact, the subject will be given a copy of the scales on Day 1 to take home so that he/she can record pruritus on Day 7 (±1 day), preferably immediately preceding or during the phone contact with the site.

In addition, **if a subject experiences pruritus** between clinic visits the subject should contact the site as soon as possible:

- to discuss the event,
- to obtain guidance on how to manage the side effect(s),
- and to get specific instructions on how to complete the VAS, 5D-itch and additional evaluations through resolution of the event.

Additional details relative to management of subjects who experience pruritus are included in a separate study binder.

### 8.3.6. Adverse Events

The PI is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in Section 9.1 of this protocol. All AEs and SAEs must be recorded in the source documents and eCRF as described below (Section 9.2). At all visits, the PI or designee should inquire about the occurrence of AEs. The following are examples of open-ended questions that may be used to obtain this information: *"How are you feeling?"*; *"Have you had any medical problems recently?"*; *"Have you taken any new medicines since your last visit/assessment?"*

It is the PI'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 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 Schedule of Assessments.

## 8.4. Clinical Laboratory and Diagnostic Procedures

All laboratory samples will be analyzed by a centralized laboratory (i.e., ICON Laboratory) or designee. 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 PI, 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 clinical significance. Clinically significant laboratory findings in the opinion of the PI must be recorded as an AE (or SAE as appropriate) (Section 9.1).

Blood samples for safety assessments should be collected predose for visits where study drug is administered in the clinic or at least 4 hours postdose if the subject took study drug at home (see Section 5.7 regarding when study drug is taken at home by the subject versus in the clinic during the visit). Additional samples collected for PK and PD analysis should be collected postdose as noted in the Schedule of Assessments. Additional clinical laboratory evaluations will be performed at other times if judged clinically appropriate by the PI, or if the safety review of the data suggests a more detailed assessment of clinical laboratory safety evaluations.

For selected biomarker analysis, serum or plasma samples should be collected for analysis of FGF-19, BAs, and C4 as indicated in the Schedule of Assessments and according to instructions provided in the laboratory reference manual.

### 8.4.1. Safety Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected according to the Schedule of Assessments. Subjects should be instructed to fast overnight for at least 8 hours prior to the blood draw for the safety laboratory testing where study drug is taken in the clinic. Where

study drug is taken at home at least 4 hours prior to the clinic visit, subjects must fast for a minimum of 4 hours prior to the blood draw for safety laboratory assessments. If subjects did not fast as indicated per protocol, the sample may be drawn anyway but the lack of fasting noted in the eCRF. 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 3.

eGFR will be calculated by the central laboratory using the MDRD equation using serum creatinine ($S_{Cr}$) and other demographic factors:

MDRD formula:

eGFR =175 x $(S_{Cr})^{-1.154}$ x$(age)^{-0.203}$ x0.742 [if female] x1.212 [if Black]

On line calculator can be found at: *https://www.kidney.org/content/mdrd-study-equation*

### 8.4.2. Noninvasive Evaluations of Fibrosis

The ELF panel combines 3 biomarkers that have been shown to correlate with the level of liver fibrosis assessed by a liver biopsy. These biomarkers include hyaluronic acid (HA), amino-terminal propeptide-of-type-III-collagen (PIIINP), and tissue-inhibitor of matrix-metaloproteinase-1(TIMP-1). These parameters along with PRO-C3 will be assessed as outlined in the Schedule of Assessments.

Fibrosis will also be estimated using the APRI, FIB-4 formulae, and the 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 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 (×109/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*

NASH FibroSure ® is a noninvasive assessment of liver status. Quantitative results of 10 biochemicals in combination with age, gender, height, and weight will be analyzed by the Central Laboratory using a computational algorithm to provide a quantitative surrogate marker (0.0 – 1.0) of liver fibrosis (Metavir F0 – F4), hepatic steatosis (0.0 – 1.0, S1 – S3), and nonalcoholic steatohepatitis (0.0 – 0.75, N0 – N2). Blood samples for analysis should be collected at Screening, Week 12 and EOT as shown in the Schedule of Assessments.

### 8.4.3. Markers of Inflammation

Markers of inflammation include fibrinogen, C-reactive protein (CRP), alpha2 macroblobulin, haptoglobin, tumor necrosis factor alpha (TNFα), tumor necrosis factor beta (TNFβ), and the

cytokines interleukin-6 (IL-6) and interleukin-1β (IL-1β). Blood for analysis of these markers will be collected as shown in the Schedule of Assessments.

### 8.4.4. Pharmacodynamic Biomarkers for FXR activity

See Table 3 and the Schedule of Assessments for a full list of biomarkers to be collected in this study.

Serum or plasma samples should be collected before the daily dose of study drug for analysis of the FGF-19 (serum), C4 and BAs as shown in the Schedule of Assessments. At the Day 1, Week 12, Week 36, and Week 72 visits, one predose and two postdose samples will be collected concomitantly with PK samples: the first postdose sample should be collected one to three hours postdose and the second postdose sample collected at least 1 hour later. If the subject took drug prior to their clinic visit, only one postdose sample should be collected.

## Table 3: Laboratory Evaluations

| | |
|---|---|
| **CHEMISTRY PANEL**<br>Alanine Aminotransferase (ALT/SGPT)<br>Albumin, Serum<br>Albumin/Globulin (A/G) Ratio (calculation)<br>Alkaline Phosphatase, Serum<br>Amylase<br>Aspartate Aminotransferase (AST/SGOT)<br>Bilirubin, Total, Indirect and Direct<br>Blood urea nitrogen (BUN)<br>BUN/Creatinine Ratio (calculation)<br>Calcium, (Serum)<br>Creatine Kinase<br>Creatinine, Serum (and eGFR [MDRD])<br>Uric Acid<br>Electrolyte Panel ($Na^+$, $K^+$, $Cl^-$, Bicarb.)<br>Phosphorus<br>Gamma Glutamyl Transferase (GGT)<br>Globulin, Total<br>Lactate Dehydrogenase (LDH)<br>Lipase<br>Protein, Total, Serum<br>HbA1c<br>HOMA indices<br>Fasting Insulinemia<br>Fasting Plasma Glucose<br>Total Cholesterol (TC)<br>Triglycerides (TG) | **HEMATOLOGY PANEL**<br>Hemoglobin<br>Hematocrit<br>Differential WBC Count (percentage and absolute): Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils<br>Mean corpuscular hemoglobin (MCH)<br>Mean corpuscular hemoglobin concentration (MCHC)<br>Mean corpuscular volume (MCV)<br>Platelets<br>Red Blood Count (RBC)<br>White Blood Cell (Count) (WBC)<br><br>**VIRAL DETECTION FOR ENTRY CRITERIA**<br>Human immunodeficiency virus (HIV)-1, HIV-2, Hepatitis B virus (HBV) (Hepatitis B surface antigen [HBsAg]), hepatitis C virus (HCV)<br><br>**MARKERS OF CV RISKS AND LIPIDS**<br>Triglycerides (TG)<br>apoB<br>Total Cholesterol (TC)<br>High Density Lipoprotein – Cholesterol (HDL-C)<br>Low-Density-Lipoprotein – Cholesterol (LDL-C)<br>Total/HDL Cholesterol (CT) Ratio<br>Adiponectin |
| **URINALYSIS**<br>Routine urinalysis to include: Color and appearance, pH, SG, Bilirubin, Glucose, Ketones, Leukocytes, Nitrite, Occult blood, Protein, Urobilinogen, Microscopic (including RBCs and WBCs) | **BIOMARKERS FOR NASH**<br>Cytokeratin (CK)18<br>GLP-1 (glucagon-like peptide-1)<br><br>**PD MARKERS FOR FXR ACTIVITY:**<br>Fibroblast growth factor (FGF)19<br>Total bile acids (BAs)<br>C4 (7α-OH-4-cholesten-3-one) |
| **PREGNANCY AND OTHER TESTS**<br>Serum pregnancy test<br>Follicle-StimulatingHormone (FSH)<br><br>**COAGULATION TEST**<br>International Normalized Ratio (INR)<br>Prothrombin Time (PT)<br>Partial thromboplastin time (PTT) | **FIBROSIS AND INFLAMMATORY MARKERS**<br>*ENHANCED LIVER FIBROSIS (ELF) PANEL*<br>-Hyaluronic acid (HA),<br>-Procollagen III amino terminal peptide (PIIINP)<br>-Tissue inhibitor of metalloproteinase 1 (TIMP-1)<br>PRO C3<br>Fibrinogen, CRP, alpha2 macroglobulin and haptoglobin<br>Tumor necrosis factor alpha and beta (TNF-α, and β)<br>IL-6. IL1β<br>AST to Platelet Ratio Index (APRI)<br>Fibrosis 4 (FIB-4)<br>NAFLD fibrosis score (NFS score), NASH FibroSure |

### 8.4.5. Pharmacokinetic Samples

Plasma samples will be collected and processed according to the procedures provided and/or approved by Enanta. Plasma PK samples will be collected as shown in the Schedule of Assessments. More detailed information will be given in the Laboratory Manual.

On all scheduled visits except for Day 7, PK samples will be collected predose. At the Day 1, Week 12, Week 36, and Week 72 visits, three PK samples should be collected, one predose and

two postdose. The first postdose sample should be collected 1 to 3 hours postdose and the second postdose sample should be collected at least one hour later. Where possible, the samples at each visit should be obtained at different times postdose relative to each other. If the subject took drug prior to their clinic visit, only one postdose sample should be collected. For subjects who discontinue treatment early, collect one postdose sample at the EOT 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.

Actual date and time of PK sample collection will be recorded in the eCRF.

#### 8.4.5.1. Pharmacokinetic Sampling for Subjects with Transaminase or ALP Elevations

For subjects with persistent transaminase or ALP elevations and evidence of liver injury, one additional sample will be collected for additional PK analysis at each visit where safety labs are obtained (see Section 10.2).

It is important that the date and time of collection for each PK blood sample be accurately recorded in the source document. In addition, the site should record the time of last dose taken at home prior to the visit.

#### 8.4.5.2. Handling and Bioanalysis of Pharmacokinetic Samples

EDP-305 and its metabolites 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 metabolites by a laboratory selected by Enanta.

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. In addition, a few samples from selected subjects randomized to placebo will also be analyzed and serve as control samples.

### 8.4.6. Pregnancy and Menopausal Laboratory Testing

All female subjects will undergo a serum pregnancy test at Screening and Baseline. In addition, all female subjects will have urine pregnancy testing at Baseline visit. A urine pregnancy test must be conducted and confirmed negative on Day 1 prior to the first dose of study drug. Thereafter, all female subjects being of child-bearing potential at the time of Screening will continue having urine pregnancy tests at each visit throughout the study. A serum pregnancy test must be completed at the EOS visit in these subjects. If the urine pregnancy test is positive, a serum pregnancy test should be obtained as soon as possible.

FSH testing will be conducted as per below guidance:

- FSH testing is not required in the following female subjects:
    - Who are of childbearing potential, or
    - Who have had a hysterectomy, bilateral oophorectomy (ovariectomy), or bilateral salpingectomy, or

- With cessation of menses ≤ 1 year at Screening as the subject is considered of childbearing potential. In such cases the subject must agree to use contraception methods as required by the protocol.
- With cessation of menses ≥ 2 years: the subject is of non-childbearing potential.

FSH testing is mandatory in female subjects with cessation of menses between 1 to 2 years. To be considered postmenopausal a subject must have an FSH level >35 mIU/mL.

Females of child-bearing potential will be given a pregnancy test kit so that they can perform a urine pregnancy test at home at Weeks 52, 60 and 68 (i.e., between clinic visits at Weeks 48 and 56, 56 and 64, and 64 and 72, respectively). If the results of either the in clinic or at home urine pregnancy test are positive, a serum pregnancy test should be conducted as soon as possible.

### 8.4.7. Liver Magnetic Resonance Imaging

All eligible subjects must undergo a liver MRI-PDFF and liver MRE during the Screening period, Week 12 and at the EOT visit. 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 (i.e., Week 72). For subjects who discontinue treatment between Weeks 10 and 12, the EOT MRI and MRE must be conducted within 1 week of the final dose of study drug. If the MRI/MRE cannot be conducted within the 7-day timeframe, then it should not be conducted and the reason noted in the source documents. For subjects who had the MRI and MRE conducted at the Week 12 visit but discontinue treatment prior to Week 36, no additional MRI and MRE will be conducted. For subjects who discontinue treatment at Week 36 or later, the MRI and MRE should be conducted within 2 weeks after discontinuing treatment.

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

### 8.4.8. Liver Biopsy

**Baseline liver biopsy:** Histological evidence of NASH from a liver biopsy read by a central histopathologist is required for study entry. The liver biopsy may be obtained during the Screening period after the subject has qualified for study entry based on all other criteria OR a sample from a previous biopsy may be used if it meets the following criteria:

- Was obtained within 26 weeks of the Screening Visit
- Is of sufficient quality to allow for a definitive diagnosis of NASH
- Has samples available for review/confirmation by the central histopathologist

If samples from the biopsy were sent to the central histopathologist and his/her assessment does not match with results provided by a local assessor, a site will be allowed to provide additional liver biopsy tissue to the central reader to be evaluated if the following conditions apply:

- The subject is considered eligible except for liver histology
- The site must request to provide additional tissue to the central reader before the subject is considered a screen failure.

Note that in all cases, the central histopathologist will provide the final liver histology assessment for study entry.

Details for collection and processing of the liver biopsy can be found in the liver biopsy guidance in the study binder.

**EOT (Week 72) liver biopsy:** End-of-treatment liver biopsies collected for analysis of the primary endpoint for subjects who have completed treatment will be performed 72 weeks after enrollment (window: 70-74 weeks). If a liver biopsy cannot be performed within the 70 to 74 week window due to extreme circumstances, the PI should consult with the Medical Monitor to determine if the window can be extended for that subject to 66 to 78 weeks.

**Early Termination:** Subjects who discontinue the study early but complete a minimum of 36 weeks of dosing should have a liver biopsy within 2 weeks following the last dose of study drug. Subjects who discontinue the study prior to completing 36 weeks of dosing should forgo the EOT biopsy.

### 8.4.9. Exploratory Research Samples

Additional blood samples for exploratory research will be collected as described in the Schedule of Assessments. These samples will be used for research to better understand markers of health and disease, and responses to medicine used to treat disease. These samples will not be used for genomic testing. Further, samples will be stored anonymously such that the subject's identity will be protected and the subjects name will not be attached to the sample. The samples will be stored for up to 1 year after the finalization of the Clinical Study Report for this study which includes study results.

Subjects may withdraw consent to participate in this exploratory research at any time. Withdrawing consent to use these samples should be done in writing to the PI. Withdrawing consent to the storage and future testing of the sample will result in destruction of the sample. However, if the subject withdraws consent after the sample has been tested, the test results and research study/sample-related information must remain in any database(s) that was created for the research study. The reason for this is to comply with regulations that require the Sponsor to make data available for review by the US FDA or other appropriate regulatory authorities if the data is used to support an application for marketing approval of EDP-305.

# 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 PI, 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 (e.g., 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 drug (e.g., 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 5.0).

### 9.2.1. Documenting and Reporting Adverse Events

All AEs regardless of the intensity, seriousness, or relationship to study drug will be reported from the time of informed consent to the end-of-study. AEs for each subject will be recorded in the subject's source documents and in the subject's AE eCRF and Clinical Trials SAE Form (if applicable).

Grade AEs (serious and non-serious) in accordance with the NCI/CTCAE scale (available at *https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0_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 (e.g., 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 (e.g., 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 PI must attempt to determine the cause of each event. Every effort will be made by the PI to assess the relationship of each AE to study drug. To ensure consistency of AE/SAE causality assessments, PI(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 4.

**Table 4: Options for Action Taken with Study Drug**

| Classification | Definition |
|---|---|
| Dose Not Changed | Study drug dose not changed in response to the AE |
| Dose Reduced | Not Applicable |
| 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 5. 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 5: 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 PI to [redacted] and Enanta within 24 hours of learning of its occurrence. In addition, all SAEs that occur after the EOS Visit and that are considered possibly 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. All SAE reporting will be done primarily via email; fax will be the back-up means of communication. All new/initial events as well as follow-up information on previously reported events should be communicated via e-mail. PIs are asked to report follow up information as soon as it becomes available, to ensure timely reporting to Health Authorities.

[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 PI for severity, relationship to the investigational study drug(s) and possible etiologies. Relationship to study drug(s) will be recorded 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 PI is required to follow the event to resolution and report the outcome of the event to the PRA Safety and Risk Management using the SAE Form.

The PI 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 PI is asked to report follow-up information as it becomes available.

Enanta 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

Females must not become pregnant while taking study drug. However, as a precaution, all subjects will be counseled to inform the PI of any pregnancy that occurs during study treatment and for 90 days after the last dose of study drug.

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 PI 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 5), 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 may request that the PI 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 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

## 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. Study drug will be discontinued once any one of the thresholds presented below is met. No repeat test is required. Reference Baseline is defined as the mean of Screening and Day 1 values. The following study drug stopping rules are applied:

- If ALT or AST increases to >5× Reference Baseline (and is at least > 5x ULN)
- If ALT or AST increases to >2× Reference Baseline (and is at least > 3x ULN) AND the increase is accompanied by
    - a concomitant total bilirubin increase to >2× Reference Baseline (and at least > 2x ULN) **OR**
    - the INR is concomitantly > 1.5
- If ALT or AST increases to >2× Reference Baseline (and is at least > 3x ULN) **AND**
    - elevations of ALT/AST are accompanied by signs or symptoms of right upper quadrant abdominal pain, anorexia, nausea, vomiting, fever, eosinophilia (> upper limit of normal of absolute eosinophilia count), and/or rash.

Refer to Section 10.2 for close monitoring guidelines 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*) provides guidance for the management of changes in liver transaminases (ALT/AST).

Close monitoring activities will be initiated:

- If ALT or AST increases > 2x Reference Baseline (and is at least > 3x ULN) OR
- If ALT or AST increases > 8x ULN (whichever comes first)

Following the initial alert, sites will be asked to perform the following laboratory tests and assessments within 48 – 72 hours.

- Blood samples must be taken prior to taking study drug on that day (i.e., predose).
    - Clinical Chemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, indirect bilirubin, ALP
    - Hematology: full red blood count
    - Coagulation: INR
    - PK sample: predose
- Physical examination for detection of accompanying clinical symptoms potentially associated with deviation in liver function e.g. right upper quadrant abdominal pain, anorexia, nausea, vomiting, fever, or rash.
- Sites will also be requested to comment/confirm
    - if the subject has any history of regular alcohol consumption exceeding 14 drinks/week for females and 21 drinks/week for males within 6 months of Screening as well as any recent relevant alcohol intake

- if the subject started any new medications recently including non-prescription medications and herbal and dietary supplement preparations, recreational drug use, special diets, or was recently exposed to environmental chemical agents

Should retest results not meet close monitoring cut-offs, a second retest will be requested within 48 – 72 hours. If the second retest is negative, the event will be closed and attributed to the fluctuating nature of liver transaminases.

The following close observation guidelines 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 (no repeat test required to confirm IMP stopping rule). The following laboratory tests and assessments will be performed at every visit until retest results no longer meet close monitoring criteria.

- Blood samples must be taken prior to taking study drug on that day (i.e., predose).
  - Clinical Chemistry: ALT, AST, GGT, total bilirubin, direct bilirubin, indirect bilirubin, ALP
  - Hematology: full red blood count
  - Coagulation: INR
  - PK sample: predose
- Physical examination for detection of accompanying clinical symptoms potentially associated with deviation in liver function e.g. right upper quadrant abdominal pain, anorexia, nausea, vomiting, fever, or rash.
- **At the first visit following confirmation of close monitoring criteria/the next visit after meeting IMP stopping rules,** a blood sample will be taken for viral hepatitis A, B, C, D, E as well as Cytomegalovirus (CMV) and Epstein Barr Virus (EBV).

The table below (Table 6) shows the recommended retest frequency based on the course of liver transaminase retest results. The recommendations were adapted from the FDA guidance on Drug-Induced Liver Injury (*FDA, 2009*).

**Table 6: Retest Frequency Recommendations**

| Trends Observed for Repeat Liver Function Test | Frequency for Repeat Tests |
|---|---|
| First 3 repeat tests (including test to confirm initial alert test result) | Every 48 – 72 hrs |
| Increasing tendency of test result | Every 48 – 72 hrs |
| Stabilization of test result | Once weekly |
| Decreasing tendency | Once weekly – every 2 weeks |

Depending on the course of the liver transaminase retest results, on a case-by-case basis, a gastroenterology or hepatology consultation or additional liver biopsy for any subject with persistent evidence of liver injury might be indicated.

If a subject lives in a remote area, they can be tested locally with the results promptly communicated to the PI site. However, testing via central lab is the preferred option.

# 11. STATISTICAL CONSIDERATIONS

## 11.1. General Considerations

Statistical analysis of this study will be the responsibility of Enanta Pharmaceuticals or its designee. Details of the statistical analysis methods will be described in the statistical analysis plan (SAP) document.

Continuous endpoints will be summarized using n, mean, standard deviation, median, 25$^{th}$ quartile, 75$^{th}$ quartile, minimum and maximum values. Categorical 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. Inferential testing will be conducted using a 2-sided alpha of 0.05, unless stated otherwise.

Any change to the data analysis methods described in the protocol will require an amendment if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report or SAP. Changes may only be made in the SAP prior to unblinding.

## 11.3. Analysis Populations

The following analysis populations are planned:

- Safety Population (SAF): All subjects who receive at least one dose of study drug. Subjects will be included in the treatment group that corresponds to the study drug received during the study.
- Intent-to-treat (ITT) Population: ITT subjects will be considered those randomized to treatment. The ITT subjects will be analyzed according to the treatment to which they were randomized. In the event the SAF is the same as ITT, only the ITT will be reported. This will be the primary efficacy population.
- Per Protocol (PP) Population: All randomized and treated subjects that do not have major protocol deviations which could unduly influence the efficacy analysis.
- PK Population: All subjects receiving active study drug and having any measurable plasma concentration of study drug at any time point.

## 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 ITT 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 SAP.

## 11.5. Method of Treatment Assignment

Subjects who meet all criteria for enrollment will be randomized to blinded treatment on Day 1 in a 1:1:1 ratio to EDP-305 2 mg, EDP-305 1.5 mg, or placebo. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign double-blind investigational product to each subject. To achieve between-group comparability the randomization will be stratified by diabetes status and use of Vitamin E and/or pioglitazone.

## 11.6. Primary Efficacy Analysis

Logistic regression models will analyze the co-primary endpoints of (1) proportion of subjects who achieve ≥1 stage improvement in fibrosis without worsening of steatohepatitis (2) resolution of steatohepatitis without worsening of liver fibrosis as determined by liver biopsy at 72 weeks. Treatment groups will be compared for each endpoint at a 0.025 significance level. A responder will be considered any subject achieving either endpoint. The proportion of responders for each endpoint will be compared using a logistic regression model with treatment group, diabetes status and use of Vitamin E and/or pioglitazone and baseline covariate NAS as effects. The odds ratio and 97.5% confidence interval will be reported as well.

A step-down sequential testing procedure will be used to control multiplicity in testing between doses. The high dose EDP-305 group (2 mg) will be compared to placebo using a two-sided alpha of 0.025 first, and if statistically significant, the EDP-305 1.5 mg group will be compared to placebo using a two-sided alpha of 0.025. The primary efficacy analyses will be performed using the ITT population.

### 11.6.1. Secondary Efficacy Analysis

Secondary endpoints will be analyzed for treatment group differences. Multiple sensitivity analyses will be performed on the primary efficacy endpoints.

For categorical endpoints (e.g., proportions) a logistic regression model testing between treatment differences with terms for diabetes status and use of Vitamin E and/or pioglitazone and baseline covariate NAS included in the model. Odds ratio and the 95% confidence intervals will be reported. If convergence is encountered the Fisher's exact test will be used to test treatment group differences.

For continuous endpoints (e.g., change from baseline) an analysis of covariance (ANCOVA) model testing treatment differences with terms for baseline diabetes status and use of Vitamin E and/or pioglitazone, baseline covariate NAS, and baseline parameter of interest included in the model. A type III sum-of-squares for the least-squares means and 95% confidence intervals will be reported.

When continuous endpoints that are repeated over visits a restricted maximum likelihood-based mixed model repeated measures (MMRM) technique may be performed. The model will include treatment, baseline covariate NAS, baseline parameter, visit, treatment-by-visit interaction as fixed effects. An unstructured variance-covariance structure will be considered to model the within-patient error. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure should be used. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. A type III sum-of-squares for the least-squares means and 95% confidence intervals will be reported.

## 11.7. Safety Endpoints

### 11.7.1. Treatment Compliance

Listing of randomization schedule and study drug dispensed with LOT number will be provided. Subjects will record study drug administration on the Drug Administration form. Treatment compliance for each subject will be calculated as the number of subjects receiving the amount of drug taken divided by the amount prescribed multiplied by 100.

### 11.7.2. Adverse Events

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. Treatment-Emergent are defined as reported AEs that first occurred or worsened during the postbaseline phase compared to baseline. The maximum severity at baseline will be used as baseline severity. If the maximum severity during postbaseline is greater than the maximum baseline severity, then event is considered Treatment-Emergent. No statistical testing will be performed.

Summaries of AEs will include the following at a minimum:

- An overall summary of AEs with a line for each of the categories provided below:
- TEAEEs
- Related TEAEs
- Maximum Severity TEAEs
- Treatment-Emergent by Severity
- Treatment-emergent AEs leading to study drug discontinuation
- AEs leading to death
- SAEs
- Related Treatment-Emergent SAEs

### 11.7.3. Clinical Laboratory Data

Laboratory assessments will be reported as mean change from baseline across scheduled visits, and as the incidence rate of shift change from baseline. Shift from baseline tables will be generated for each treatment group for selected analytes. Laboratory shifts will be displayed as

treatment-emergent abnormal, high, or low results. The following details the summary types where LLN = Lower limit of the normal range, ULN = Upper limit of the normal range.

For categorical tests: Treatment-emergent abnormal is defined as a change from normal at baseline to abnormal at any postbaseline visit

For continuous tests:

- Treatment-emergent high is defined as a change from a result less than or equal to the high limit at baseline to a value greater than the high limit at any time postbaseline.

  Results will be reported according to any value greater than the high limit, any value greater than 2x ULN and 3x ULN

- Treatment-emergent low is defined as a change from a result greater than or equal to the low limit at baseline to a value less than the low limit at any time postbaseline

  Results will be reported according to any value less than the lower limit, any value less than 2x LLN and 3x LLN.

### 11.7.4. Electrocardiogram Data

The QT interval has an inverse relationship with heart rate. The measured QT intervals will be corrected for heart rate in order to determine prolongation relative to baseline. The QT/QTc interval will be corrected based on Fridericia's correction: $QTc = QT/(RR\ interval)^{1/3}$, in seconds. The QT parameters will be summarized by observed and change from baseline over visits.

A categorical analysis of QT/QTc will be based on the number and percentage of subjects meeting or exceeding the following:

- Absolute QT/QTc interval prolongation
  - QTc interval > 450
  - QTc interval > 480
  - QTc interval > 500
- Change from Baseline in QTc interval
  - QTc interval increases from baseline >30
  - QTc interval increase from baseline >60.

### 11.7.5. Vital Signs

The incidence rate of subjects with treatment-emergent vital sign changes at any postbaseline visit will be summarized. Specific criteria for the classification of treatment-emergent will be documented in the SAP. Vital sign observed, change, and percent change will be summarized by treatment over visits.

### 11.7.6. Concomitant Medications

The number and percentage of subjects taking concomitant medications will be coded according to latest WHO ATC level 4 and WHO preferred term. Summaries will be provided by ATC level 4 and preferred term. Subjects in the safety population will be summarized by treatment group.

### 11.7.7. Physical Examinations

Physical examination data will be provided in data listings.

## 11.8. Pruritus Analyses

Descriptive statistics will be provided for patient reported outcomes such as the 5D-itch scale, VAS, and other assessments. Observed, change from baseline, and percent change from baseline results will be presented by visit and treatment group. Additional modeling may be performed if data permits. Further analysis of all pruritus assessment tools will be described in detail in the SAP.

## 11.9. Non-invasive Tests (NITs)

Descriptive statistics will be provided, including observed, change from baseline, and percentage change from baseline by visit and treatment group. These tests include imaging (MRI-PDFF, MRE), and non-invasive fibrosis markers. Additional ANCOVA modeling will be performed across timepoints as appropriate. Further analysis of all NITs will be described in detail in the SAP.

## 11.10. Pharmacokinetic Analyses

Summary of plasma concentration data will be descriptive in nature. Available plasma concentration-time data in the PK population will be summarized by treatment group. Mean plasma concentration time figures may be created for EDP305 and its metabolites, as allowed by the data. Additional details will be provided in the SAP.

## 11.11. Pharmacodynamic Analyses

A descriptive summary of C4, FGF-19, and BA will be provided, including change from baseline and percentage change from baseline by visit and treatment group. Graphical summaries will be provided.

## 11.12. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between PK of EDP-305 and measures of PD activity (e.g. C4, FGF-19, BA) will be summarized, as allowed by the data.

## 11.13. Quality of Life Scales (SF-36 and CLDQ-NASH) and Cardiovascular risk score Analyses (ASCVD)

Each scale will be scored and summarized by author suggested scoring and analysis methods, as appropriate. Descriptive statistics will be provided, including observed and change from baseline by visit and treatment group. Complete detail of how each scale is scored and analyzed will be described in detail in the SAP.

[redacted]

[redacted]

## 11.15. Multiplicity

Strongest control of type I error at 0.05 will include an equal Bonferroni split alpha (0.025) for each of the co-primary endpoints. Multiple active dose groups will be compared to placebo (high dose versus placebo, low dose versus placebo). The high dose group for each will be analyzed first for each endpoint. If statistical significance at the 0.025 level is achieved the low dose group will be tested.

## 11.16. Subgroup and Covariate Analysis

Subgroup analyses will be performed on the primary and secondary endpoints, primarily. A logistic regression model will be planned when categorical endpoints are analyzed. The model will include treatment and stratification factors as fixed effects, with subgroup and subgroup-by-treatment interaction as well. Odds ratios and 95% confidence intervals will be reported. For continuous endpoints an ANCOVA model with treatment and stratification factors as fixed effects in the model, with subgroup and subgroup-by-treatment interaction as well.

Various study populations may be used. Forrest plots will be performed to visually describe the association.

# 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 PI 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 PI to ensure that IRB/EC approval is obtained before implementation of the amended procedures. It is also the responsibility of the PI 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 for regulatory purposes.

### 12.1.3. Written Informed Consent

The PI 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 PI 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 and its designees, regulatory agencies, and IRBs/ECs. As the study sponsor, Enanta 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 PI and Enanta. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., 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 PI 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. There will be limited data entered in the eCRF for Screen Failed subjects. It is the PI'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 PI, 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 PI 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 and/or their designee and recorded as deviations as appropriate in the eCRF.

## 12.3. Study Monitoring

Representatives of Enanta or its designee will monitor this study until completion. Monitoring will be conducted through on-site visits with the PI 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 ensure 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 PI agrees to allow the IRB/EC, representatives of Enanta, 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 or its designee may conduct a quality assurance audit of this study. If such an audit occurs, the PI 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 PI 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 that the investigations of EDP-305 have been discontinued or for 2 years following marketing approval of the drug, after which time Enanta 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 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 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 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. Enanta 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 to seek patent protection of any invention contained therein

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# 14. APPENDICES

## Appendix 1: Schedule of Assessments

| *Study Event* | Screening[1] | Study Assessments per Planned Study Day/Week | | | | | | | | | | Phone Contact[2] | EOT | EOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Visit Day/Week* | D-70 to D-1 | D1[3] | D7[4] | W2 | W4 | W8 | W12 | Wks 16, 20, 24, 28, 32 | W36 | W40 & W44 | W48, W56, W64 (Every 8 weeks) | W52, W60, W68 | W72[5] | W76 |
| *Visit Windows* | | | ±1d | ±2d | ±2d | ±2d | ±3d | ±3d | ±3d | ±3d | ±3d | ±3d | ±3d | ±3d |
| ICF[6]; Demography; Medical History | x | | | | | | | | | | | | | |
| Inclusion/Exclusion | x | | | | | | | | | | | | | |
| Liver Biopsy (with centralized reading) | x[7] | | | | | | | | | | | | x | |
| Elastrography: Liver Stiffness Assessment (MRE) | x | | | | | | x | | | | | | x | |
| NASH FibroSure® | x | x | | | | | x | | | | | | x | |
| APRI, FIB-4, and NFS | | x | | | | | x | | | | | | x | |
| FSH[8]; HIV, HCV, and HBV | x | | | | | | | | | | | | | |
| Pregnancy Test[9] | x | x | | | x | x | x | x | x | x | x | | x | x |
| At Home Pregnancy Tests (Phone Contact) [10] | | | | | | | | | | | | x | | |
| Height, Weight and BMI[11] | x | x | | | | | x | | x | | | | x | x |
| Physical Exam[12] | x | x | | x | x | x | x | x | x | x | x | | x | x |
| Vital Signs[13] | x | x | | x | x | x | x | x | x | x | x | | x | x |
| Body Temperature | x | x | | | | | | | | | | | | x |
| ECG | x | x | | | | | x | W24 only | x | | W48 & W64 only | | x | |
| Safety Lab. Tests[14] | x | x | | x | x | x | x | x | x | x | x | | x | x |
| Pruritus: Visual Analogue Score, 5D-itch scales[15] | | x | x | x | x | x | x | x | x | x | x | | x | x |
| QoL Scales[16] | | x | | | | | x | W24 only | x | | W48 only | | x | x |
| Cardiovascular Score (ASCVD) | | x | | | | | | | | | | | x | |
| PT/PTT and INR | x | x | | x | x | x | x | x | x | x | x | | x | x |
| CV Markers[17] | | x | | x | x | x | x | x | x | x | x | | x | x |
| MRI-PDFF | x | | | | | | x | | | | | | x | |
| Inflammatory Markers[18, 19] | | x | | | | | x | | | | | | x | |
| ELF Panel, PRO C3 [17] | | x | | | | | x | | | | | | x | |
| FGF-19, C4, BA[20] | | x | | x | x | x | x | x | x | x | x | | x | |
| PK samples[21] | | x | | x | x | x | x | x | x | x | x | | x | |
| CK-18 and GLP-1[17] | | x | | | | | x | W24 only | x | | W48 only | | x | |
| Study Drug Dosing[22] | | Daily Dosing | | | | | | | | | | | | |
| Drug Accountability | | x | x | x | x | x | x | x | x | x | x | x | x | |
| Concomitant Medication | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| AE/SAE | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Exploratory research samples[17] | | x | | | | | x | W24 only | x | | W48 only | | x | |

[1] Screening assessments should be conducted within 70 days prior to the first dose of study drug (ie, Study Days -70 to -1).
[2] At Weeks 52, 60 and 68, the site will contact the subject by phone to verify results of the home pregnancy test (for female subjects of child-bearing potential) and assess drug accountability, concomitant medications and AE/SAEs.
[3] On Day 1, all samples are to be collected predose; two additional PK and PD samples will be collected postdose as noted in Sections 8.4.4 and 8.4.5.
[4] Day 7 is a phone contact, not an in-clinic visit.
[5] Subjects should take their last dose of study drug at the Week 72 visit. Subjects who return for their EOT Visit after Week 72, should stop dosing during Week 72 as instructed by the site. Subjects who discontinue the study early should complete the EOT procedures within one week following discontinuation of study drug. For subjects who discontinued between Weeks 10 and 12, an MRI and MRE must be conducted within one week following the last dose of study drug (if it cannot be conducted within one week, it should not be conducted and the reason recorded in the source documents). For subjects who had the MRI and MRE conducted at the Week 12 visit but discontinue treatment prior to Week 36, no additional MRI and MRE will be conducted. For subjects who discontinue treatment at Week 36 or later, the MRI and MRE should be conducted within 2 weeks after discontinuing treatment, and only one PK sample will be obtained.
[6] Informed consent must be obtained prior to conducting any study-specific procedures or assessments.
[7] The biopsy may be obtained either 1) during the Screening window or 2) within 26 weeks prior to the Screening visit. If done during the study screening window, the biopsy should be performed once all other I/E criteria have been met.
[8] FSH testing required only in female subjects with cessation of menses between 1 to 2 years
[9] Serum pregnancy testing: All female subjects will undergo a serum pregnancy test at Screening and Baseline. In addition, all female subjects will have urine pregnancy testing at Baseline visit. Thereafter, all female subjects being of child-bearing potential at the time of Screening will continue having urine pregnancy tests at each visit throughout the study. A serum pregnancy test must be completed at the EOS visit in these subjects. If the urine pregnancy test is positive, a serum pregnancy test should be obtained as soon as possible.
[10] Urine pregnancy tests will be provided to females of child-bearing potential so that they can perform the test at home on Weeks 52, 60 and 68. If the urine pregnancy test is positive, a serum pregnancy test should be obtained as soon as possible.
[11] Height to be assessed at Screening only.
[12] Full physical exam (PE) at Screening, Week 12, and EOS Visit; subsequent PE should be targeted to review new signs and symptoms.
[13] Vital Signs include heart rate, respiratory rate, blood pressure, and will be measured predose.
[14] Safety laboratory tests include chemistry (including liver function tests), hematology, and urinalysis and should be collected predose at all visits; See Table 3 for details. eGFR will be calculated at all visits based on the MDRD formula. HbA1c will be obtained at Screening, Baseline, week 12, and Week 72..
[15] Pruritus scales (up to 2 scales) will be utilized to measure pruritus for every subject regardless of whether or not a subject experiences pruritus. Please refer to Section 8.3.5 and additional details included in the study binder.
[16] QoL includes SF-36 and CLDQ-NASH. In addition, Dermatology Life Quality Index (DLQI) will be completed at each in-clinic visit by subjects who reported pruritus until resolution. Additional details can be found in the study binder.
[17] Lipids and CV risk markers to be collected are detailed in Table 3.
[18] Markers of inflammation include fibrinogen, CRP, IL-6, IL-1β, TNF-α, TNF-β, alpha2 macroglobulin and haptoglobin (See Table 3).
[19] One sample will be collected from all subjects predose.
[20] Samples should be collected before the subject takes the daily dose of study drug. On Day 1 and Weeks 12, 36, and 72, samples should be collected predose and two samples postdose; the first postdose sample will be collected 1 to 3 hours after dosing and the second collected at least 1 hour later. At all other visits, samples will be collected only predose. If the subject took drug prior to their clinic visit, only one postdose sample should be collected.
[21] PK predose samples should be collected before the daily dose of study drug. On Day 1 and Weeks 12, 36, and 72, one PK sample should be collected predose and two samples postdose; the first postdose sample should be collected 1 to 3 hours postdose and the second postdose sample at least 1 hour later. At all other visits, PK samples will be collected predose. If the subject took drug prior to their clinic visit, only one postdose sample should be collected. For subjects who discontinue treatment early, collect one postdose sample at the EOT visit. For subjects with persistent transaminase or ALP elevations and evidence of liver injury and who remain on study drug, the one additional PK sample will be collected at each visit where safety labs are obtained.
[22] See Section 5.7 for details.