CLINICAL STUDY PROTOCOL

A Phase 2a, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of EYP001a in Patients With Nonalcoholic Steatohepatitis

Investigational Product: EYP001a
Protocol Number: EYP001-202
EudraCT Number: 2018-003119-22

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SIGNATURE PAGE

STUDY TITLE: A Phase 2a, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of EYP001a in Patients With Nonalcoholic Steatohepatitis

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature	Date
DocuSigned by: Pietro SCALFARO B96563AB23574A4...	3/24/2020

Pietro Scalfaro, MD
Chief Medical Officer
ENYO Pharma SA

INVESTIGATOR AGREEMENT

By signing below, I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by ENYO Pharma SA to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to ENYO Pharma SA and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by ENYO Pharma SA, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Ethics Committee regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Phase 2a, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of EYP001a in Patients With Nonalcoholic Steatohepatitis

PROTOCOL NUMBER: EYP001-202

INVESTIGATIONAL PRODUCT: EYP001a

PHASE: 2a

INDICATION: Nonalcoholic steatohepatitis (NASH)

OBJECTIVES:

The primary objective is to determine the efficacy and safety profiles of EYP001a versus placebo on liver fat content (LFC) from baseline to Week 12 in patients with NASH.

The secondary objectives are the following:

- To explore the pharmacokinetics (PK) of EYP001a
- To evaluate pharmacodynamic (PD) effects of EYP001a on bile acid-related markers as appropriate
- To assess the effects of EYP001a on lipid and metabolic profiles
- To assess the safety of EYP001a with statin coadministration
- To assess the effects of EYP001a on noninvasive biomarkers of liver fibrosis and inflammation

POPULATION:

Inclusion Criteria

A patient who meets all of the following criteria will be eligible to participate in the study:

1. Provides signed written informed consent and agrees to comply with the study protocol.
2. Is a male or female aged 18 years or older.
3. Has a suspected diagnosis of NASH during the Screening Period (up to 12 weeks before dosing), defined as follows:
    a. Baseline serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be established by at least 2 samples obtained at least 4 weeks and no more than 12 weeks apart. One sample can be obtained from the patient's medical history and 1 sample can be obtained during the Screening Period, or both samples can be obtained during the Screening Period. If the values of ALT or AST in both samples are within normal ranges, the variability of the marker is assumed adequate for randomization. If the values of ALT or AST are higher than normal values, the patient will be eligible for

enrollment provided the increase from the first to second sample is ≤40%. If the values from sample 1 are higher than those from sample 2 (ie, there is a decrease), the patient will be eligible despite a >40% difference. A third sample can be collected if an increase from sample 1 to sample 2 exceeds the 40% limit. If sample 3 exceeds the 40% limit (compared to sample 1), this increase shall prompt the search for clinical signs or symptoms of liver impairment, and the patient will not be eligible for enrollment. Baseline AST values should be >20 U/L. See Appendix I for central laboratory normal reference ranges.

b. Normal average baseline levels of alkaline phosphatase (ALP). See Appendix I for central laboratory normal reference ranges. Total bilirubin (TBL) levels should be ≤22.2 µmol/L (1.3 mg/dL).

   Note: Baseline serum ALP and TBL should be established by at least 2 samples obtained at least 4 weeks and no more than 12 weeks apart. One sample can be obtained from the patient's medical history and 1 sample can be obtained during the Screening Period, or both samples can be obtained during the Screening Period. If the values of ALP or TBL in both samples are within normal ranges, the variability of the marker is assumed adequate for randomization. If the values of ALP or TBL are higher than normal values, the patient will be eligible for enrollment provided the increase from the first to second sample is ≤40%. If the values from sample 1 are higher than those from sample 2 (ie, there is a decrease), the patient will be eligible despite a >40% difference. A third sample can be collected if an increase from sample 1 to sample 2 exceeds the 40% limit. If sample 3 exceeds the 40% limit (compared to sample 1), this increase shall prompt the search for clinical signs or symptoms of liver impairment, and the patient will not be eligible for enrollment.

c. Liver stiffness compatible with liver fibrosis stage F2 or F3 determined by FibroScan® vibration-controlled transient elastography assessment cut-off value ≥8.5 kPa.

d. FibroScan controlled attenuation parameter (CAP) for steatosis with cut-off values >300 dB/m.

   Note: Patients do not need to undergo a CAP assessment if their medical records indicate a magnetic resonance imaging (MRI)-proton density fat fraction (MRI-PDFF) LFC ≥10% within 12 months prior to screening.

   Note: Histology within 12 months prior to screening will supersede FibroScan entry criteria if the following criteria are met: NASH with fibrosis stage F2 to F3, defined as portal fibrosis with few septa (F2) or bridging septa between central and portal veins (F3), and nonalcoholic fatty liver disease (NAFLD) activity score ≥4, including a minimum of 1 point each for ballooning and inflammation. However, if a patient participated in a previous study with a NASH investigational drug between 365 and 60 days prior to being screened for this study, the histology information will only be considered if the biopsy was performed after the end of the patient's participation in the previous study.

e. LFC ≥10% as measured by MRI-PDFF.

4. Is not of childbearing potential (as defined in Inclusion Criterion 5) or, if of childbearing potential, is not pregnant as confirmed by a negative serum human chorionic gonadotropin test at screening and is not planning a pregnancy during the course of the study.

5. Women of childbearing potential and male patients with female partners must agree to use highly effective birth control throughout the duration of the study and for 90 days after stopping study drug. Patients who are using hormonal contraceptives or intrauterine devices should be instructed to use an additional barrier contraceptive measure during the study such as a male or female condom with spermicide or diaphragm. Highly effective is defined as birth control methods that result in a failure rate of <1% per year when used consistently and correctly. Methods of highly effective birth control include the following:

   a. Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation.

      - Oral.
      - Intravaginal.
      - Transdermal.

   b. Progesterone-only hormonal contraception associated with inhibition of ovulation.

      - Oral.
      - Injectable.
      - Implantable.

   c. Intrauterine device.

   d. Intrauterine hormone-releasing system.

   e. Vasectomized partner (provided that the partner is the sole sexual partner of the woman of childbearing potential).

   f. Sexual abstinence (complete abstinence from sexual intercourse if this is the patient's usual and preferred lifestyle).

   Note: A woman is considered of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile. A postmenopausal state is defined as no menses for ≥12 consecutive months without an alternative medical cause. A follicle-stimulating hormone level in the postmenopausal range will be used to confirm a postmenopausal state in women ≤55 years of age. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Exclusion Criteria

A patient who meets any of the following criteria will be excluded from participation in the study:

1. Is an employee of a clinical research organization, vendor, or Sponsor involved with this study.
2. Has known non-NASH liver disease, including, but not limited to, alcoholic liver disease, autoimmune disease, human immunodeficiency virus, hepatitis B virus, active hepatitis C virus (HCV), Wilson's disease, hemochromatosis, primary biliary cholangitis, primary sclerosing cholangitis, drug-induced liver injury, bile duct obstruction, or suspected or known liver cancer.

Note: HCV antibody (HCV Ab) positive individuals are not eligible, with the following 2 exceptions: (a) Patients previously treated with a registered drug for viral hepatitis C with at least a 1-year period since documented sustained virologic response may be eligible if HCV ribonucleic acid (RNA) is below the limit of detection (LOD) and if all other eligibility criteria are met, and (b) patients with presence of HCV Ab if HCV RNA is below the LOD at screening without treatment (ie, spontaneous clearance) may be eligible if all other eligibility criteria are met.

3. Has history of cirrhosis or liver decompensation, including ascites, hepatic encephalopathy, or presence of esophageal varices.
4. Has known history of alcohol abuse or daily heavy alcohol consumption (females: more than 14 units of alcohol per week; males: more than 21 units of alcohol per week [1 unit of alcohol is equivalent to a half pint of beer {285 mL}, 1 measure of spirits {25 mL}, or 1 glass of wine {125 mL}]). Has an Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score of ≥3 points for men and women AND a full Alcohol Use Disorders Identification Test (AUDIT) score of ≥8 points at screening.

   Note: Only patients with AUDIT-C scores ≥3 points at screening will receive the full AUDIT and will be excluded if they score ≥8 points on the full AUDIT. Patients with AUDIT-C scores <3 points will not receive the full AUDIT.
5. Has Gilbert's syndrome with direct bilirubin >1 × upper limit of normal (ULN).
6. Is pregnant or breastfeeding.
7. Has clinically relevant immunosuppression, including, but not limited to, immunodeficiency conditions such as common variable hypogammaglobulinemia.
8. Has a known preexisting medical or psychiatric condition that could interfere with the patient's ability to provide informed consent or participate in study conduct, or that may confound study findings.
9. Has, in the opinion of the Investigator, clinically significant cardiovascular or cerebrovascular disease within 90 days prior to the first study drug administration, including, but not limited to, myocardial infarction, acute coronary syndrome, revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or ischemic stroke, or implanted defibrillator or pacemaker.
10. Has participated in any drug study within 90 days prior to the first study drug administration in the current study.
11. Has had major surgery within 90 days prior to the first study drug administration in the current study.
12. Has a history of relevant drug and/or food allergies. The term "relevant" applies if any of the following allergy conditions are met:
    a. Has had several episodes of drug-induced urticaria or other immediate allergic signs (eg, rhinoconjunctivitis, respiratory) (≥2 in total at whatever time in medical history and with 1 or several drugs).

b. Has ongoing urticaria episodes (attributed to whatever allergen) or has other active history of immediate type reaction allergies (eg, allergic rhinoconjunctivitis, allergic asthma, or latex allergy).

c. Has had a moderate or severe allergic reaction (≥Grade 2 per the World Allergy Organization reference table, ie, urticaria alone with a Grade 1 is not relevant).

d. Has any allergic condition that might require an emergency epinephrine injection (similar to the EpiPen® Auto-Injector).

13. Has a history of hypersensitivity to the study drug or to any of the excipients or placebo.

14. Unable to undergo an MRI-PDFF due to:

a. Contraindication to MRI examination.

b. Severe claustrophobia impacting ability to perform MRI during the study, despite mild sedation/treatment with a short half-life (ie, <20 hours) anxiolytic.

c. Body weight or girth exceeding the scanner capacities.

15. Is using any of the following disallowed medications:

a. Anticancer drug(s), immunomodulator(s), or immunosuppressant(s) within 90 days or 5 half-lives prior to screening, whichever is longer, or any drug historically associated with NAFLD for >2 weeks in the year prior to screening (eg, amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, or valproic acid or other known hepatotoxins at the Investigator or Medical Monitor's discretion).

b. Vitamin E (>400 IU/day), glitazones, glucagon-like peptide-1 receptor agonists, ursodeoxycholic acid, or obeticholic acid within 90 days prior to screening.

c. Agents (including herbal over-the-counter weight loss preparations) or medications known to significantly impact body weight within 90 days prior to screening (eg, sibutramine, phenetamine, and orlistat).

d. Bile acid sequestrants (eg, cholestyramine) or lipid-modifying agents (eg, fibrates or ezetimibe) other than rosuvastatin, atorvastatin, simvastatin, pravastatin, fluvastatin, or lovastatin.

e. Agents that are substrates for cytochrome P450 (CYP) 2C8 or CYP2C9 and have a narrow therapeutic index (eg, warfarin).

16. Has prior or planned (during the study period) bariatric surgery (eg, gastroplasty or Roux-en-Y gastric bypass).

17. Has type 1 diabetes mellitus.

18. Has type 2 diabetes mellitus (T2DM) and hemoglobin A1c >9.5% or has not been on a stable dose of antidiabetic medication for at least 90 days prior to screening.

19. Has had total body weight loss of >5% within 6 months or since a liver biopsy, if applicable.

20. Has any of the following exclusionary laboratory results at screening:
    a. ALT >5 × ULN, AST >5 × ULN.
    b. International normalized ratio ≥1.3, unless on anticoagulant therapy.
    c. Platelet count <lower limit of normal.
    d. Estimated glomerular filtration rate <50 mL/min/1.73 m^2 (the Modification of Diet in Renal Disease formula).
    e. Creatine kinase (CK) >ULN in patients on concomitant statin therapy and CK >3 × ULN in all other patients.
    f. Thyroid-stimulating hormone >1.5 × ULN or abnormal free triiodothyronine or free thyroxine.

    Note: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor if any of the above laboratory abnormalities are found.
21. Has history of clinically significant gastrointestinal disease (especially: cholecystectomy prior to age 25 years, peptic ulcerations, gastrointestinal bleeding, inflammatory bowel disease, or bariatric surgery); renal, hematologic, endocrine, oncologic, pulmonary, immunologic, or cardiovascular disease; neurologic or psychiatric disease (including any use of addictive substances such as regular opioid treatment and/or any use of illicit drugs); or any other condition, which, in the opinion of the Investigator, would jeopardize the safety of the patient or impact the validity of the study results.
22. Has a body mass index >45 kg/m^2.

STUDY DESIGN AND DURATION:

This is a 2-part, randomized, double-blind, multicenter, placebo-controlled study to evaluate the safety and efficacy of EYP001a in patients with NASH who likely have stage F2 to F3 fibrosis at approximately 50 global clinical sites. Overall, approximately 114 eligible patients will be enrolled: 24 patients in Part A (Safety Run-in Cohort), followed by 90 patients in Part B.

In Part A, 24 patients will be randomized on Day 1 to 1 of 4 parallel treatment groups: 100 mg EYP001a twice daily (BID), 200 mg EYP001a once daily (QD), 400 mg EYP001a QD, or placebo BID. In Part B, 90 patients will be randomized on Day 1 to 1 of 3 parallel treatment groups: 100 mg EYP001a QD, 200 mg EYP001a QD, or placebo QD.

Randomization will be stratified by statin use (yes, no) and T2DM status (yes, no) at screening in Part A, and by statin use (yes, no) and LFC (stratification factor with 3 categories: LFC<16%, 16%≤LFC<22%, and 22%≤LFC) in Part B at screening.

The following sequence of screening procedures will be applied to each patient who signs an informed consent form: 1) eligibility based on clinical and biological inclusion and exclusion criteria; 2) eligibility based on FibroScan criteria as described in Inclusion Criterion 3; and 3) confirmation of eligibility based on MRI-PDFF results. A patient who is first designated as a screen failure prior to being randomized may be rescreened upon Sponsor or designee approval. If the patient was screen failed after the MRI-PDFF was completed, the original MRI-PDFF scan may be utilized for rescreening, provided it was obtained within 1 month prior to rescreening.

Part A (Safety Run-in Cohort)

Participation in Part A of the study will consist of a Screening Period (up to 12 weeks prior to Day 1), a 12-week Treatment Period, and a Follow-up Visit at Week 14; total study duration is up to 182 days. All eligibility criteria must be confirmed prior to dosing on Day 1.

The 12-week Treatment Period in Part A will include 7 study visits on the following days: Days 1, 7, 14, 21, 28, 56, and 84. Clinical, hematological, chemical, PD, and PK parameters will be assessed throughout the study. Intense PK/PD profiling on Days 1 and 14 will require 12-hour inpatient monitoring and 24-hour post-morning dose blood collection. Safety and tolerability assessments will include the monitoring of adverse events; adverse events of special interest (AESIs) (ie, pruritus, drug-induced liver injury, and all muscle-related adverse events); serious adverse events (SAEs); and findings from physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory parameters.

Throughout the study, all treatment-emergent adverse events (TEAEs), clinical assessments, and clinical laboratory parameters will be closely monitored against the criteria for drug-induced liver injury and muscle toxicity as detailed in the Clinical Safety Monitoring Plan (Appendix E). All adverse events will be assessed and reported using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grading system. Additional safety measurements will be performed at the discretion of the Investigator (or delegate). Except during the Safety Run-in Period, plasma from blood samples will be collected at each visit and stored for protocol-related safety testing or exploratory analyses.

Part B (Remaining Patients)

Patients in Part B will be randomized on Day 1 to 1 of 3 parallel treatment groups: 100 mg EYP001a QD, 200 mg EYP001a QD, or placebo QD, with approximately 30 patients in each group. Pruritus-related tolerance issues will be addressed by a 2-step study drug titration strategy for the highest dose treatment group (ie, 200 mg QD): all patients randomized to an active treatment group will start with an initial dose of 100 mg QD for the first 2 weeks of treatment (Days 1 to 14). Patients randomized to the 200 mg QD treatment group will be uptitrated to 200 mg QD starting Day 15 until Day 84, while patients randomized to the 100 mg QD treatment group will maintain a 100 mg QD dose throughout their participation. The study treatment assignment strategy will ensure that blind is maintained.

Randomization will be stratified by statin use (yes, no) and LFC (stratification factor with 3 categories: LFC<16%, 16%≤LFC<22%, and 22%≤LFC) at screening.

Participation in Part B of the study will consist of a Screening Period (up to 12 weeks prior to Day 1), a 12-week Treatment Period, and a Follow-up Visit at Week 14; total study duration is up to 182 days. All eligibility criteria must be confirmed prior to dosing on Day 1.

The 12-week Treatment Period in Part B will include 7 study visits on the following days: Days 1, 14, 28, 42, 56, 70, and 84. Clinical, hematological, chemical, PD, and PK parameters will be assessed throughout the study. The safety and tolerability assessments will include the monitoring of adverse events; AESIs (ie, elevation of transaminases and all muscle-related adverse events); SAEs; and findings from physical examinations, vital signs, ECGs, and clinical laboratory parameters.

Throughout the study, all TEAEs, clinical assessments, and clinical laboratory parameters will be closely monitored against the criteria for drug-induced liver injury and muscle toxicity as detailed in the Clinical Safety Monitoring Plan (Appendix E). All adverse events will be assessed and reported using the National Cancer Institute CTCAE Version 5.0 grading system. Additional safety measurements will be performed at the discretion of the Investigator (or delegate). At screening and on Days 1, 14, 28, 56, and 84; and at the End of Study (EOS) and Early Termination (ET) Visits, plasma from blood samples will be stored for protocol-related safety testing or exploratory analyses.

Data Safety Monitoring Committee and Interim Analyses

An external, independent Data Safety Monitoring Committee (DSMC) will review all available unblinded preliminary safety, PK, and PD results when any stopping rules are met, per the Clinical Safety Monitoring Plan (Appendix E). In Part B, the DSMC will be promptly notified for further review if any patients experience ALT, AST, or bilirubin elevations 2 × above baseline values.

In addition, all available unblinded preliminary safety, PK, and PD results will be comprehensively reviewed during 2 interim analysis timepoints:

- The first interim analysis will be performed at the end of the Safety Run-in Period, after the last of the 24 patients randomized in Part A has completed Day 28 (Week 4). It is anticipated that at the time of the first interim analysis, approximately 10 patients will have completed Day 84 (Week 12) of Part A.
- A second interim analysis will be performed when 50% of patients in Part B have completed Day 56 (Week 8).

The interim analyses will be performed on all available primary and secondary endpoints according to the DSMC charter, which describes the overall guidelines, composition, roles, and responsibilities of the independent DSMC for this study, including the selection of DSMC members, timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings, data analysis recommendations, and DSMC relationships with other parties participating in the conduct of this study. Patient accrual will continue throughout the period of DSMC review. The DSMC will advise on the accrual of the remaining patients per protocol or on any amendments that are necessary for safety reasons.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

EYP001a will be supplied as 100 and 200 mg immediate-release coated tablets for oral administration.

Placebo tablets for oral administration will appear identical to EYP001a.

EFFICACY VARIABLES:

The primary efficacy variable is absolute change in LFC as measured by MRI-PDFF from baseline to Week 12.

The secondary efficacy variables include the following:

- Proportion of patients with ≥5% absolute reduction in LFC as measured by MRI-PDFF from baseline to Week 12

- Proportion of patients with ≥10% absolute reduction in LFC as measured by MRI-PDFF at Week 12
- Proportion of patients with ≥20% absolute reduction in LFC as measured by MRI-PDFF at Week 12
- Proportion of patients with a relative reduction in LFC ≥20% as measured by MRI-PDFF at Week 12
- Proportion of patients with a relative reduction in LFC ≥30% as measured by MRI-PDFF at Week 12
- Percent change (relative reduction) in LFC as measured by MRI-PDFF from baseline to Week 12
- Change and percent change in imaging-derived mean iron-corrected T1 from baseline to Week 12
- Change and percent change in waist to hip ratio from baseline to Week 12 (Part B only)
- Change and percent change in waist to height ratio from baseline to Week 12 (Part B only)
- Change in the following biomarkers of liver fibrosis and inflammation: ALT, AST, AST/ALT ratio, adiponectin, high sensitivity C-reactive protein, interleukin 6, tumor necrosis factor alpha, cytokeratin-18, fibronectin, hyaluronic acid, procollagen type III N-terminal peptide, tissue inhibitor of metalloproteinases-1 (and derived enhanced liver fibrosis score), Pro-C3, and chitinase-3-like protein 1 (also known as YKL-40) from baseline to Week 4, Week 8, and Week 14/ET, as applicable

PHARMACOKINETIC VARIABLES:

In Part A, during the Safety Run-in Period, intense PK sampling will occur on Day 1 (±1 day) and Day 14 (±1 day) at the following timepoints: 0 (predose), 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose; samples will be collected in the fasted state predose to 4 hours postdose, inclusive. Sparse PK samples will be collected for all other visits. Plasma samples to assess trough concentrations of EYP001a will be collected predose (fasting) in the morning and 2 hours postdose (an optional sample may also be collected at 6 hours postdose) at the following visits: Days 7, 21, 28, 56, and 84. A sample will also be collected at the EOS and ET Visits.

In Part B, sparse PK sampling will occur predose (fasting) at the following visits: Days 1, 14, 28, 56, and 84. A sample will also be collected at the EOS and ET Visits.

At the ET Visit (if applicable), the PK sample should be collected within 24 to 48 hours of last intake of study drug. The date and time of the PK draw and the last dose of study drug must be recorded in the electronic case report form (eCRF).

Pharmacokinetic samples will be collected in a fasted state, defined as nothing by mouth except water for ≥6 hours, at all predose sampling timepoints (in Parts A and B) and at the 1- to 4-hour postdose timepoints (inclusive) on Days 1 and 14 of Part A. For BID dosing, PK timepoints will be based on the time of morning dosing.

PHARMACODYNAMIC VARIABLES:

In Part A, intense PD sampling will occur on Day 1 (±1 day) and Day 14 (±1 day) at the following timepoints: 0 (predose, fasting), 4 (fasting), 6, 10, 12, and 24 hours postdose. Sparse PD sampling will also occur predose (fasting) and 2 hours postdose at the following visits: Days 28, 56, and 84. A sample will also be collected at the EOS and ET Visits.

In Part B, sparse PD sampling will occur predose (fasting) at the following visits: Days 1, 14, 28, 56, and 84. A sample will also be collected at the EOS and ET Visits.

At the ET Visit (if applicable), the PD sample should be collected within 24 to 48 hours of last intake of study drug. The date and time of the PD draw and the last dose of study drug must be recorded in the eCRF.

Pharmacodynamic samples will be collected in a fasted state, defined as nothing by mouth except water for ≥6 hours, at all predose sampling timepoints (in Parts A and B) and at the 4-hour postdose timepoint on Days 1 and 14 in Part A. For BID dosing, PD sampling timepoints will be based on the time of morning dosing.

Parameters will be measured in plasma samples using a validated method. Pharmacodynamic sampling will assess plasma levels of 7αhydroxy-4-cholesten-3-one; fibroblast growth factor 19; and total, primary, and secondary bile acids (such as chenodeoxycholic acid, deoxycholic acid, lithocholic acid, and/or others as appropriate).

SAFETY VARIABLES:

Safety and tolerability assessments will include the monitoring of adverse events; AESIs (ie, pruritus [Part A only], drug-induced liver injury [Part A only], elevation of transaminases [Part B only], and all muscle-related adverse events); SAEs; and findings from physical examinations, vital signs, ECGs, and clinical laboratory parameters.

Throughout the study, all TEAEs, clinical assessments, and clinical laboratory parameters will be closely monitored against the criteria for drug-induced liver injury and muscle toxicity as detailed in the Clinical Safety Monitoring Plan (Appendix E).

All adverse events will be assessed and reported using the National Cancer Institute CTCAE Version 5.0 grading system. Additional safety measurements will be performed at the discretion of the Investigator (or delegate).

STATISTICAL ANALYSES:

Analysis Populations

The Intent-to-Treat (ITT) Population includes all patients who are randomized and administered at least 1 dose of study drug. Patients without a Week 12 or end of treatment MRI-PDFF assessment will be imputed as nonresponders.

The Safety Population is identical to the ITT Population.

The modified ITT (mITT) Population includes patients from the ITT Population who have valid baseline and Week 12 MRI-PDFF measurements of LFC.

The Per-Protocol Population includes all patients from the mITT Population who finish the 12-week Treatment Period without any major protocol violations. The analysis of LFC as measured by MRI-PDFF will be repeated on the Per-Protocol Population to test the robustness of results.

Efficacy Analysis

The efficacy analyses of LFC as measured by MRI-PDFF will be conducted on the ITT Population and repeated on the mITT and Per-Protocol Populations. The analysis of other efficacy variables will be based on the ITT Population.

For efficacy variables, observed data and change and/or percent change from baseline will be summarized using descriptive statistics and graphs per dose group and visit as appropriate.

The primary efficacy analysis will be performed on the ITT Population. Missing MRI-PDFF values at Week 12 or ET will be imputed based on the missing at random assumption using multiple imputation.

The primary efficacy analysis will be performed on the change in LFC as measured by MRI-PDFF from baseline to Week 12 or ET using an analysis of covariance (ANCOVA) model with baseline fat fraction as a covariate and treatment, use of statin comedication at screening (stratification factor: use of statin [yes, no]), and T2DM status (yes, no) in Part A, and by statin use (yes, no) and LFC at screening (stratification factor with 3 categories: LFC<16%, 16%≤LFC<22%, and 22%≤LFC) in Part B, as factors. Pairwise treatment comparisons between each EYP001a dose and placebo will be conducted from the ANCOVA model with least-square means, standard errors, 95% confidence intervals, and p-values being presented. To adjust the 3 tests (each EYP001a dose and placebo) for multiplicity in order to control the family-wise type I error at 0.025 one-sided, the Bonferroni method will be used.

The primary efficacy results will subsequently be analyzed by adding liver stiffness measurements and CAP values at enrollment as additional factors.

The statistical analysis of secondary efficacy variables based on change from baseline to Week 12 will be conducted with a similar ANCOVA model, while secondary efficacy variables measured at multiple timepoints will be analyzed by mixed effect model repeated measures model. The responder (categorical) variables will be analyzed by a Cochran-Mantel-Haenszel test, stratified by statin comedication use and T2DM status at screening in Part A and statin comedication and LFC at screening in Part B. The analysis of the responder variables will be repeated using logistic regression models, adjusting for treatment, statin comedication at screening, and T2DM status at screening. Patients without a Week 12 or end of treatment MRI-PDFF assessment will be imputed as nonresponders. All secondary efficacy variables will be summarized using descriptive statistics.

In addition, the anticipated EYP001-202 efficacy results will serve as validation of an in silico NASH disease model, which was built based on public and expert knowledge and combined with the Phase 1 PK and PD EYP001 results. The model integrates 309 liver farnesoid X receptor-related biological variables and 1320 parameters and explores the effect of different EYP001 treatment regimens on NASH-relevant efficacy endpoints in a virtual population. Iterations of the model will support future explorations of development strategies with different EYP001 Phase 2 and 3 study designs.

Sensitivity Analysis

Sensitivity analyses will be conducted by repeating the primary efficacy analysis based on:

- The ITT Population with missing MRI-PDFF values at Week 12 or ET imputed using the multiple imputation with tipping point method based on the missing not at random assumption
- The mITT Population

Pharmacodynamic Analysis

Pharmacodynamic parameters, observed data, and change and/or percent change from baseline will be summarized using descriptive statistics and graphs per dose group and visit, as appropriate.

Pharmacokinetic Analysis

Plasma concentrations of EYP001a will be listed for all patients with available EYP001a plasma concentrations in treatment groups that include EYP001a or placebo. All concentrations below the limit of quantification will be labeled as such in the concentration data listings and will be treated as 0 in the summary statistics.

Listings of individual patient plasma concentrations and actual blood sampling times and graphs of concentration versus time will be prepared by dose. Plasma concentrations will be summarized by and compared among different doses using descriptive statistics.

Safety Analysis

Baseline for physical examinations, all vital signs, 12-lead ECG measurements, pruritus questionnaire (Part A only), and clinical laboratory assessments will be defined as the last evaluation done before the first administration of study drug in each dose group on Day 1.

Safety variables will be tabulated and presented for the Safety Population.

The original terms used in the eCRF by Investigators to identify adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities. All adverse events will be assessed and reported using the National Cancer Institute CTCAE Version 5.0 grading system. A TEAE is defined as a new or worsening adverse event after the first dose of study drug. The percentage of patients with TEAEs will be summarized for each dose group by system organ class and preferred term. The study drug-related TEAEs and SAEs will be summarized in the same fashion. The TEAEs will also be summarized by system organ class, preferred term, and maximum severity. All SAEs and TEAEs leading to early discontinuation will be listed.

The safety of EYP001a with statin coadministration will be assessed based on the difference in frequency of TEAEs between treatment groups.

The clinical laboratory analytes, vital signs, and ECGs at each visit and their change from baseline will be summarized descriptively. Laboratory abnormalities based on predefined normal ranges will be tabulated by dose group showing patient counts and percentages. A listing of patients with any laboratory results outside the reference ranges will be provided if appropriate.

SAMPLE SIZE DETERMINATION:

The sample size of 114 randomized patients (n = 24 patients in Part A and n = 90 in Part B [n = 30 patients per treatment group]) is based on the efficacy endpoint: absolute change in LFC as measured by MRI-PDFF from baseline to Week 12, assuming that the treatment difference

between each active treatment group with placebo is at least 5.1% with a common standard deviation of 5.8%.

With a 2-sample Z-test with the power of 0.8 and an overall family-wise 1-sided alpha of 0.025 (or each active versus placebo alpha = 0.0125 after Bonferroni adjustment), 26 patients per treatment group will be needed to complete the Week 12 Visit. With the consideration of an approximately 13% dropout rate before Week 12, 30 patients will be randomized per treatment group in Part B.

SITES: Approximately 50 global clinical sites

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUDIT	Alcohol Use Disorders Identification Test
AUDIT-C	Alcohol Use Disorders Identification Test-Concise
BID	Twice daily
BMI	Body mass index
C4	7αhydroxy-4-cholesten-3-one
CAP	Controlled attenuation parameter
CFR	Code of Federal Regulations
CK	Creatine kinase
C_{max}	Maximum observed plasma concentration
CRA	Clinical Research Associate
cT1	Iron-corrected T1
CTA	Clinical trial authorization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EIU	Exposure in Utero
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
FGF19	Fibroblast growth factor 19
FXR	Farnesoid X receptor
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody

Abbreviation	Definition
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LDL-C	Low-density lipoprotein cholesterol
LFC	Liver fat content
LOD	Limit of detection
LSM	Liver stiffness measurement
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging-proton density fat fraction
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
po	Orally
QD	Once daily
RNA	Ribonucleic acid
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
T2DM	Type 2 diabetes mellitus
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach the maximum observed plasma concentration
ULN	Upper limit of normal
VCTE	Vibration-controlled transient elastography
WHO	World Health Organization
WHR	Waist to hip ratio
WHtR	Waist to height ratio

1 INTRODUCTION AND BACKGROUND INFORMATION

Nonalcoholic steatohepatitis (NASH) is the most common chronic liver disorder in western countries and involves steatosis, defined as liver fat content (LFC) >5%, leading to inflammation with hepatocyte injury. It is estimated that more than 5% of the population has advanced NASH. Its main consequence is liver fibrosis, which can progress to cirrhosis and hepatocellular carcinoma. Currently no registered drug therapy exists for this disease, which represents an important challenge.

Clinical studies show evidence linking liver fat improvements in NASH with histological improvements. A study with ezetimibe for 24 weeks showed that histologic responders had approximately 30% relative LFC reduction on magnetic resonance imaging (MRI)-proton density fat fraction (MRI-PDFF) relative to a 2% increase for nonresponders.[1] Findings in the FLINT study with farnesoid X receptor (FXR) agonist obeticholic acid showed that with reductions in LFC of ≥30%, there were greater odds of histologic response based on 2-point nonalcoholic fatty liver disease (NAFLD) activity score reduction.[2]

A randomized, double-blind, placebo-controlled study with recombinant injected fibroblast growth factor 19 (FGF19) drug NGM282 for 12 weeks showed robust efficacy with -9.7% to -11.9% significant absolute LFC changes assessed via MRI-PDFF, as compared to -0.9% for placebo.[3] An extension of this main study with a small group of patients (n = 22) who were assessed with paired MRI-PDFF and liver histology at baseline and Week 12[4] adds to the growing body of evidence showing how improvements in LFC may translate into histological changes.

Improvements in liver histology are accepted surrogate endpoints for registration studies because they eventually translate to lower rates of liver transplant and liver disease progression. While there have not been enough studies conducted to demonstrate with scientific certainty that improvements in LFC assessed by noninvasive measurements, like MRI-PDFF, lead to clinically relevant outcomes, MRI-PDFF is an accepted endpoint of early stage proof-of-concept NASH studies.

EYP001a is an agonist of the FXR, a key regulator of bile, lipid, and glucose metabolism, currently under clinical investigation as a new therapy for a functional cure of chronic hepatitis B virus (HBV) infection. In an experimental rodent model of NASH,[5] EYP001a analogue def2572 has been shown to reduce liver steatosis, inflammation, apoptosis, and fibrosis. Moreover, FXR activation with the bile improved the histological features of NASH in patients with noncirrhotic NASH.[2]

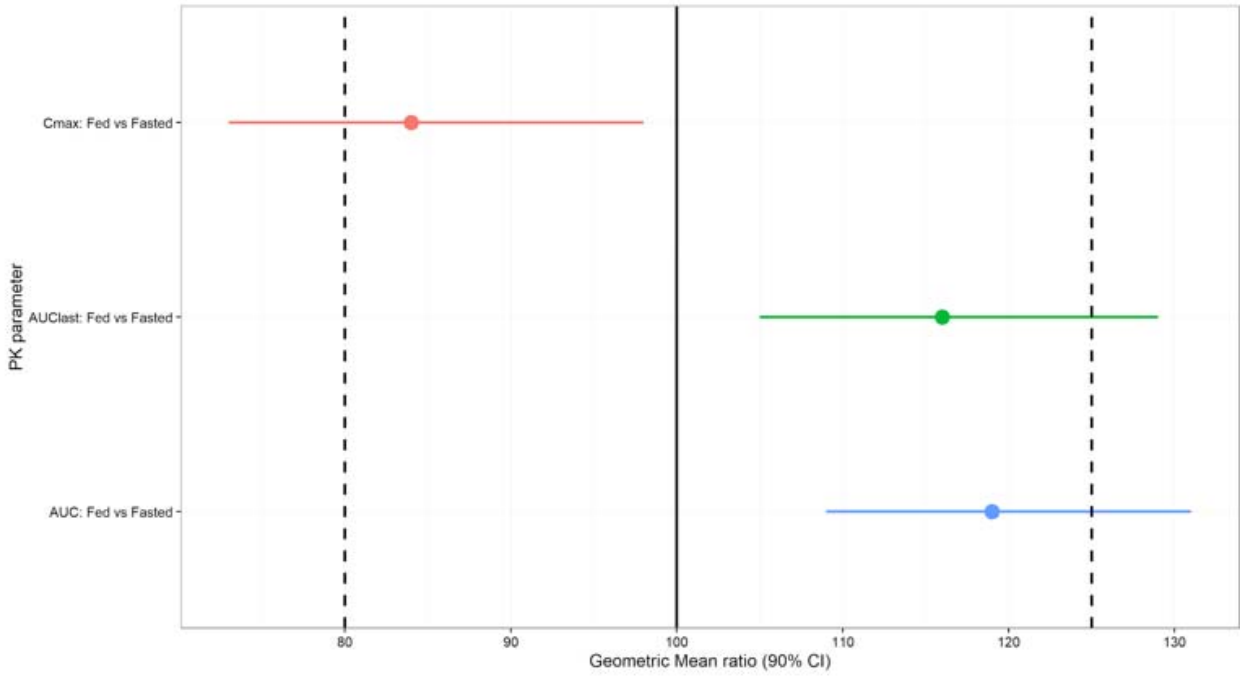
1.1 Rationale

The purpose of this Phase 2a study is to assess the effects of EYP001a compared with placebo on markers of LFC, inflammation, and fibrosis with respect to safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and lipid/metabolic profiles in patients with NASH with likely stage F2 to F3 fibrosis.

EYP001a Phase 1 data in healthy subjects showed that EYP001a was well tolerated after single and multiple oral administration from 30 to 800 mg (single ascending dose) and from 60 to 500 mg (multiple ascending dose). After single administration of EYP001a up to 500 mg, maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) from time 0 to infinite time seemed linear, but increased less than proportionally at the single-dose

level of 800 mg. After multiple administrations, C_{max} and AUC increased less than proportionally to the dose. In general, C_{max} and AUC were lower after repeated administrations compared to single administration. EYP001a elimination was on average fast: apparent elimination half-life associated with the terminal slope of the semilogarithmic EYP001a concentration-time curve was around 2 to 3 hours, with a tendency for faster elimination after multiple dosing. In 11 patients with chronic HBV infection randomized to 4 cross-over single-dose oral treatment periods receiving 300 mg EYP001a fasted or fed, either in the morning or evening, the relative EYP001a bioavailability and FXR-related PD were assessed. EYP001a PK in HBV patients seemed to be slightly influenced by food, with a delay of a few hours (ie, time to reach C_{max} [T_{max}]) in the absorption process, leading to a lower C_{max}. EYP001a exposure (ie, AUC) appeared to be higher under food conditions, but the variability of EYP001a PK and the small number of patients (n = 11) prevented a demonstration of bioequivalence on C_{max}, AUC from time 0 to the time of the last quantifiable concentration, and AUC. Finally, for all dosing conditions, despite similar rapid EYP001a elimination, FGF19 and 7αhydroxy-4-cholesten-3-one (C4) showed a prolonged FXR target engagement over at least 24 hours, which was not influenced by fasting or fed condition or by morning or evening administration.

Figure 1. Effects of Food Intake on EYP001a Pharmacokinetic Parameters

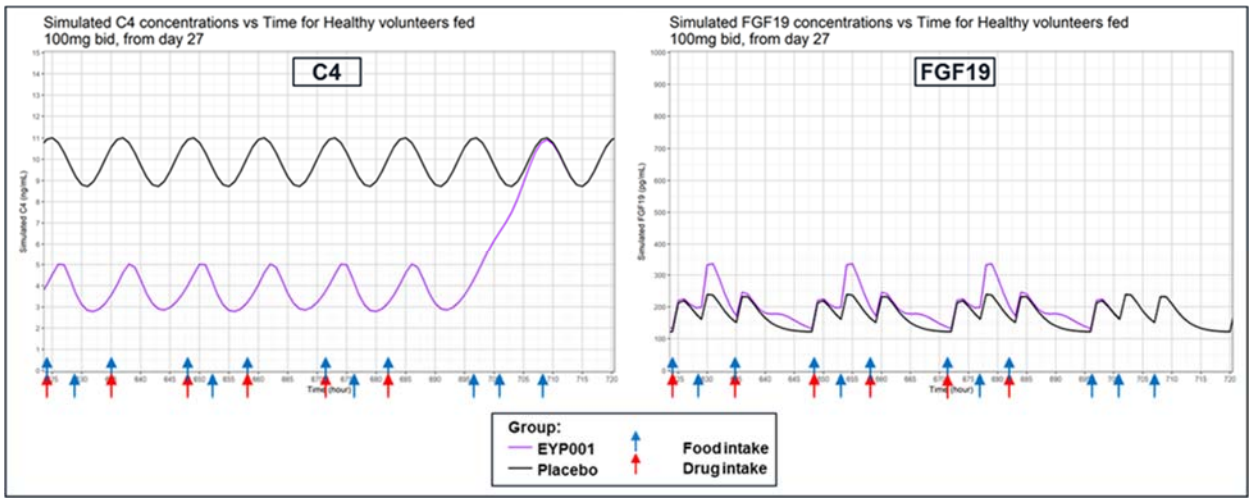


AUC = area under the plasma concentration-time curve; AUC_{last} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed plasma concentration; PK= pharmacokinetic; vs = versus.

Population PK/PD models linking EYP001a and FGF19, and C4 plasma concentrations originating from Phase 1 data (Studies EYP001-C01, EYP001-102, EYP001-103, and EYP001-104) were built. The PK model reflects an absorption phase slowed down by food intake (an increase of T_{max} and slight decrease of C_{max}) but with similar bioavailability. Pharmacodynamic modeling for C4 and FGF19 shows that C4 baseline production follows a circadian rhythm (periodicity = 12 hours) with no link with FGF19 production. An indirect response model with inhibition of C4 production

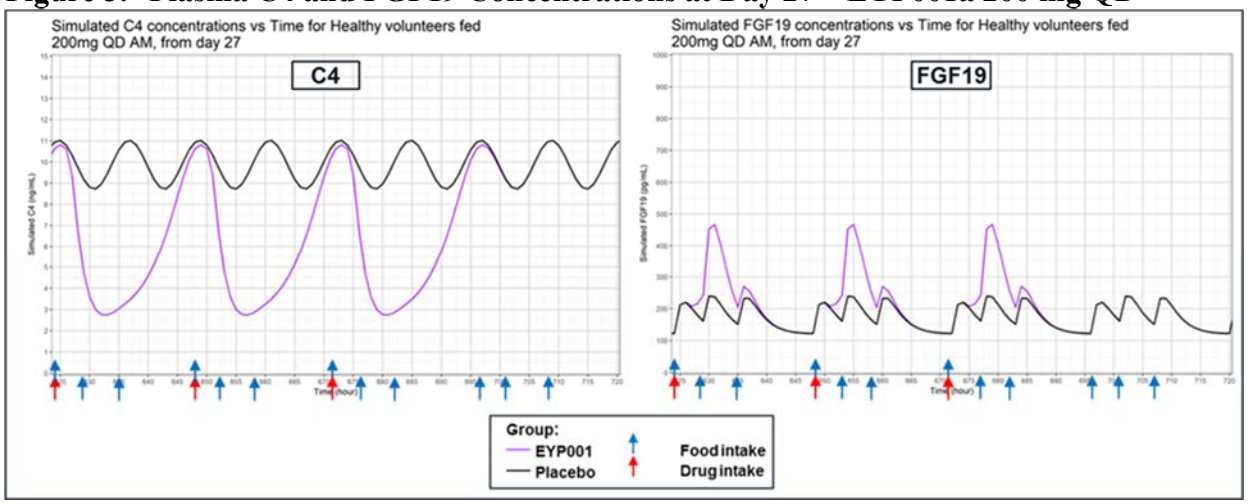
by EYP001a was simulated. The FGF19 baseline was impacted by meal intake. An indirect response model with stimulation of the FGF19 production by EYP001a was simulated.

Figure 2. Plasma C4 and FGF19 Concentrations From Day 27 – EYP001a 100 mg BID



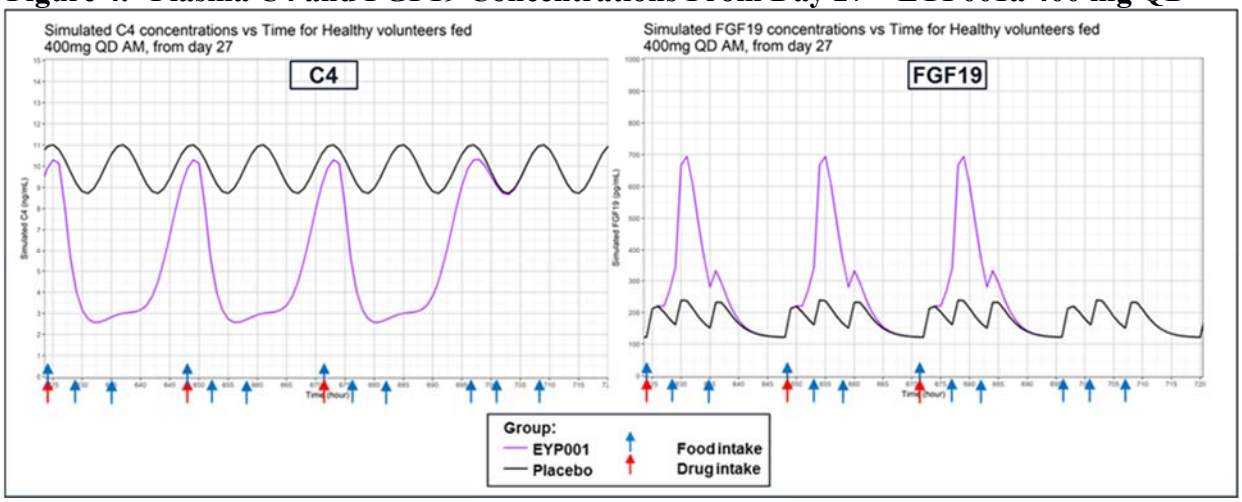
Purple curves are simulated profiles with EYP001a administered 100 mg BID (red arrows indicate 7:00 am and 6:00 pm dosing) with food (blue arrows indicate meals). Black curves are placebo, ie, physiological changes.
BID = twice daily; C4 = 7αhydroxy-4-cholesten-3-one; FGF19 = fibroblast growth factor 19; vs = versus.

Figure 3. Plasma C4 and FGF19 Concentrations at Day 27 – EYP001a 200 mg QD



Purple curves are simulated profiles with EYP001a administered 200 mg QD (red arrows indicate dosing at 7:00 am) with food (blue arrows indicate meals). Black curves are placebo, ie, physiological changes.
C4 = 7αhydroxy-4-cholesten-3-one; FGF19 = fibroblast growth factor 19; QD = once daily; vs = versus.

Figure 4. Plasma C4 and FGF19 Concentrations From Day 27 – EYP001a 400 mg QD



Purple curves are simulated profiles with EYP001a administered 400 mg QD (red arrows indicate dosing at 7:00 am) with food (blue arrows indicate meals). Black curves are placebo, ie, physiological changes.
C4 = 7αhydroxy-4-cholesten-3-one; FGF19 = fibroblast growth factor 19; QD = once daily; vs = versus.

The maximal reduction of PD biomarker C4 (approximate levels of 2 to 3 ng/mL) reflecting FXR engagement was already reached with 100 mg twice daily (BID) dosing and was not further decreased with higher doses. As expected, increasing the EYP001a dose increased PD biomarker FGF19 concentrations, but without having an additional substantial effect on C4 concentrations. Comparing a cumulative similar dose administered over 24 hours (ie, 400 mg once daily [QD] versus 200 mg BID), it appears that the dosing regimen of EYP001a decisively impacts C4 levels, with a return to baseline with both QD regimens. Fibroblast growth factor 19 response was, however, more impacted by the time of dosing (morning dosing versus evening dosing); the FGF19 C_{max} was the highest with 400 mg QD morning dosing.

Based on the exploratory graphical EYP001a PK analysis of the effect of estimated glomerular filtration rate (eGFR) (computed from the Modification of Diet in Renal Disease [MDRD] formula[6]), an eGFR between 60 and 89 mL/min/1.73 m^2 could potentially decrease the EYP001a apparent clearance by approximately 10%. Because the elimination pathway of EYP001a is mainly via liver metabolism, as investigated in animal and in vitro human hepatocyte studies and the known relative bioavailability dose-dependent 20% to 50% decrease after repeated administrations, an influence of a mild renal impairment on EYP001a elimination (corresponding to an eGFR reduction to 60 to 89 mL/min/1.73 m^2) is considered minor and not clinically meaningful. Overall, in patients with mild renal impairment, the risk of observing any clinically relevant increase in exposure of EYP001a at the highest dose to be tested in this study (ie, 400 mg QD), is very unlikely. EYP001a was safe and well tolerated with a proportional increase up to 500 mg QD. In this study, dosing up to 400 mg QD in patients with mild renal impairment is not expected to present a risk to patient safety and will contribute (via sparse PK sampling) to the existing population PK model, thus helping to refine PK profiling in patients with mild renal impairment.

Taken together, the Phase 1 data combined with a PK/PD population simulation model support the doses and dosing regimen selected for this study. The results of this study are expected to support the conduct of a pivotal study to explore the efficacy of EYP001a for NASH for an a priori 12-month therapy duration.

1.2 Risk/Benefit

1.2.1 Phase 1 Experience in Healthy Subjects and Patients With Chronic Hepatitis B Virus Infection

Overall, in 4 Phase 1 studies, including 3 completed studies (EYP001-C01, EYP001-102, and EYP001-104) and in 1 study that is clinically complete but pending the clinical study report (EYP001-103; data as of 27 August 2018), EYP001a has been safe and well tolerated and showed engagement of FXR with pharmacology effects expected to be related to the hepatobiliary system and lipid metabolism.

From the available data, no off-target effect has been demonstrated. In healthy human subjects and patients with chronic HBV infection, no clinically significant changes in safety laboratory parameters were observed with 15 days of repeated oral doses of EYP001a from 60 to 500 mg QD. Gastrointestinal adverse events (nausea, dyspepsia, diarrhea, and vomiting) were mostly seen with high doses, were short-lasting, and exclusively mild with few of moderate intensity. There were no clinically significant changes in vital signs or 12-lead electrocardiograms (ECGs). EYP001a showed no potential for QT prolongation in QT-EYP001a concentration analysis, performed per the recent International Council on Harmonisation (ICH) Guidance for concentration-response analysis.[7]

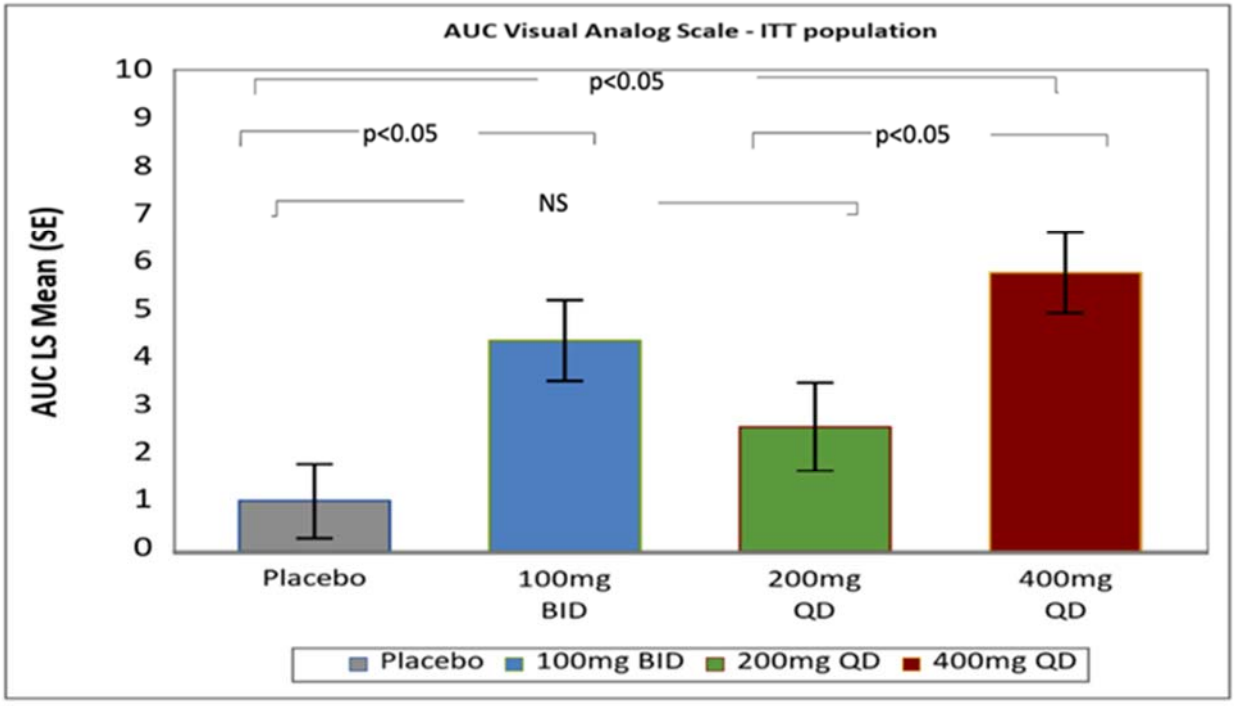
Study EYP001-103 determined the safety and tolerability of 4-week oral administration of EYP001a in patients with chronic HBV infection when given as monotherapy (Part A) or in combination with pegylated interferon alpha-2a (Part B). Oral doses of 300 mg QD, 400 mg QD, 200 mg BID, and 150 mg BID showed isolated increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (ie, without changes in bilirubin, alkaline phosphatase [ALP], or gamma-glutamyltransferase [GGT]) in 15 of 33 Part A patients and in 10 of 25 Part B patients. Grade 3/4 transient ALT/AST increases were observed in 3 patients: in 2 of these patients, the increases were attributed to hepatic flare; results in the third patient were not consistent with hepatic flare. Grade 1 increases in ALT/AST were observed in another 11 patients. Of the 10 of 25 patients in Part B with elevated liver function test values, 3 patients were in the placebo plus pegylated interferon group, 3 patients were in the EYP001a 150 mg BID group, and 4 patients were in the EYP001a 300 mg QD group. Alanine aminotransferase/AST elevations occurred in patients with chronic HBV infection, and 8 patients in the study had values above the upper limit of normal (ULN) at screening or predose. They also occurred when starting antiviral therapy. Therefore, ALT/AST changes were expected in Study EYP001-103 and were not interpreted as a sign of liver toxicity.

1.2.2 Experience in Nonalcoholic Steatohepatitis

After database lock of Part A of the current protocol, EYP001-202, an unscheduled interim analysis was performed on all endpoints collected on the 24 patients enrolled in the Safety Run-in Cohort. The review showed that EYP001a was safe in male and female NASH patients with stage F2 to F3 fibrosis. The most frequent (>20% in any treatment group) treatment-emergent adverse events (TEAEs) were pruritus and nausea. Nausea occurred in 2 of 6 (33.3%) patients in the 400 mg QD dose group, nausea was not experienced by patients in other dose groups. Pruritus reported by Investigators occurred in 5 of 6 (83.3%) patients in the 100 mg BID dose group, 3 of 5 (60.0%) patients in the 200 mg QD dose group, 5 of 6 (83.3%) patients in the 400 mg QD dose group, and no (0%) patients in the placebo group, although 4 of 7 (57.1%) patients in the placebo

group reported pruritus on the visual analog scale. Interestingly, patients receiving the 200 mg QD EYP001a dose reported less intense pruritus (Figure 5).

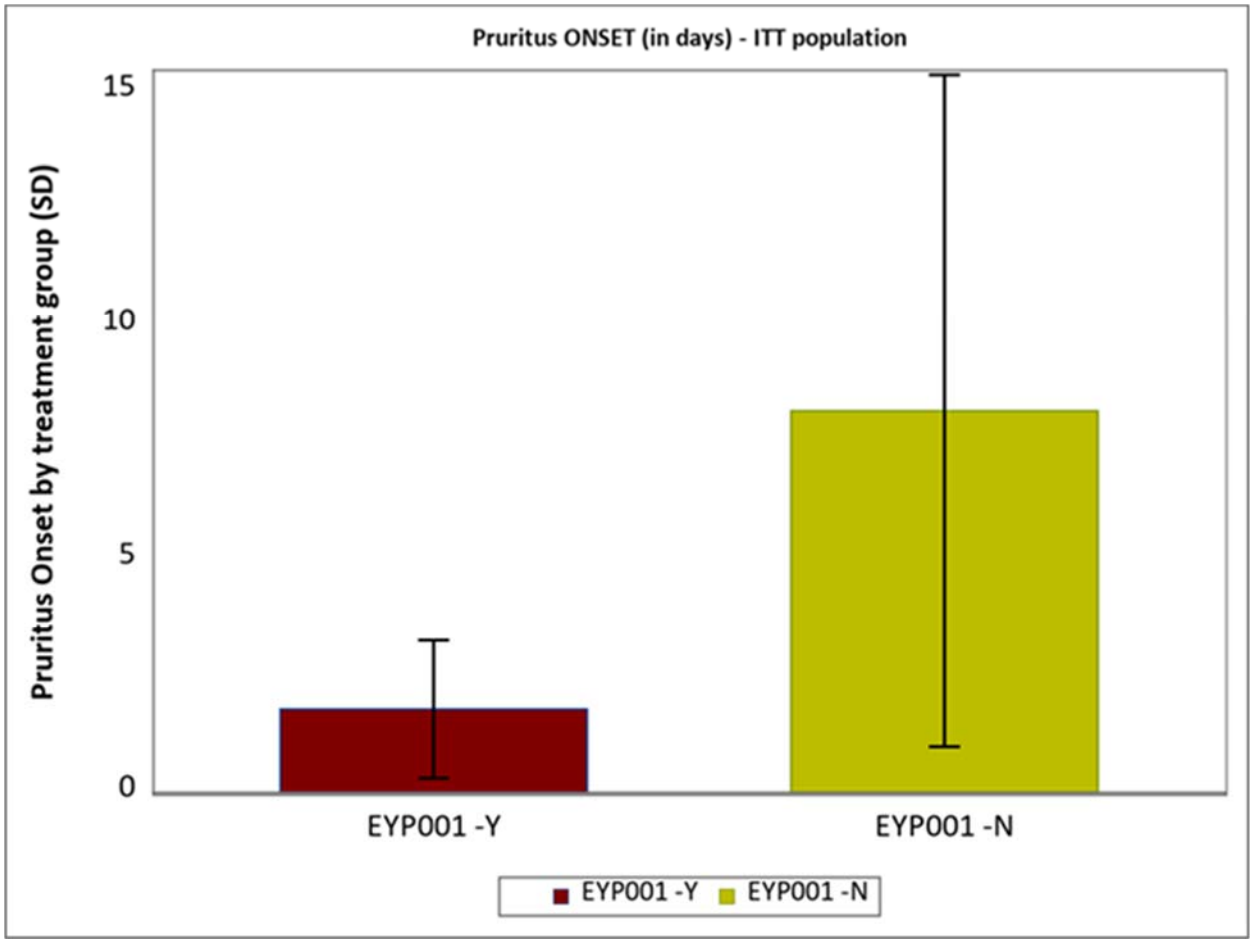
Figure 5. Pruritus Intensity Reported by Patient on the Visual Analogue Scale (0 to 10) Over the Treatment Period (AUC Integrated and Normalized)



AUC = area under the plasma concentration-time curve; BID = twice daily; ITT = Intent-to-Treat; LS = least square; NS = not significant; QD = once daily; SE = standard error.

In the pooled analysis of all EYP001 subjects with pruritus, it appeared that NASH subjects who early-terminated their participation due to pruritus experienced pruritus during the first week, while NASH subjects who completed their participation experienced pruritus later (Figure 6).

Figure 6. Pruritus Onset in Days for Intent-to-Treat Population



ITT = Intent-to-Treat; SD = standard deviation.

A higher than expected pruritus rate in NASH subjects was observed during Part A of this study, compared to tolerability results from previous clinical studies of EYP001a in healthy subjects and patients with chronic HBV infection. This increased pruritus rate is explained by a higher than expected plasma exposure of EYP001a in NASH patients. Two reasons are imputed for this increased exposure. The first is the use of a new galenic tablet formulation with significantly higher bioavailability compared to the previously used capsules. The second is an approximately 25% higher exposure in NASH patients compared to healthy subjects, see Section 5.2. No unexpected or out of target organ TEAEs were observed.

Two Grade 3 (1 in the 100 mg BID dose group and 1 in the 400 mg QD dose group) and 1 Grade 2 (in the 100 mg BID dose group) elevations of transaminases were observed around Week 8 without signs of liver impairment (ie, no signs or symptoms of acute liver failure, protein synthesis, bilirubin, or glucose metabolism dysfunction) or drug-induced liver injury. Of note, 5 of 7 (71.4%) subjects in the placebo group versus 3 of 5 (60.0%) subjects in the 200 mg QD EYP001 group had ALT values >1 × ULN. However, none of these subjects had elevations of transaminases defined as Grade 2 (or higher). Increases in ALT >3 × ULN were seen in 4 of 24 (16.7%) subjects (1 in the placebo group) in Part A, which compares to a similar rate reported recently with other FXR agonists under development (eg, 11.8% in the Tropifexor Phase 2 study).[8] Of note, 2 of

3 (66.7%) subjects with Grade 2 or 3 ALT increases had a body mass index (BMI) >40 kg/m^2 (55.2 and 40.5 kg/m^2) and 1 had a BMI of 38.6 kg/m^2 at screening. The nature of obesity-related health risks is similar in all populations, although the specific level of risk associated with a given level of obesity may vary with race/ethnicity, age, gender, and societal conditions. Disease risk for cardiovascular disease is highest in subjects with extreme obesity (Class III BMI ≥40 kg/m^2). Body mass index correlates with total body fat on a population basis; however, it has limitations in predicting excess body fat associated with health risk on an individual basis. Overall the BMI upper limit of >45 kg/m^2 leading to exclusion was, therefore, added to the enrollment criteria.

In an ongoing Phase 1 study (EYP001-107), 10 NASH subjects were exposed over 9 days to the same EYP001a dose levels and formulation as those tested in Part A of this study (EYP001-202). The EYP001a formulation is detailed in Section 3.3, Drug Product, of the Investigator's Brochure. Preliminary results indicate no changes in liver enzymes.

No signs of muscle toxicity (creatine kinase [CK] increase) were observed, despite the finding that more than 50% of patients were on stable statin therapy during EYP001 therapy. This confirmed the Sponsor's expectation that the coadministration of EYP001a with pravastatin, rosuvastatin, simvastatin, or atorvastatin, which are substrates for organic anion transporting polypeptides 1B1 and 1B3, is appropriate for EYP001a, with no clinically meaningful drug-drug interactions to be expected.

Finally, despite the small sample size of the Safety Run-in Part A Cohort, EYP001a met the primary endpoint with a significant and clinically meaningful LFC reduction (-6.3% absolute reduction and -35.3% relative reduction in the pooled analysis, driven by the 200 mg QD and 400 mg QD doses). In addition, EYP001a significantly reduced weight and waist circumference, and improved liver biology (ALT from Week 1 to Week 4 and GGT throughout treatment) and the noninvasive imaging fibro-inflammatory biomarker (iron-corrected T1 [cT1]), all related to NASH severity.

1.2.3 Overall Risk/Benefit

Overall, clinical data from Phase 1 and preliminary Phase 2 NASH studies showed that EYP001a was safe at oral doses up to 500 mg QD, administered over 2 (highest dose 500 mg QD) to 12 weeks (highest dose 400 mg QD). Oral dosing with 400 mg QD and 100 mg, 150 mg, or 200 mg BID, however, led to a significant increase in pruritus episodes. NASH patients treated with the 200 mg QD EYP001a dose interestingly reported less intense pruritus (Figure 5).

Four Grade 3/4 transient ALT/AST increases were observed in HBV patients (2 were attributed to hepatic flares and 2 were consistent with changes expected in chronically infected HBV patients when starting antiviral therapy). In F2 to F3 NASH patients, 2 Grade 3 (1 in the 100 mg BID dose group and 1 in the 400mg QD dose group) and 1 Grade 2 (100 mg BID dose group) elevations of transaminases were observed. No elevation of transaminases was observed in the EYP001a 200 mg QD dose group. Similar rates of elevations of transaminase were reported with other FXR agonists under development. Although such changes are known to occur in NASH patients, either due to an acute, transient, not identified toxin, like alcohol, or in connection with excessive eating associated with hepatocellular injury in obese patients,[9] a causal relationship between investigational drug EYP001a and ALT/AST increase cannot be excluded. Therefore, patients will be carefully monitored every 2 weeks for clinical and liver laboratory assessments (AST, ALT, total bilirubin, and ALP) with the stopping rules applied as outlined in the Clinical Safety

Monitoring Plan (Appendix E). In Part B, the Data Safety Monitoring Committee (DSMC) will be promptly notified for further review if any patients experience ALT, AST, or bilirubin elevations 2 × above baseline values.

In line and within the range of reported changes for other investigational FXR agonists, as well as the Food and Drug Administration (FDA) and European Medicines Agency-approved FXR agonist OCALIVA® (synthetic bile salt), EYP001a may modify lipid blood profiles. This appears to be a class effect with an unknown risk in the long term and requires monitoring in patients considered for chronic treatment with an FXR agonist. The potential risks of long-term high-density lipoprotein cholesterol and low-density lipoprotein cholesterol (LDL-C) profile modifications need to be weighed against the possible therapy benefits – additional information from ongoing and future studies will be sought for a complete and accurate determination of this potential risk.

Overall, based on available nonclinical and clinical data for EYP001a, prior knowledge with other FXR agonists showing favorable effect on liver growth and regeneration and prevention or resolution of liver fibrosis, and the preliminary safety and positive efficacy results from Part A of the study, the risk/benefit profile of EYP001a is judged as acceptable for further exploration in patients with NASH.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to determine the efficacy and safety profiles of EYP001a versus placebo on LFC from baseline to Week 12 in patients with NASH.

2.2 Secondary Objectives

The secondary objectives are the following:

- To explore the PK of EYP001a
- To evaluate PD effects of EYP001a on bile acid-related markers as appropriate
- To assess the effects of EYP001a on lipid and metabolic profiles
- To assess the safety of EYP001a with statin coadministration
- To assess the effects of EYP001a on noninvasive biomarkers of liver fibrosis and inflammation

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a 2-part, randomized, double-blind, multicenter, placebo-controlled study to evaluate the safety and efficacy of EYP001a in patients with NASH who likely have stage F2 to F3 fibrosis at approximately 50 global clinical sites. Overall, approximately 114 eligible patients will be enrolled: 24 patients in Part A (Safety Run-in Cohort), followed by 90 patients in Part B.

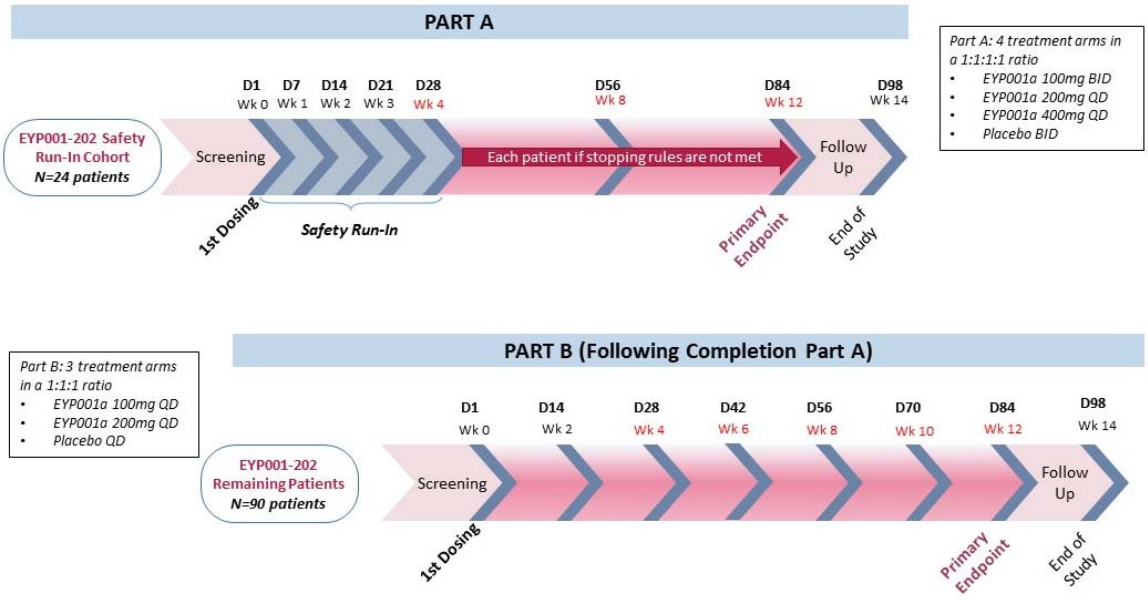
In Part A, 24 patients will be randomized on Day 1 to 1 of 4 parallel treatment groups: 100 mg EYP001a BID, 200 mg EYP001a QD, 400 mg EYP001a QD, or placebo BID. In Part B, 90 patients will be randomized on Day 1 to 1 of 3 parallel treatment groups: 100 mg EYP001a QD, 200 mg EYP001a QD, or placebo QD.

Randomization will be stratified by statin use (yes, no) and type 2 diabetes mellitus (T2DM) status (yes, no) at screening in Part A, and by statin use (yes, no) and LFC (stratification factor with 3 categories: LFC <16%, 16%≤LFC<22%, and 22%≤LFC) in Part B at screening.

The following sequence of screening procedures will be applied to each patient who signs an informed consent form (ICF): 1) eligibility based on clinical and biological inclusion and exclusion criteria; 2) eligibility based on FibroScan® criteria as described in Inclusion Criterion 3; and 3) confirmation of eligibility based on MRI-PDFF results. A patient who is first designated as a screen failure prior to being randomized may be rescreened upon Sponsor or designee approval. If the patient was screen failed after the MRI-PDFF was completed, the original MRI-PDFF scan may be utilized for rescreening, provided it was obtained within 1 month prior to rescreening.

For a schematic of the study design, see Figure 7.

Figure 7. Study Design



BID = twice daily; D = Day; DSMC = Data Safety Monitoring Committee; QD = once daily; Wk = Week.

This study will consist of 2 parts: Part A will include a Safety Run-in Period during the Treatment Period. Screening for Part B will begin after completion of data review on the Safety Run-in Period

of Part A and recommendation from the DSMC. The first 24 eligible patients (approximately 6 randomized patients in each group) will be assessed during the Safety Run-in Period with a frequent monitoring schedule (weekly visits during the first month of treatment and visits every 4 weeks thereafter during the remainder of the Treatment Period) and intense PK profiling on Days 1 and 14. Sparse PK sampling will be performed during all other study visits.

Part A (Safety Run-in Cohort)

Participation in Part A of the study will consist of a Screening Period (up to 12 weeks prior to Day 1), a 12-week Treatment Period, and a Follow-up Visit at Week 14; total study duration is up to 182 days. All eligibility criteria must be confirmed prior to dosing on Day 1.

The 12-week Treatment Period in Part A will include 7 study visits on the following days: Days 1, 7, 14, 21, 28, 56, and 84. Clinical, hematological, chemical, PD, and PK parameters will be assessed throughout the study. Intense PK/PD profiling on Days 1 and 14 will require 12-hour inpatient monitoring and 24-hour post-morning dose blood collection. Safety and tolerability assessments will include the monitoring of adverse events; adverse events of special interest (AESIs) (ie, pruritus, drug-induced liver injury, and all muscle-related adverse events); serious adverse events (SAEs); and findings from physical examinations, vital signs, ECGs, and clinical laboratory parameters.

Throughout the study, all TEAEs, clinical assessments, and clinical laboratory parameters will be closely monitored against the criteria for drug-induced liver injury and muscle toxicity as detailed in the Clinical Safety Monitoring Plan (Appendix E). All adverse events will be assessed and reported using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 grading system. Additional safety measurements will be performed at the discretion of the Investigator (or delegate). Except during the Safety Run-in Period, plasma from blood samples will be collected at each visit and stored for protocol-related safety testing or exploratory analyses.

Part B (Remaining Patients)

Patients in Part B will be randomized on Day 1 to 1 of 3 parallel treatment groups: 100 mg EYP001a QD, 200 mg EYP001a QD, or placebo QD, with approximately 30 patients in each group. Pruritus-related tolerance issues will be addressed by a 2-step study drug titration strategy for the highest dose treatment group (ie, 200 mg QD): all patients randomized to an active treatment group will start with an initial dose of 100 mg QD for the first 2 weeks of treatment (Days 1 to 14). Patients randomized to the 200 mg QD treatment group will be uptitrated to 200 mg QD starting Day 15 until Day 84, while patients randomized to the 100 mg QD treatment group will maintain a 100 mg QD dose throughout their participation. The study treatment assignment strategy will ensure that blind is maintained.

Randomization will be stratified by statin use (yes, no) and LFC (stratification factor with 3 categories: LFC<16%, 16%≤LFC<22%, and 22%≤LFC) at screening.

Participation in Part B of the study will consist of a Screening Period (up to 12 weeks prior to Day 1), a 12-week Treatment Period, and a Follow-up Visit at Week 14; total study duration is up to 182 days. All eligibility criteria must be confirmed prior to dosing on Day 1.

The 12-week Treatment Period in Part B will include 7 study visits on the following days: Days 1, 14, 28, 42, 56, 70, and 84. Clinical, hematological, chemical, PD, and PK parameters will be

assessed throughout the study. The safety and tolerability assessments will include the monitoring of adverse events; AESIs (ie, elevation of transaminases and all muscle-related adverse events); SAEs; and findings from physical examinations, vital signs, ECGs, and clinical laboratory parameters.

Throughout the study, all TEAEs, clinical assessments, and clinical laboratory parameters will be closely monitored against the criteria for drug-induced liver injury and muscle toxicity as detailed in the Clinical Safety Monitoring Plan (Appendix E). All adverse events will be assessed and reported using the National Cancer Institute CTCAE Version 5.0 grading system. Additional safety measurements will be performed at the discretion of the Investigator (or delegate). At screening and on Days 1, 14, 28, 56, and 84; and at the End of Study (EOS) and Early Termination (ET) Visits, plasma from blood samples will be stored for protocol-related safety testing or exploratory analyses.

Data Safety Monitoring Committee and Interim Analyses

An external, independent DSMC will review all available unblinded preliminary safety, PK, and PD results when any stopping rules are met, per the Clinical Safety Monitoring Plan (Appendix E). In Part B, the DSMC will be promptly notified for further review if any patients experience ALT, AST, or bilirubin elevations 2 × above baseline values.

In addition, all available unblinded preliminary safety, PK, and PD results will be comprehensively reviewed during 2 interim analysis timepoints:

- The first interim analysis will be performed at the end of the Safety Run-in Period, after the last of the 24 patients randomized in Part A has completed Day 28 (Week 4). It is anticipated that at the time of the first interim analysis, approximately 10 patients will have completed Day 84 (Week 12) of Part A.
- A second interim analysis will be performed when 50% of patients in Part B have completed Day 56 (Week 8).

The interim analyses will be performed on all available primary and secondary endpoints according to the DSMC charter, which describes the overall guidelines, composition, roles, and responsibilities of the independent DSMC for this study, including the selection of DSMC members, timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings, data analysis recommendations, and DSMC relationships with other parties participating in the conduct of this study. Patient accrual will continue throughout the period of DSMC review. The DSMC will advise on the accrual of the remaining patients per protocol or on any amendments that are necessary for safety reasons.

Efficacy Assessments

Liver fat content will be assessed by MRI-PDFF using a standardized imaging acquisition calibration protocol[10] and central readings will be performed at screening (as baseline value) and Week 12. The ET assessment will be performed only for patients on study drug for ≥4 weeks.

Imaging for cT1 will be assessed centrally; T1 mapping allows in vivo tissue characterization, and measurements can be adjusted for the iron level, as high iron levels in the presence of fibrosis can lead to “pseudo-normal” T1, yielding an unbiased cT1. This noninvasive test has shown good correlation with histological liver fibrosis in a cohort of patients with mixed liver disease etiologies

undergoing clinically indicated liver biopsy[11] and has been shown to correlate with fibro-inflammatory disease and predict clinical outcomes in patients with chronic liver disease.[12]

Harrison et al showed that cT1 correlated with NAFLD activity score ($p=0.514$, $p<0.001$) and accurately identified patients with steatosis, stratified those with NASH or simple steatosis, and reliably excluded clinically significant liver disease with superior negative predictive value (83.3%) to liver stiffness (42.9%) and enhanced liver fibrosis score (57.1%). Furthermore, the experimental NASH drug NGM282 was recently reported to correlate histological NASH improvement with cT1 readout and improve fibrosis and NASH-related histology in 12 weeks in patients with biopsy-confirmed NASH, which is preceded by significant decreases in hepatic steatosis, liver transaminases, and fibrosis markers at 6 weeks.[13] See Banerjee et al for further support of the relevance of T1 mapping technique for fibrosis.[14]

The anticipated EYP001-202 efficacy results will serve as validation of an in silico NASH disease model, which was built based on public and expert knowledge and combined with the Phase 1 PK and PD EYP001 results.[15] The model integrates 309 liver FXR-related biological variables and 1320 parameters and explores the effect of different EYP001 treatment regimens on NASH-relevant efficacy endpoints in a virtual population. Iterations of the model will support future explorations of development strategies with different EYP001 Phase 2 and 3 study designs.

3.2 Stopping Rules

Dosing of a patient may be discontinued for any of the following events:

- One occurrence of an SAE assessed to be definitely or probably related to dosing with the study drug. See Section 9.1.3.
- Confirmation of any of the study drug discontinuation criteria as described in the Clinical Safety Monitoring Plan (Appendix E).
- CK ≥5 × ULN.
- Signs/symptoms of acute coronary syndrome.
- Confirmed cardiac troponin I concentration increase (performed centrally) from baseline and >ULN.
- Occurrence of any condition that, in the opinion of the Investigator, significantly jeopardizes the wellbeing and safety of the patient and is assessed to be probably related to dosing with the study drug.
- Clinically significant changes in vital signs or ECGs (such as arrhythmias) or in the safety laboratory tests assessed to be probably (ie, no alternative explanation likely) related to dosing with the study drug. A “possible” relationship is not considered to require a suspension of treatment.

If 2 or more patients meet study drug stopping criteria, dosing should be suspended or terminated for the remaining patients. The DSMC must review all safety data and provide clearance prior to dosing any additional patients.

For clinical sites in the United Kingdom or European Union, in the case of study halt, the study may only be restarted after Medicines & Healthcare Products Regulatory Agency or National Competent Authority approval, respectively, via a substantial protocol amendment.

If a patient experiences a Grade 5 CTCAE toxicity, or if more than 2 patients develop a ≥Grade 3 CTCAE toxicity in the same category, the study will be paused and safety reports will be submitted to the DSMC for review and clearance prior to dosing any additional patients.

Reinitiation of study drug may be considered after consultation with the Medical Monitor.

3.3 Study Indication

The indication for this study is the treatment of patients with NASH.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Screening Strategy

The following sequence of screening procedures will be applied to each patient who signs an ICF: 1) eligibility based on clinical and biological inclusion and exclusion criteria; 2) eligibility based on FibroScan® criteria as described in Inclusion Criterion 3; and 3) confirmation of eligibility based on MRI-PDFF results.

A patient who is first designated as a screen failure prior to being randomized may be rescreened upon Sponsor or designee approval. If the patient was screen failed after the MRI-PDFF was completed, the original MRI-PDFF scan may be utilized for rescreening, provided it was obtained within 1 month prior to rescreening.

4.2 Inclusion Criteria

A patient who meets all of the following criteria will be eligible to participate in the study:

1. Provides signed written informed consent and agrees to comply with the study protocol.
2. Is a male or female aged 18 years or older.
3. Has a suspected diagnosis of NASH during the Screening Period (up to 12 weeks before dosing), defined as follows:[16,17]

    a. Baseline serum ALT and AST should be established by at least 2 samples obtained at least 4 weeks and no more than 12 weeks apart. One sample can be obtained from the patient's medical history and 1 sample can be obtained during the Screening Period, or both samples can be obtained during the Screening Period. If the values of ALT or AST in both samples are within normal ranges, the variability of the marker is assumed adequate for randomization. If the values of ALT or AST are higher than normal values, the patient will be eligible for enrollment provided the increase from the first to second sample is ≤40%. If the values from sample 1 are higher than those from sample 2 (ie, there is a decrease), the patient will be eligible despite a >40% difference. A third sample can be collected if an increase from sample 1 to sample 2 exceeds the 40% limit. If sample 3 exceeds the 40% limit (compared to sample 1), this increase shall prompt the search for clinical signs or symptoms of liver impairment, and the patient will not be eligible for enrollment. Baseline AST values should be >20 U/L. See Appendix I for central laboratory normal reference ranges.

    b. Normal average baseline levels of ALP. See Appendix I for central laboratory normal reference ranges. Total bilirubin (TBL) levels should be ≤22.2 µmol/L (1.3 mg/dL).

    Note: Baseline serum ALP and TBL should be established by at least 2 samples obtained at least 4 weeks and no more than 12 weeks apart. One sample can be obtained from the patient's medical history and 1 sample can be obtained during the Screening Period, or both samples can be obtained during the Screening Period. If the values of ALP or TBL in both samples are within normal ranges, the variability of the marker is assumed adequate for randomization. If the values of ALP or TBL are higher than normal values, the patient will be eligible for enrollment provided the increase from the first to second sample is ≤40%. If the values from sample 1 are higher than those from sample 2 (ie, there is a decrease), the patient will be eligible despite a >40% difference. A third sample can be

collected if an increase from sample 1 to sample 2 exceeds the 40% limit. If sample 3 exceeds the 40% limit (compared to sample 1), this increase shall prompt the search for clinical signs or symptoms of liver impairment, and the patient will not be eligible for enrollment.

c. Liver stiffness compatible with liver fibrosis stage F2 or F3 determined by FibroScan vibration-controlled transient elastography assessment cut-off value ≥8.5 kPa.

d. FibroScan controlled attenuation parameter (CAP) for steatosis with cut-off values >300 dB/m.

Note: Patients do not need to undergo a CAP assessment if their medical records indicate an MRI-PDFF LFC ≥10% within 12 months prior to screening.

Note: Histology within 12 months prior to screening will supersede FibroScan entry criteria if the following criteria are met: NASH with fibrosis stage F2 to F3, defined as portal fibrosis with few septa (F2) or bridging septa between central and portal veins (F3), and NAFLD activity score ≥4, including a minimum of 1 point each for ballooning and inflammation. However, if a patient participated in a previous study with a NASH investigational drug between 365 and 60 days prior to being screened for this study, the histology information will only be considered if the biopsy was performed after the end of the patient's participation in the previous study.

e. LFC ≥10% as measured by MRI-PDFF.

4. Is not of childbearing potential (as defined in Inclusion Criterion 5) or, if of childbearing potential, is not pregnant as confirmed by a negative serum human chorionic gonadotropin (hCG) test at screening and is not planning a pregnancy during the course of the study.

5. Women of childbearing potential and male patients with female partners must agree to use highly effective birth control throughout the duration of the study and for 90 days after stopping study drug. Patients who are using hormonal contraceptives or intrauterine devices should be instructed to use an additional barrier contraceptive measure during the study such as a male or female condom with spermicide or diaphragm. Highly effective is defined as birth control methods that result in a failure rate of <1% per year when used consistently and correctly. Methods of highly effective birth control include the following:

a. Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation.

- Oral.
- Intravaginal.
- Transdermal.

b. Progesterone-only hormonal contraception associated with inhibition of ovulation.

- Oral.
- Injectable.
- Implantable.

c. Intrauterine device.

d. Intrauterine hormone-releasing system.

e. Vasectomized partner (provided that the partner is the sole sexual partner of the woman of childbearing potential).

f. Sexual abstinence (complete abstinence from sexual intercourse if this is the patient's usual and preferred lifestyle).

Note: A woman is considered of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile. A postmenopausal state is defined as no menses for ≥12 consecutive months without an alternative medical cause. A follicle-stimulating hormone level in the postmenopausal range will be used to confirm a postmenopausal state in women ≤55 years of age. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

4.3 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from participation in the study:

1. Is an employee of a clinical research organization, vendor, or Sponsor involved with this study.
2. Has known non-NASH liver disease, including, but not limited to, alcoholic liver disease, autoimmune disease, human immunodeficiency virus (HIV), HBV, active hepatitis C virus (HCV), Wilson's disease, hemochromatosis, primary biliary cholangitis, primary sclerosing cholangitis, drug-induced liver injury, bile duct obstruction, or suspected or known liver cancer.

   Note: HCV antibody (HCV Ab) positive individuals are not eligible, with the following 2 exceptions: (a) Patients previously treated with a registered drug for viral hepatitis C with at least a 1-year period since documented sustained virologic response may be eligible if HCV ribonucleic acid (RNA) is below the limit of detection (LOD) and if all other eligibility criteria are met, and (b) patients with presence of HCV Ab if HCV RNA is below the LOD at screening without treatment (ie, spontaneous clearance) may be eligible if all other eligibility criteria are met.
3. Has history of cirrhosis or liver decompensation, including ascites, hepatic encephalopathy, or presence of esophageal varices.
4. Has known history of alcohol abuse or daily heavy alcohol consumption (females: more than 14 units of alcohol per week; males: more than 21 units of alcohol per week [1 unit of alcohol is equivalent to a half pint of beer {285 mL}, 1 measure of spirits {25 mL}, or 1 glass of wine {125 mL}]). Has an Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score of ≥3 points for men and women AND a full Alcohol Use Disorders Identification Test (AUDIT) score of ≥8 points at screening.

   Note: Only patients with AUDIT-C scores ≥3 points at screening will receive the full AUDIT and will be excluded if they score ≥8 points on the full AUDIT. Patients with AUDIT-C scores <3 points will not receive the full AUDIT.
5. Has Gilbert's syndrome with direct bilirubin >1 × ULN.
6. Is pregnant or breastfeeding.

7. Has clinically relevant immunosuppression, including, but not limited to, immunodeficiency conditions such as common variable hypogammaglobulinemia.
8. Has a known preexisting medical or psychiatric condition that could interfere with the patient's ability to provide informed consent or participate in study conduct, or that may confound study findings.
9. Has, in the opinion of the Investigator, clinically significant cardiovascular or cerebrovascular disease within 90 days prior to the first study drug administration, including, but not limited to, myocardial infarction, acute coronary syndrome, revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or ischemic stroke, or implanted defibrillator or pacemaker.
10. Has participated in any drug study within 90 days prior to the first study drug administration in the current study.
11. Has had major surgery within 90 days prior to the first study drug administration in the current study.
12. Has a history of relevant drug and/or food allergies. The term "relevant" applies if any of the following allergy conditions are met:
    a. Has had several episodes of drug-induced urticaria or other immediate allergic signs (eg, rhinoconjunctivitis, respiratory) (≥2 in total at whatever time in medical history and with 1 or several drugs).
    b. Has ongoing urticaria episodes (attributed to whatever allergen) or has other active history of immediate type reaction allergies (eg, allergic rhinoconjunctivitis, allergic asthma, or latex allergy).
    c. Has had a moderate or severe allergic reaction (≥Grade 2 per the World Allergy Organization reference table, ie, urticaria alone with a Grade 1 is not relevant).
    d. Has any allergic condition that might require an emergency epinephrine injection (similar to the EpiPen® Auto-Injector).
13. Has a history of hypersensitivity to the study drug or to any of the excipients or placebo.
14. Unable to undergo an MRI-PDFF due to:
    a. Contraindication to MRI examination.
    b. Severe claustrophobia impacting ability to perform MRI during the study, despite mild sedation/treatment with a short half-life (ie, <20 hours) anxiolytic.
    c. Body weight or girth exceeding the scanner capacities.
15. Is using any of the following disallowed medications:
    a. Anticancer drug(s), immunomodulator(s), or immunosuppressant(s) within 90 days or 5 half-lives prior to screening, whichever is longer, or any drug historically associated with NAFLD for >2 weeks in the year prior to screening (eg, amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, or valproic acid or other known hepatotoxins at the Investigator or Medical Monitor's discretion).

b. Vitamin E (>400 IU/day), glitazones, glucagon-like peptide-1 receptor agonists, ursodeoxycholic acid, or obeticholic acid within 90 days prior to screening.

c. Agents (including herbal over-the-counter weight loss preparations) or medications known to significantly impact body weight within 90 days prior to screening (eg, sibutramine, phenetamine, and orlistat).

d. Bile acid sequestrants (eg, cholestyramine) or lipid-modifying agents (eg, fibrates or ezetimibe) other than rosuvastatin, atorvastatin, simvastatin, pravastatin, fluvastatin, or lovastatin.

e. Agents that are substrates for cytochrome P450 (CYP) 2C8 or CYP2C9 and have a narrow therapeutic index (eg, warfarin).

16. Has prior or planned (during the study period) bariatric surgery (eg, gastroplasty or Roux-en-Y gastric bypass).
17. Has type 1 diabetes mellitus.
18. Has T2DM and hemoglobin A1c >9.5% or has not been on a stable dose of antidiabetic medication for at least 90 days prior to screening.
19. Has had total body weight loss of >5% within 6 months or since a liver biopsy, if applicable.
20. Has any of the following exclusionary laboratory results at screening:

    a. ALT >5 × ULN, AST >5 × ULN.

    b. International normalized ratio ≥1.3, unless on anticoagulant therapy.

    c. Platelet count <lower limit of normal.

    d. eGFR <50 mL/min/1.73 m^2 (MDRD formula[6]).

    e. CK >ULN in patients on concomitant statin therapy and CK >3 × ULN in all other patients.

    f. Thyroid-stimulating hormone >1.5 × ULN or abnormal free triiodothyronine or free thyroxine.

    Note: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor if any of the above laboratory abnormalities are found.

21. Has history of clinically significant gastrointestinal disease (especially: cholecystectomy prior to age 25 years, peptic ulcerations, gastrointestinal bleeding, inflammatory bowel disease, or bariatric surgery); renal, hematologic, endocrine, oncologic, pulmonary, immunologic, or cardiovascular disease; neurologic or psychiatric disease (including any use of addictive substances such as regular opioid treatment and/or any use of illicit drugs); or any other condition, which, in the opinion of the Investigator, would jeopardize the safety of the patient or impact the validity of the study results.
22. Has a BMI >45 kg/m^2.

4.4 Withdrawal Criteria

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- Patient withdrawal of consent or request of discontinuation from the study for any reason
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol
- Patient meeting any of the stopping rules
- Any SAE, clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient
- Pregnancy
- Requirement of prohibited concomitant medication
- Patient failure to comply with protocol requirements or study-related procedures
- Termination of the study by the Sponsor or the regulatory authority

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the ET Visit. The reason for patient withdrawal must be documented in the electronic case report form (eCRF).

In the case of patients lost to follow-up, multiple attempts to contact the patient must be made and documented in the patient's medical records before a patient can be registered as being lost to follow-up. Multiple attempts are considered 3 telephone calls. If the patient does not respond, a letter must be sent to the patient. If no response is received a month after the letter was sent, the patient can be registered as lost to follow-up.

In general, withdrawn patients will not be replaced during the study. However, during the Safety Run-in Period in Part A, withdrawn patients will be replaced if less than 16 of the planned 24 patients complete the Day 28 Visit. In such a situation, the withdrawn patients will be replaced with an appropriate number of new patients to ensure that between 16 and 24 patients complete the Day 28 Visit of Part A (ie, complete the Safety Run-in Period).

5 STUDY TREATMENTS

5.1 Treatment Groups

Approximately 114 eligible patients with NASH will be randomized. In Part A, 24 patients will be randomized into 4 parallel treatment groups as outlined in Table 1. In Part B, 90 patients will be randomized into 3 parallel treatment groups as outlined in Table 2.

Table 1. Study Treatment Groups and Dosing Regimens – Part A

Treatment Group	Morning Regimen: 2 Tablets [1]	Evening Regimen: 1 Tablet [2]
Placebo	2 tablets of placebo	1 tablet of placebo
100 mg BID	1 tablet of 100 mg EYP001a and 1 tablet of placebo	1 tablet of 100 mg EYP001a
200 mg QD	2 tablets of 100 mg EYP001a	1 tablet of placebo
400 mg QD	2 tablets of 200 mg EYP001a	1 tablet of placebo

1. With breakfast, except during intense PK/PD sampling on Days 1 and 14 of Part A, when dosing will occur with water only.
2. With dinner.

BID = twice daily; PD = pharmacodynamic(s); PK = pharmacokinetic(s); QD = once daily.

Table 2. Study Treatment Groups and Dosing Regimens – Part B

Treatment Group	Morning Regimen: 1 Tablets [1]
Placebo	1 tablet of placebo
100 mg QD	1 tablet of 100 mg EYP001a
200 mg QD	1 tablet of 100 mg EYP001a from Day 1 to Day 14 1 tablet of 200 mg EYP001a from Day 15 to Day 84

1. With breakfast.

QD = once daily.

5.2 Rationale for Dosing

EYP001a Phase 1 data in healthy subjects showed that EYP001a was well tolerated after single and multiple oral administrations from 30 to 800 mg (single ascending dose) and from 60 to 500 mg (multiple ascending dose). For all dosing conditions, despite similar rapid EYP001a elimination, FGF19 and C4 showed a prolonged FXR target engagement up to at least 24 hours, which was not influenced by fasting or fed condition or by morning or evening administration (Study EYP001-102). EYP001a was safe in HBV subjects treated over 4 weeks with doses of EYP001a 100 mg QD, 150 mg BID, 200 mg QD, 200 mg BID, 300 mg QD, and 400 mg QD. The most frequent TEAEs were headache, pruritus, abdominal pain, and diarrhea. Pruritus was mostly seen with BID administration and was of mild or moderate intensity and lasted for 5 to 36 days. In addition, the QD doses showed better tolerance with few pruritus TEAEs.

Population PK/PD simulations for C4 and FGF19, based on preliminary modeling, support the doses and dosing regimens selected for Part A of this study: 100 mg BID versus 200 mg QD and 400 mg QD. The expected differences in C4 and FGF19 (AUC at 24 hours) at steady state between EYP001a and placebo treatments were assessed in simulations in healthy subjects and in patients with chronic HBV infection. The selected regimen and doses suggest that, in NASH patients, relevant C4 and FGF19 changes (C4 decrease and FGF19 increase) will occur. Patients with NASH were expected to have values that fell between those simulated in healthy subjects and in subjects with HBV.

The preliminary and unblinded analysis of Part A of the current study, EYP001-202, showed that EYP001a was safe in 24 male and female patients with stage F2 to F3 NASH. A higher than expected pruritus rate (60% for patients treated with the 200 mg QD dose and 83% for patients treated with the 100 mg BID and 400 mg QD doses) was observed. Patients who received 200 mg QD EYP001a interestingly reported less intense pruritus as compared to other dose groups (Figure 5, Section 1.2.2). Also, NASH subjects who early-terminated their participation due to pruritus experienced pruritus during the first week, while NASH subjects who completed their participation experienced pruritus later (Figure 6, Section 1.2.2). These observations support an EYP001a uptitration strategy to improve tolerance of pruritus.

The higher pruritus occurrence was explained by an unexpected substantially higher EYP001a plasma exposure compared to the exposure previously observed in healthy subjects (Table 3 and Table 4). This difference can be explained by a different formulation of study drug, with the current tablet formulation leading to a higher bioavailability compared to the previously used capsule formulation. In addition, an approximately 50% to 79% higher exposure in NASH patients compared to healthy subjects was also noted in an ongoing Phase 1 trial (EYP001-107), which can be explained by a slower elimination in NASH subjects compared to healthy subjects (Table 5).

Table 3. Study EYP001-202 Part A: Median PK Parameters at Day 1 and Day 14

PK Visit	Day 1			Day 14		
Arm	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng.h/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng.h/mL)
200 mg QD NASH (n=5 & 2)	2220	4.00	11,983	2875	2.50	8459
400 mg QD NASH (n=6 & 4)	3565	2.00	16,495	2055	1.50	6897

NOTE: Because of data inconsistencies in the 100 mg BID dosing history, the PK data could not be estimated.
AUC_{0-24h} = area under the plasma concentration-time curve from time 0 to 24 hours; BID = twice daily; C_{max} = maximum observed plasma concentration; NASH = nonalcoholic steatohepatitis; PK = pharmacokinetic; QD = once daily; T_{max} = time to reach the maximum observed plasma concentration.

Table 4. Study EYP001-C01 Healthy: Median PK Parameters at Day 1 (SAD) and Day 14 (MAD)

PK Visit	Day 1			Day 14		
Arm	C_{max} (ng/mL)	T_{max} (h)	AUC_{Inf} (ng.h/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{Inf} (ng.h/mL)
250 mg QD HV (n=6)	1440	2.25	5540	946	2.75	2738
500 mg QD HV (n=6)	2790	2.50	10,182	1700	2.50	5619

AUC_{Inf} = area under the plasma concentration-time curve from time 0 to infinite time; C_{max} = maximum observed plasma concentration ; HV = healthy volunteer; MAD = multiple ascending dose; PK = pharmacokinetic; QD = once daily; SAD = single ascending dose; T_{max} = time to reach the maximum observed plasma concentration.

Table 5. Study EYP001-107: Median PK Parameters at Day 1 and Day 8

PK Visit	Day 1			Day 8		
Arm	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng.h/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng.h/mL)
200 mg QD NASH (n=3)	2350	4.00	10,365	983	2.00	4012
400 mg QD NASH (n=4)	2085	5.00	20,830	1800	3.13	9239
400 mg QD HV (n=4)	2175	2.03	11,614	1870	3.00	6115

AUC_{0-24h} = area under the plasma concentration-time curve from time 0 to 24 hours; C_{max} = maximum observed plasma concentration ; HV = healthy volunteer; NASH = nonalcoholic steatohepatitis; PK = pharmacokinetic; QD = once daily; T_{max} = time to reach the maximum observed plasma concentration.

Finally, the PK profile of EYP001a in NASH patients confirmed the known decrease in exposure at Day 14: Day 14/Day 1 AUC ratio was 0.4 to 0.7 for the 200 mg QD and 400 mg QD dose groups, respectively, and C_{max} ratio was 0.6 to 1.3 for the 200 mg QD and 400 mg QD dose groups, respectively. No accumulation was noted. A similar decrease in exposure over time was also previously seen in healthy subjects (Table 3, Table 4, and Table 5) and in patients with chronic HBV infection.

The safety profiling in Part A showed 2 Grade 3 (1 in the 100 mg BID dose group and 1 in the 400 mg QD dose group) and 1 Grade 2 (in the 100 mg BID dose group) elevations of transaminases around Week 8 without signs of liver impairment (ie, no signs or symptoms of acute liver failure, protein synthesis, bilirubin, or glucose metabolism dysfunction) or drug-induced liver injury. Of note, 5 of 7 (71.4%) patients in the placebo group versus 3 of 5 (60.0%) patients in the 200 mg QD EYP001 dose group had ALT values >1 × ULN. However, none of these patients had elevations of transaminases defined as Grade 2 (or higher). In Part A, increases in ALT >3 × ULN were seen in 4 of 24 (16.7%) patients (1 in the placebo group), which compares to a similar rate reported recently with other FXR agonists under development (eg, 11.8% in the Tropifexor Phase 2 study).[8]

Importantly, in the Part A Safety Run-in Cohort, EYP001a met the primary endpoint with a significant and clinically meaningful -6.3% absolute liver fat reduction. EYP001a also significantly reduced weight and waist circumference, and improved liver biology (ALT initially, and GGT) and the fibro-inflammatory biomarker (cT1), all known to relate to NASH severity. Interestingly, the noninvasive biomarker for liver fibro-inflammation (cT1) showed the largest improvement in the 200 mg QD EYP001a dose group (-116 msec versus -69 and -43 msec in the 100 mg BID and 400 mg QD EYP001a dose groups, respectively).

Overall, the 200 mg QD dose and a new lower 100 mg QD dose will be further tested in Part B of this study because they are expected to optimally balance risk/benefit. Pruritus-related tolerance issues will be addressed by a 2-step study drug titration strategy for the highest dose treatment group (ie, 200 mg QD): all patients randomized to an active treatment group will start with an initial dose of 100 mg QD for the first 2 weeks of treatment (Days 1 to 14). Patients randomized to the 200 mg QD treatment group will be uptitrated to 200 mg QD starting Day 15 until Day 84, while patients randomized to the 100 mg QD treatment group will maintain a 100 mg QD dose throughout their participation. The study treatment assignment strategy will ensure that blind is maintained. The 100 mg BID and 400 mg QD dose levels will be discontinued.

5.3 Randomization and Blinding

This study follows a randomized, double-blind, placebo-controlled design. Patients in Part A will be randomized via the Interactive Response Technology (IRT) system to 1 of 4 parallel treatment groups on Day 1 in a 1:1:1:1 ratio. However, prerandomization will occur within the IRT system at least 7 days prior to randomization. Patients in Part B will be randomized via the IRT system to 1 of 3 parallel treatment groups on Day 1 in a 1:1:1 ratio. Prerandomization is not applicable in Part B.

Both EYP001a and placebo will be provided as tablets for oral administration and will be identical in appearance.

Prerandomization/randomization information will be concealed from the Investigators and the patients until the end of the study, with the exception of an emergency situation involving a patient that required unblinding of the treatment assignment.

5.3.1 Stratification

Randomization will be stratified by statin use (yes, no) and T2DM status (yes, no) in Part A, and by statin use (yes, no) and LFC (stratification factor with 3 categories: LFC<16%, 16%≤LFC<22%, and 22%≤LFC) in Part B at screening. Randomization can occur after eligibility check on Day -3, at the earliest, and prior to dosing on Day 1 at the latest.

5.4 Breaking the Blind

Until formal conclusion of the study, patients, Investigators, and all clinical site personnel will remain blinded to treatment allocation, except in the event of a medical emergency that necessitates unblinding. In the event of a medical emergency, when knowledge of the patient's treatment assignment would influence the patient's clinical care, the clinical site will be able to unblind the patient via the IRT system. In the case of unblinding, the IRT system will send a blinded notification to study team members to let them know that a patient was unblinded.

In preparation for the DSMC meeting, Part A data were unblinded and analyzed by an independent statistician and presented to the DSMC. The study team remained blinded during this analysis. Due to the DSMC decision to update dosing arms, all Part A data were locked and unblinded data were sent to the unblinded Sponsor statistician.

When 50% of patients have completed the Week 8 visit in Part B, the DSMC will review all available primary and secondary endpoints according to the DSMC charter. The conclusions and recommendations of the DSMC will be shared blindly with the clinical sites.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The drug product will be supplied as immediate-release coated tablets for oral administration. Excipients include lactose monohydrate, microcrystalline cellulose, crospovidone, sodium lauryl sulfate, silicon dioxide, and magnesium stearate. Placebo tablets will appear identical to EYP001a.

For Part A, all study drug (EYP001a and placebo) will be packaged in blister packs and wallets. One wallet will contain 2 weeks of study drug (ie, 14 days of EYP001a or placebo) as per the randomization schedule. Morning and evening tablets will be clearly labeled.

For Part B, all study drug (EYP001a and placebo) will be packaged in blister packs and carton boxes. One box will contain 3 weeks of study drug (ie, 3 blister strips or 21 days of EYP001a or placebo) as per the randomization schedule.

5.5.2 Study Drug Preparation and Dispensing

For Part A, study drug will be dispensed as 100 and 200 mg tablets for oral administration at Weeks 0, 2, 4, and 8 by blinded clinical site personnel. Patients will receive enough study drug to last until the next visit.

For Part B, study drug will be dispensed as 100 and 200 mg tablets for oral administration at Weeks 0, 2, 4, 6, 8, and 10 by blinded clinical site personnel. Patients will receive enough study drug to last until the next visit.

5.5.3 Study Drug Administration

EYP001a is only available for oral administration. The study drug should be administered with noncarbonated water.

For Part A, patients will take 2 tablets in the morning during breakfast and 1 tablet in the evening during dinner.

For Part B, patients will take 1 tablet in the morning during breakfast.

On study visit days, patients should come fasted to the clinical site and take their morning dose during breakfast at the clinical site, following blood sample collection, except during intense PK/PD sampling on Days 1 and 14 of Part A, when dosing will occur with water only.

5.5.4 Treatment Compliance

In Part A, patient diaries will be reviewed to assess compliance throughout the study. In Parts A and B, the quantity of study drug dispensed to and returned by the patient will be counted. If the patient is not compliant with study drug intake, the Investigator should discuss this with the patient.

If study drug compliance drops below 80% at any given time during the Treatment Period, the Investigator or designee should discuss compliance with the patient and counsel the patient appropriately. Noncompliance includes missed doses in addition to taking the wrong dose. The Investigator must encourage compliance with the study drug and with the study procedures at all times.

5.5.5 Storage and Accountability

Study drug should be stored in a cool, dry place (15°C to 25°C or 59°F to 77°F) (stable from 5°C to 40°C, with 75% relative humidity).

The Investigator or appropriately trained designee will maintain an accurate record of the receipt of the study drug shipment, including the date and quantity received. Refer to the Pharmacy Manual for further information.

In addition, an accurate drug dispensing record will be kept that specifies the amount of study drug dispensed to each patient and the date of dispensing.

A drug accountability inventory record to account for all dispensing and return of any used and unused study drug must be maintained and available by the clinical site staff for inspection at any time. At the end of the study, the study drug will be reconciled, and copies of the complete record of study drug accountability will be provided to the Sponsor.

5.6 Prior and Concomitant Medications and/or Procedures

Unless medically warranted, all concomitant medications should remain stable from screening through the EOS Visit.

5.6.1 Excluded Medications and/or Procedures

Excluded medications and procedures include the following:

- Anticancer drugs, immunomodulators, and immunosuppressants within 90 days or 5 half-lives prior to screening, whichever is longer
- Drugs historically associated with NAFLD for >2 weeks in the year prior to screening (eg, amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens at doses greater than those used for hormone replacement, anabolic steroids, or valproic acid or other known hepatotoxins at the Investigator or Medical Monitor's discretion)
- Vitamin E (>400 IU/day), glitazones, glucagon-like peptide-1 receptor agonists, ursodeoxycholic acid, or obeticholic acid within 90 days prior to screening
- Agents (including herbal over-the-counter weight loss preparations) or medications known to significantly impact body weight within 90 days prior to screening (eg, sibutramine, phenetamine, and orlistat)
- Bile acid sequestrants (eg, cholestyramine) or lipid-modifying agents (eg, fibrates or ezetimibe) other than rosuvastatin, atorvastatin, simvastatin, pravastatin, fluvastatin, or lovastatin
- Agents that are substrates for CYP2C8 or CYP2C9 and have a narrow therapeutic index (eg, warfarin)
- Prior or planned (during the study period) bariatric surgery (eg, gastroplasty or Roux-en-Y gastric bypass)
- Major surgery within 90 days prior to the first study drug administration

5.6.2 Restricted Medications and/or Procedures

Patients receiving statin therapy (rosuvastatin, atorvastatin, simvastatin, pravastatin, fluvastatin, or lovastatin are the only allowable statins) need to be on stable therapy for at least 90 days prior to the first administration of study drug. If LDL-C increases >10 mg/dL at Week 2, the statin dose may be increased and titrated up at the following visit if the LDL-C remains 5% above the baseline value.

For patients without statin therapy at baseline, if LDL-C increases ≥25% from Day 1 to Day 14, rosuvastatin 20 mg QD will be introduced and titrated up to 40 mg QD at the following visit if LDL-C remains 5% above the baseline value.

Patients receiving other lipid-lowering treatments need to be on stable therapy for at least 90 days prior to the first study drug administration and must agree to remain on a stable regimen for their entire participation in the study. Patients with T2DM should be on a stable dose of antidiabetic medication for at least 90 days prior to screening and must agree to remain on a stable regimen for their entire participation in the study.

Close monitoring is required for comedication agents that are substrates for CYP2C8 or CYP2C9.

5.6.3 Documentation of Prior and Concomitant Medication Use

All concomitant medications must be recorded in the eCRF. Any medication taken on or after the date the patient signs informed consent will be recorded in the eCRF. Any changes to concomitant medication dosing during the study will be captured in the eCRF and closely monitored.

6 STUDY PROCEDURES

Blood sample collection will be prioritized starting with the safety sample.

All blood samples should be collected while the patient is in a fasted state, defined as nothing by mouth except water for ≥6 hours.

A ±3-day window is acceptable for all visits during the Treatment Period, except for Days 1 and 14 in Part A, when the window is ±1 day.

6.1 Informed Consent

Written informed consent for the study will be obtained from all patients before any protocol-specific procedures are performed.

6.2 Screening Period (Parts A and B) (Weeks -12 to -1)

The following procedures will be performed during the Screening Period (Weeks -12 to -1):

- Obtain informed consent.
- Evaluate inclusion/exclusion criteria.
- Obtain demographics and medical history.
- Record prior and concomitant medications.
- Perform complete physical examination.
- Measure height and body weight and calculate BMI.
- Measure waist circumference (Part A only).
- Measure waist and hip circumferences (Part B only).
- Calculate waist to hip ratio (WHR) and waist to height ratio (WHtR) (Part B only).
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Administer the AUDIT-C test. Patients with AUDIT-C scores ≥3 points at screening will receive the full AUDIT and will be excluded if they score ≥8 points on the full AUDIT. Patients with AUDIT-C scores <3 points will not receive the full AUDIT.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
    - Anti-HCV, anti-HIV, and anti-HBV status and HCV RNA reflexive testing, except if viral serology data are already available in the patient's medical history/records and obtained within 90 days prior to screening.
    - Chemistry, hematology, coagulation, and lipid and metabolic profile.
    - Serum pregnancy test (only for women of childbearing potential).

- Follicle-stimulating hormone test (only for women ≤55 years of age, to confirm postmenopausal state).
- Plasma storage.

- Collect urine sample for urinalysis.
- Perform 12-lead ECG.
- Perform FibroScan.
- Perform MRI-PDFF and cT1 imaging if FibroScan values (liver stiffness measurement [LSM] and CAP) are within eligibility range.
- Assess adverse events.

6.3 Treatment Period (Weeks 0 to 12)

6.3.1 Part A: Safety Run-in Period (Weeks 0 to 4)

6.3.1.1 Day 1 (Week 0)

The following procedures will be performed on Day 1 (Week 0):

- Review inclusion/exclusion criteria and confirm patient eligibility.
- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist circumference.
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Intense PD profile (predose [fasting] and 4 [fasting], 6, 10, 12, and 24 hours postdose).
  - Liver fibrosis and inflammation.
  - Intense PK profile (predose and 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose [samples will be collected in the fasted state predose to 4 hours postdose, inclusive]).
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Randomize eligible patients prior to dosing.
- Assess pruritus.
- Assess adverse events.

- Dispense patient diary.
- Dispense study drug and provide dosing instructions.

6.3.1.2 Day 7 (Week 1)

The following procedures will be performed on Day 7 (Week 1):

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist circumference.
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Liver fibrosis and inflammation.
  - Sparse PK profile (predose [fasting] and 2 hours postdose; optional sample at 6 hours postdose).
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Perform 12-lead ECG.
- Assess pruritus.
- Assess adverse events.

6.3.1.3 Day 14 (Week 2)

The following procedures will be performed on Day 14 (Week 2):

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist circumference.
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Administer the AUDIT-C test.
- Counsel on diet/lifestyle.

- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Intense PD profile (predose [fasting] and 4 [fasting], 6, 10, 12, and 24 hours postdose).
  - Intense PK profile (predose and 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose [samples will be collected in the fasted state predose to 4 hours postdose, inclusive]).
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Perform 12-lead ECG.
- Assess pruritus.
- Assess adverse events.
- Collect returned used/unused study drug and assess compliance.
- Dispense new study drug and provide dosing instructions.

6.3.1.4 Day 21 (Week 3)

The following procedures will be performed at Day 21 (Week 3):

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist circumference.
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Administer the AUDIT-C test.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Liver fibrosis and inflammation.
  - Sparse PK (predose [fasting] and 2 hours postdose; optional sample at 6 hours postdose).
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Perform 12-lead ECG.
- Assess pruritus.
- Assess adverse events.

6.3.1.5 Day 28 (Week 4)

The following procedures will be performed at Day 28 (Week 4):

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist circumference.
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Administer the AUDIT-C test.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Sparse PD profile (predose [fasting] and 2 hours postdose).
  - Liver fibrosis and inflammation.
  - Sparse PK profile (predose [fasting] and 2 hours postdose; optional sample at 6 hours postdose).
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Perform 12-lead ECG.
- Assess pruritus.
- Assess adverse events.
- Collect returned used/unused study drug and assess compliance.
- Dispense new study drug and provide dosing instructions.

6.3.2 Part A: Continued Treatment Period (Weeks 5 to 12)

6.3.2.1 Day 56 (Week 8)

The following procedures will be performed on Day 56 (Week 8):

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist circumference.

- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Administer the AUDIT-C test.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Sparse PD profile (predose [fasting] and 2 hours postdose).
  - Liver fibrosis and inflammation.
  - Sparse PK profile (predose [fasting] and 2 hours postdose; optional sample at 6 hours postdose).
  - Plasma storage.
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Perform 12-lead ECG.
- Assess pruritus.
- Assess adverse events.
- Collect returned used/unused study drug and assess compliance.
- Dispense new study drug and provide dosing instructions.

6.3.2.2 Day 84 (Week 12)

The following procedures will be performed on Day 84 (Week 12):

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist circumference.
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Administer the AUDIT-C test.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Sparse PD profile (predose [fasting] and 2 hours postdose).

  - Sparse PK profile (predose [fasting] and 2 hours postdose; optional sample at 6 hours postdose).
  - Plasma storage.
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Perform 12-lead ECG.
- Perform MRI-PDFF and cT1 imaging.
- Perform FibroScan vibration-controlled transient elastography (VCTE) (optional).
- Assess pruritus.
- Assess adverse events.
- Collect returned used/unused study drug and assess compliance.

6.3.3 Part B: Treatment Period (Weeks 0 to 12)

6.3.3.1 Day 1 (Week 0)

The following procedures will be performed at Day 1 (Week 0):

- Review inclusion/exclusion criteria and confirm patient eligibility.
- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist and hip circumferences.
- Calculate WHR and WHtR.
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Sparse PD (predose [fasting]).
  - Liver fibrosis and inflammation.
  - Sparse PK (predose [fasting]).
  - Plasma storage.
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Randomize eligible patients prior to dosing.

- Assess adverse events.
- Dispense study drug and provide dosing instructions.

6.3.3.2 Day 14 (Week 2)

The following procedures will be performed at Day 14 (Week 2):

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist and hip circumferences.
- Calculate WHR and WHtR.
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Sparse PD (predose [fasting]).
  - Sparse PK (predose [fasting]).
  - Plasma storage.
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Perform 12-lead ECG.
- Assess adverse events.
- Collect returned used/unused study drug and assess compliance.
- Dispense new study drug and provide dosing instructions.

6.3.3.3 Day 28 (Week 4)

The following procedures will be performed at Day 28 (Week 4):

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist and hip circumferences.
- Calculate WHR and WHtR.

- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Administer the AUDIT-C test.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Sparse PD (predose [fasting]).
  - Liver fibrosis and inflammation.
  - Sparse PK (predose [fasting]).
  - Plasma storage.
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Perform 12-lead ECG.
- Assess adverse events.
- Collect returned used/unused study drug and assess compliance.
- Dispense new study drug and provide dosing instructions.

6.3.3.4 Day 42 (Week 6)

The following procedures will be performed at Day 42 (Week 6):

- Record changes in concomitant medications.
- Collect blood sample for the following:
  - Chemistry for assessment of ALT, AST, ALP, GGT, and total bilirubin.
- Assess adverse events.
- Collect returned used/unused study drug and assess compliance.
- Dispense new study drug and provide dosing instructions.

6.3.3.5 Day 56 (Week 8)

The following procedures will be performed at Day 56 (Week 8):

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist and hip circumferences.
- Calculate WHR and WHtR.

- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Administer the AUDIT-C test.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Sparse PD (predose [fasting]).
  - Liver fibrosis and inflammation.
  - Sparse PK (predose [fasting]).
  - Plasma storage.
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Perform 12-lead ECG.
- Assess adverse events.
- Collect returned used/unused study drug and assess compliance.
- Dispense new study drug and provide dosing instructions.

6.3.3.6 Day 70 (Week 10)

The following procedures will be performed at Day 70 (Week 10):

- Record changes in concomitant medications.
- Collect blood sample for the following:
  - Chemistry for assessment of ALT, AST, ALP, GGT, and total bilirubin.
- Assess adverse events.
- Collect returned used/unused study drug and assess compliance.
- Dispense new study drug and provide dosing instructions.

6.3.3.7 Day 84 (Week 12)

The following procedures will be performed at Day 84 (Week 12):

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist and hip circumferences.
- Calculate WHR and WHtR.

- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Administer the AUDIT-C test.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - Sparse PD (predose [fasting]).
  - Sparse PK (predose [fasting]).
  - Plasma storage.
- Collect urine sample for urinalysis and pregnancy test. If the pregnancy test is positive, perform serum hCG test.
- Perform 12-lead ECG.
- Perform MRI-PDFF and cT1 imaging.
- Perform FibroScan VCTE (optional).
- Assess adverse events.
- Collect returned used/unused study drug and assess compliance.

6.4 End of Study Follow-Up Visit (Parts A and B) (Week 14)

The following procedures will be performed at the EOS Follow-up Visit at Day 98 (Week 14):

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist circumference (Part A only).
- Measure waist and hip circumferences (Part B only).
- Calculate WHR and WHtR (Part B only).
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - PD.
  - Serum pregnancy test.

  - Liver fibrosis and inflammation.
  - PK.
  - Plasma storage.
- Collect urine sample for urinalysis.
- Perform 12-lead ECG.
- Assess pruritus (Part A only).
- Assess adverse events.

6.5 Early Termination Visit and Withdrawal Procedures (Parts A and B)

The end of treatment for patients completing the study is Day 84 (Week 12).

Patients who discontinue early from the study for any reason before completion of the Treatment Period will be requested to return to the clinic for an ET Visit within a maximum of 48 hours after their last intake of study drug, regardless of how many days they participated in the study.

Patients who discontinue early from the study for any reason after completion of the Treatment Period and before the EOS Follow-up Visit will be requested to return to the clinic for an ET Visit as soon as possible and no later than the planned EOS Follow-up Visit.

For patients who are withdrawn from the study prior to completion, all ET procedures will be performed at an ET Visit. These procedures include the following:

- Record changes in concomitant medications.
- Perform brief physical examination.
- Measure body weight and calculate BMI.
- Measure waist circumference (Part A only).
- Measure waist and hip circumferences (Part B only).
- Calculate WHR and WHtR (Part B only).
- Collect vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Administer the AUDIT-C test.
- Counsel on diet/lifestyle.
- Collect blood sample for the following:
  - Chemistry, hematology, coagulation, and lipid and metabolic profile.
  - PD (preferably within 24 to 48 hours of last intake of study drug).
  - Liver fibrosis and inflammation.
  - Serum pregnancy test.

  - PK (preferably within 24 to 48 hours of last intake of study drug).
  - Plasma storage.
- Collect urine sample for urinalysis.
- Perform 12-lead ECG.
- Perform MRI-PDFF and cT1 imaging only for patients on study drug ≥4 weeks.
- Perform FibroScan VCTE (optional).
- Assess pruritus (Part A only).
- Assess adverse events.
- Collect returned used/unused study drug and assess compliance.

7 EFFICACY ASSESSMENTS

In addition to the efficacy assessments listed below, this study plans to validate an in silico NASH disease model that predicts responders and nonresponders to EYP001a.

7.1 Efficacy Variables

7.1.1 Primary Efficacy Variables

The primary efficacy variable is absolute change in LFC as measured by MRI-PDFF from baseline to Week 12.

7.1.2 Secondary Efficacy Variables

The secondary efficacy variables include the following:

- Proportion of patients with ≥5% absolute reduction in LFC as measured by MRI-PDFF from baseline to Week 12
- Proportion of patients with ≥10% absolute reduction in LFC as measured by MRI-PDFF at Week 12
- Proportion of patients with ≥20% absolute reduction in LFC as measured by MRI-PDFF at Week 12
- Proportion of patients with a relative reduction in LFC ≥20% as measured by MRI-PDFF at Week 12
- Proportion of patients with a relative reduction in LFC ≥30% as measured by MRI-PDFF at Week 12
- Percent change (relative reduction) in LFC as measured by MRI-PDFF from baseline to Week 12
- Change and percent change in imaging-derived mean cT1 from baseline to Week 12
- Change and percent change in WHR from baseline to Week 12 (Part B only)
- Change and percent change in WHtR from baseline to Week 12 (Part B only)
- Change in the following biomarkers of liver fibrosis and inflammation: ALT, AST, AST/ALT ratio, adiponectin, high sensitivity C-reactive protein, interleukin 6, tumor necrosis factor alpha, cytokeratin-18, fibronectin, hyaluronic acid, procollagen type III N-terminal peptide, tissue inhibitor of metalloproteinases-1 (and derived enhanced liver fibrosis score), Pro-C3, and chitinase-3-like protein 1 (also known as YKL-40) from baseline to Week 4, Week 8, and Week 14/ET, as applicable

8 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

Pharmacokinetic (EYP001a concentrations) and PD (C4 and FGF19 concentrations) data will be added to the current PK/PD database, and population PK/PD models will be reassessed to investigate potential influence of NASH on PK/PD relationships.

8.1 Pharmacokinetic Variables

In Part A, during the Safety Run-in Period, intense PK sampling will occur on Day 1 (±1 day) and Day 14 (±1 day) at the following timepoints: 0 (predose), 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose; samples will be collected in the fasted state predose to 4 hours postdose, inclusive. Sparse PK samples will be collected for all other visits. Plasma samples to assess trough concentrations of EYP001a will be collected predose (fasting) in the morning and 2 hours postdose (an optional sample may also be collected at 6 hours postdose) at the following visits: Days 7, 21, 28, 56, and 84. A sample will also be collected at the EOS and ET Visits.

In Part B, sparse PK sampling will occur predose (fasting) at the following visits: Days 1, 14, 28, 56, and 84. A sample will also be collected at the EOS and ET Visits.

At the ET Visit (if applicable), the PK sample should be collected within 24 to 48 hours of last intake of study drug. The date and time of the PK draw and the last dose of study drug must be recorded in the eCRF.

Pharmacokinetic samples will be collected in a fasted state, defined as nothing by mouth except water for ≥6 hours, at all predose sampling timepoints (in Parts A and B) and at the 1- to 4-hour postdose timepoints (inclusive) on Days 1 and 14 of Part A. For BID dosing, PK timepoints will be based on the time of morning dosing.

8.2 Pharmacodynamic Variables

In Part A, intense PD sampling will occur on Day 1 (±1 day) and Day 14 (±1 day) at the following timepoints: 0 (predose, fasting), 4 (fasting), 6, 10, 12, and 24 hours postdose. Sparse PD sampling will also occur predose (fasting) and 2 hours postdose at the following visits: Days 28, 56, and 84. A sample will also be collected at the EOS and ET Visits.

In Part B, sparse PD sampling will occur predose (fasting) at the following visits: Days 1, 14, 28, 56, and 84. A sample will also be collected at the EOS and ET Visits.

At the ET Visit (if applicable), the PD sample should be collected within 24 to 48 hours of last intake of study drug. The date and time of the PD draw and the last dose of study drug must be recorded in the eCRF.

Pharmacodynamic samples will be collected in a fasted state, defined as nothing by mouth except water for ≥6 hours, at all predose sampling timepoints (in Parts A and B) and at the 4-hour postdose timepoint on Days 1 and 14 in Part A. For BID dosing, PD sampling timepoints will be based on the time of morning dosing.

Parameters will be measured in plasma samples using a validated method. Pharmacodynamic sampling will assess plasma levels of C4; FGF19; and total, primary, and secondary bile acids (such as chenodeoxycholic acid, deoxycholic acid, lithocholic acid, and/or others as appropriate).[18]

9 SAFETY ASSESSMENTS

Safety and tolerability assessments will include the monitoring of adverse events; AESIs (ie, pruritus [Part A only], drug-induced liver injury [Part A only], elevation of transaminases [Part B only], and all muscle-related adverse events); SAEs; and findings from physical examinations, vital signs, ECGs, and clinical laboratory parameters.

Throughout the study, all TEAEs, clinical assessments, and clinical laboratory parameters will be closely monitored against the criteria for drug-induced liver injury and muscle toxicity as detailed in the Clinical Safety Monitoring Plan (Appendix E).

All adverse events will be assessed and reported using the National Cancer Institute CTCAE Version 5.0 grading system. Additional safety measurements will be performed at the discretion of the Investigator (or delegate).

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until the EOS Visit. Patients should be instructed to report any adverse event that they experience to the Investigator, whether or not they think the event is due to study drug. Beginning at the time of informed consent, Investigators should make an assessment for adverse events and record the event on the appropriate adverse event eCRF. Beginning with receipt of first dose of study drug, any adverse event that occurs during the Treatment Period will be recorded as a TEAE on the appropriate eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure itself.

Any medical condition already present at screening should be recorded as medical history and not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an adverse event: worsening of preexisting condition.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as adverse events, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or

are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an adverse event. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an adverse event if any of the following are applicable:

- If an intervention is required as a result of the abnormality (such as a re-test being made more than 1 time)
- If action taken with the study drug is required as a result of the abnormality
- Based on the clinical judgment of the Investigator

9.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.

9.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For EYP001a, the reference safety information is included in the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

9.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess all adverse events using the National Cancer Institute CTCAE Version 5.0 grading system.

Causality Assessment

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

- Definite: An adverse event that is consistent with the suspected type of reaction known for the drug, in line with the reasonable temporal order after treatment, and is alleviated or disappears upon discontinuation of the study drug.
- Probable: An adverse event that is consistent with the suspected type of reaction known for the drug, in line with the reasonable temporal order after treatment, alleviates or disappears upon discontinuation of the study drug, but could also be caused by the clinical conditions of the study patient or other factors.
- Possible: An adverse event that is consistent with the suspected type of reaction known for the drug, not in line with the reasonable temporal order after treatment, and could also be caused by the clinical conditions of the study patient or other factors.
- Improbable: An adverse event that is inconsistent with the suspected type of reaction known for the drug, not in line with the reasonable temporal order after treatment, and could also be caused by the clinical conditions of the study patient or other factors.

- Not related: An adverse event that is inconsistent with the suspected type of reaction known for the drug, not in line with the reasonable temporal order from administration of the study drug, or that can be easily explained by other factors, such as underlying diseases, complication, concomitant drugs, and concurrent treatment.

The following factors should also be considered:

- The temporal sequence from study drug administration-
  - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant drug-
  - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the patient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

See Section 4.4 for withdrawal criteria.

9.1.4 Adverse Events of Special Interest

The Investigator will monitor each patient for clinical and laboratory evidence for predefined AESIs throughout the patient's participation in this study.

In Part A, events of pruritus, drug-induced liver injury, and all muscle-related adverse events will be monitored as AESIs during this study; the Investigator will assess and record these events on a separate AESI form. Pruritus will be assessed using a visual analog scale and 5-D questionnaire (degree, duration, direction, disability, and distribution) itch scale at each study visit after screening. See Appendix C and Appendix D.

In Part B, events of elevation of transaminases and all muscle-related adverse events will be monitored as AESIs during this study; the Investigator will assess and record these events on a separate AESI form.

During the course of the study, additional AESIs may be identified by the Sponsor; the Investigator will assess and record in detail any additional information on AESIs on an SAE form (whether or not the event meets seriousness criteria in Section 9.2), to be submitted within 24 hours of awareness of the event.

Adverse events of special interest must be recorded on the eCRF and sent to the ENYO safety designee via fax or email within 24 hours.

Safety Contact Information
PharmaLex
Telephone: +34 976 204 400
Fax: +34 976 204 402
Email: EnyoSafety@pharmalex.com

9.2 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening adverse event.
    - Note: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations.
    - Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a preexisting condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- An important medical event.
    - Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

9.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 14 days following the last administration of study drug must be reported to ENYO Pharma SA (hereinafter, ENYO) and its safety designee within 24 hours of the knowledge of the occurrence.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study and also complete and submit the SAE form to the safety vendor. When the form is completed, ENYO safety personnel and its safety designee will be notified electronically by the EDC system that an event has been added. If the event meets serious criteria and it is not possible to access the EDC system, send an email to the ENYO safety designee or call the ENYO safety designee SAE reporting line (contact information listed below), and fax/email the completed paper SAE form to the ENYO safety designee within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to the ENYO safety designee via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

Safety Contact Information
PharmaLex
Telephone: +34 976 204 400
Fax: +34 976 204 402
Email: EnyoSafety@pharmalex.com

9.4 Pregnancy Reporting

If a patient becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug(s) immediately and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

A pregnancy is not considered to be an adverse event or SAE; however, it must be reported to the ENYO safety designee within 24 hours of knowledge of the event (contact information listed in Section 9.3) The ENYO safety designee will then provide the Investigator/clinical site the Exposure in Utero (EIU) form for completion. The Investigator/clinical site must complete the EIU form and fax/email it back to the ENYO safety designee.

If the female partner of a male patient becomes pregnant while the patient is receiving study drug or within the safety follow-up period defined in the protocol, the Investigator should notify the ENYO safety designee and ENYO safety personnel as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the follow-up EIU form should be faxed/emailed to the ENYO safety designee and ENYO safety personnel. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

9.5 Expedited Reporting

The Sponsor/designee will report all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA, applicable competent authorities in all the countries concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, applicable competent authorities concerned, and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to an investigational medicinal product.

9.6 Special Situation Reports

Special situation reports include reports of EYP001a or statin overdose, misuse, abuse, and medication error.

- **Overdose:** Refers to the administration of a quantity of EYP001a or statin given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the patient has taken additional dose(s) or the Investigator has reason to suspect that the patient has taken additional dose(s).
- **Misuse:** Refers to situations where EYP001a or statin is intentionally and inappropriately used in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is persistent or sporadic, intentional excessive use of EYP001a or statin, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of EYP001a or statin by a healthcare professional, patient, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors. Cases of patients missing doses of study drug are not considered reportable as medication error.

All special situation events as described above must be documented and captured in the eCRF. All adverse events associated with these special situation reports should be reported as adverse events or SAEs as well as recorded on the adverse event eCRF and/or the SAE report form. Details of the signs and symptoms, clinical management, and outcome should be provided, when available.

9.7 Medical History

Medical history, including information on prior and concomitant medication, will be collected for all patients at screening. Data from previous liver biopsies are not a prerequisite for enrollment but should be collected if available in the patient's medical record.

9.8 Clinical Laboratory Evaluations

Clinical safety laboratory parameters will be measured or calculated at study visits specified in Appendix A. Profiles for hematology, coagulation, serum chemistry, lipid and metabolic parameters, and urinalysis will be evaluated from samples collected after ≥6 hours of fasting (nothing by mouth except water). Further analysis of urine sediment or urine microscopy will be performed when there are any abnormalities on any of the following 3 dipstick results: leukocyte esterase, blood, or nitrite, and if judged clinically significant by the Investigator. See Appendix B for a complete list of laboratory analytes.

For women of childbearing potential, a serum hCG test will be performed at screening and the EOS and ET Visits. Urine hCG testing will be performed at visits specified in Appendix A. If a urine hCG test is positive, a serum hCG test will be performed.

Follicle-stimulating hormone level will be measured at screening to confirm postmenopausal state in women ≤55 years of age.

Anti-HBV, anti-HCV, and anti-HIV will be assessed at screening, and HCV RNA will be reflexively tested. Samples will be collected for central laboratory analysis except if viral serology data is already available in patient's medical history/records and obtained within 90 days prior to screening.

Plasma from blood samples obtained at screening and at study visits specified in Appendix A, including EOS and ET Visits, will be stored for protocol-related safety testing or exploratory analyses.

Blood sampling procedures, including information on blood volume, collection tubes, sample processing, storage, and shipping are provided in the Laboratory Manual.

The safety of statin coadministration will be assessed at study visits specified in Appendix A by monitoring CK levels.

Technical details on laboratory parameters (methods and commercial kit[s]) will be specified in the Laboratory Manual.

Additional laboratory testing may be required in response to adverse events and laboratory findings as described in the Clinical Safety Monitoring Plan (Appendix E). Laboratory abnormalities should be reported as an adverse event if any of the following is applicable:

- If an intervention is required as a result of the abnormality (such as a re-test being performed more than 1 time)
- If action taken with the study drug is required as a result of the abnormality

9.9 Vital Signs and Anthropometrics

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) and anthropometrics (height, body weight, BMI, waist circumference, hip circumference [Part B only], WHR [Part B only], and WHtR [Part B only]) will be assessed as specified in Appendix A.

Blood pressure will be measured using a standardized process:

- Clinical site staff will assess blood pressure with the patient in the sitting position after 5 minutes of rest and before any blood draws.
- Clinical site staff will use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery.
- Clinical site staff will record the arm used for the measurement and use the same arm throughout the study.
- Clinical site staff will measure and record the blood pressure.

Blood pressure will be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device. A blood pressure reading will be repeated 1 to 2 minutes later, and the second reading will also be recorded to the nearest 2 mmHg mark.

Waist circumference will be measured using a standardized process:

- Measure the waist circumference at the end of several consecutive natural breaths, at a level parallel to the floor, midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid axillary line. The tape should be placed around the abdomen at the level of this midway point and a reading taken when the tape is snug but does not compress the skin.[19]

Hip circumference will be measured using a standardized process:

- Measure the hip circumference at a level parallel to the floor, at the largest circumference of the buttocks. The tape should be placed around the hips and a reading taken when the tape is snug but does not compress the skin.

9.10 Electrocardiograms

Single 12-lead ECGs will be performed at screening; on Days 7 (Part A only), 14, 21 (Part A only), 28, 56, and 84; and at the EOS and ET Visits after the patient has been resting in the supine position for at least 10 minutes. The ECG will include 12 standard leads and will be recorded at a paper speed of 25 mm/sec. QT interval corrected for heart rate using Fridericia's formula will be measured.

In case of evident bad quality of the tracing (eg, muscle tremor), the ECG will be repeated. See Appendix A.

9.11 Physical Examinations

A complete physical examination (including general appearance; eyes, ears, nose, and throat; head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatological; neurological systems; mental status; and extremities) will be performed at screening. Brief, symptom-directed physical examinations will be performed in Part A at each study visit after screening and in Part B on Days 1, 14, 28, 56, and 84; and at the EOS and ET Visits. See Appendix A.

9.12 Pruritus Assessments

In Part A, the pruritus visual analog scale and 5-D questionnaire (degree, duration, direction, disability, and distribution) itch scale will be assessed at each study visit after screening. See Appendix A.

In Part B, pruritus will be reported as any other adverse event. If a patient reports pruritus, the visual analog scale and the 5-D questionnaire (degree, duration, direction, disability, and distribution) itch scale will be administered.

9.12.1 Pruritus Management – Guidance to Investigators

Mostly mild to moderate pruritus has been observed in clinical trials with EYP001a and has also been reported with other FXR agonists and in patients with NASH. Pruritus is also part of the natural disease symptomatology of NASH and independent of any pharmacological treatment. Tolerance to pruritus may develop over continuous, uninterrupted dosing or after a short (few days) interruption of EYP001a (empirical observations).

The following 3-level therapeutic approach to pruritus should be applied:

1. Topical non-pharmacological or over-the-counter interventions to improve pruritus may be tried and can be advised to patients. These include application of moisturizers, cooling agents, and antihistamines; or taking cool showers/showering in the morning, using clear/gentle soaps and laundry detergents, application of cold packs or fabric strips soaked in cold water, avoidance of wool or other irritating fabrics, and wearing loose-fitting clothing.
2. In the case of no improvement of pruritus, a drug holiday of 2 days to a maximum of 5 days may be implemented.
3. In the case pruritus prevails and requires systemic oral pharmacological treatment, it is encouraged to seek advice from the Medical Monitor. Recommended possible comedications for pruritus are: naltrexone (25 to 50 mg/day orally [po]), ondansetron (4 to 24 mg/day po), hydroxyzine (25 to 75 mg/day po), sertraline (25 to 75 mg/day po), and gabapentin 300 mg/day po).

   Note: Bile acid sequestrants are excluded medications, the concomitant use of naltrexone with gabapentin is disallowed.

9.13 Drug-Induced Liver Injury and Muscle Toxicity Monitoring

Throughout the study, all TEAEs, clinical assessments, and clinical laboratory parameters will be closely monitored against the criteria for drug-induced liver injury and muscle toxicity as detailed in the Clinical Safety Monitoring Plan (Appendix E). The Clinical Safety Monitoring Plan describes the actions with regard to the study drug that are required upon clinical findings and confirmation of laboratory abnormalities suggestive of muscle toxicity or liver injury of varying degrees as a function of baseline findings.

9.14 Diet and Lifestyle Counseling

Diet and lifestyle counseling will occur as per standard of care. Diet and lifestyle counseling will be performed in Part A at each study visit and in Part B at screening and on Days 1, 14, 28, 56, and 84; and at the EOS and ET Visits. High-level dietary and physical activity guidelines will be provided and documented in the eCRF.

10 STATISTICS

10.1 Analysis Populations

The Intent-to-Treat (ITT) Population includes all patients who are randomized and administered at least 1 dose of study drug. Patients without a Week 12 or end of treatment MRI-PDFF assessment will be imputed as nonresponders unless otherwise specified.

The Safety Population is identical to the ITT Population.

The modified ITT (mITT) Population includes patients from the ITT Population who have valid baseline and Week 12 MRI-PDFF measurements of LFC.

The Per-Protocol Population includes all patients from the mITT Population who finish the 12-week Treatment Period without any major protocol violations. The analysis of LFC as measured by MRI-PDFF will be repeated on the Per-Protocol Population to test the robustness of results.

10.2 Statistical Methods

10.2.1 Analysis of Efficacy

The primary and secondary efficacy analyses are described in the sections below. The efficacy analyses of LFC as measured by MRI-PDFF will be conducted on the ITT Population and repeated on the mITT and Per-Protocol Populations. The analysis of other efficacy variables will be based on the ITT Population.

For efficacy variables, observed data and change and/or percent change from baseline will be summarized using descriptive statistics and graphs per dose group and visit as appropriate.

10.2.1.1 Primary efficacy analysis

The primary efficacy analysis will be performed on the ITT Population. Missing MRI-PDFF values at Week 12 or ET will be imputed based on the missing at random assumption using multiple imputation.

The primary efficacy analysis will be performed on the change in LFC as measured by MRI-PDFF from baseline to Week 12 or ET using an analysis of covariance (ANCOVA) model with baseline fat fraction as a covariate and treatment, use of statin comedication at screening (stratification factor: use of statin [yes, no]), and T2DM status (yes, no) in Part A, and by statin use (yes, no) and LFC at screening (stratification factor with 3 categories: LFC<16%, 16%≤LFC<22%, and 22%≤LFC) in Part B, as factors. Pairwise treatment comparisons between each EYP001a dose and placebo will be conducted from the ANCOVA model with least-square means, standard errors, 95% confidence intervals, and p-values being presented. To adjust the 3 tests (each EYP001a dose and placebo) for multiplicity in order to control the family-wise type I error at 0.025 one-sided, the Bonferroni method will be used.

The primary efficacy results will subsequently be analyzed by adding LSMs and CAP values at enrollment as additional factors.

10.2.1.2 Sensitivity analysis

Sensitivity analyses will be conducted by repeating the primary efficacy analysis based on:

- The ITT Population with missing MRI-PDFF values at Week 12 or ET imputed using the multiple imputation with tipping point method based on the missing not at random assumption
- The mITT Population

10.2.1.3 Secondary efficacy analysis

The statistical analysis of secondary efficacy variables based on change from baseline to Week 12 will be conducted with a similar ANCOVA model, while secondary efficacy variables measured at multiple timepoints will be analyzed by mixed effect model repeated measures model.

The responder (categorical) variables will be analyzed by a Cochran-Mantel-Haenszel test, stratified by statin comedication use and T2DM status at screening in Part A and statin comedication and LFC at screening in Part B. The analysis of the responder variables will be repeated using logistic regression models, adjusting for treatment, statin comedication at screening, and T2DM status at screening. Patients without a Week 12 or end of treatment MRI-PDFF assessment will be imputed as nonresponders. All secondary efficacy variables will be summarized using descriptive statistics.

10.2.1.4 Validation of nonalcoholic steatohepatitis disease model

The anticipated EYP001-202 efficacy results will serve as validation of an in silico NASH disease model, which was built based on public and expert knowledge and combined with the Phase 1 PK and PD EYP001 results.[15] The model integrates 309 liver FXR-related biological variables and 1320 parameters and explores the effect of different EYP001 treatment regimens on NASH-relevant efficacy endpoints in a virtual population. Iterations of the model will support future explorations of development strategies with different EYP001 Phase 2 and 3 study designs.

10.2.2 Pharmacodynamic Analysis

Pharmacodynamic parameters, observed data, and change and/or percent change from baseline will be summarized using descriptive statistics and graphs per dose group and visit, as appropriate.

10.2.3 Pharmacokinetic Analysis

Plasma concentrations of EYP001a will be listed for all patients with available EYP001a plasma concentrations in treatment groups that include EYP001a or placebo. All concentrations below the limit of quantification will be labeled as such in the concentration data listings and will be treated as 0 in the summary statistics.

Listings of individual patient plasma concentrations and actual blood sampling times and graphs of concentration versus time will be prepared by dose. Plasma concentrations will be summarized by and compared among different doses using descriptive statistics.

10.2.4 Analysis of Safety

Baseline for physical examinations, all vital signs, 12-lead ECG measurements, pruritus questionnaire (Part A only), and clinical laboratory assessments will be defined as the last evaluation done before the first administration of study drug in each dose group on Day 1.

Safety variables will be tabulated and presented for the Safety Population.

10.2.4.1 Adverse events

The original terms used in the eCRF by Investigators to identify adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). All adverse events will be assessed and reported using the National Cancer Institute CTCAE Version 5.0 grading system. A TEAE is defined as a new or worsening adverse event after the first dose of study drug. The percentage of patients with TEAEs will be summarized for each dose group by system organ class and preferred term. The study drug-related TEAEs and SAEs will be summarized in the same fashion. The TEAEs will also be summarized by system organ class, preferred term, and maximum severity. All SAEs and TEAEs leading to early discontinuation will be listed.

The safety of EYP001a with statin coadministration will be assessed based on the difference in frequency of TEAEs between treatment groups.

10.2.4.2 Laboratory values

The clinical laboratory analytes at each visit and change from baseline will be summarized descriptively. Abnormalities based on predefined normal ranges will be tabulated by dose group showing patient counts and percentages. A listing of patients with any laboratory results outside the reference ranges will be provided if appropriate.

10.2.4.3 Vital signs, anthropometrics, and electrocardiograms

Vital signs, anthropometrics, and ECGs at each visit assessed and change from baseline will be summarized descriptively.

10.2.4.4 Prior and concomitant medications

Prior and concomitant medications will be coded with the World Health Organization (WHO) Drug Dictionary. A prior medication is defined as any medication taken by the patient before the first dose of study drug. A concomitant medication is defined as any medication taken by the patient at the same time or after the first dose of study drug. Number and frequency of patients taking prior and concomitant medications will be tabulated and listed.

10.2.5 Demographic and Baseline Characteristics

For all patients who receive at least 1 dose of study drug, descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be performed for age, gender, race and ethnicity, BMI, waist circumference, WHR (Part B only), WHtR (Part B only), body weight, and height.

10.2.6 Interim Analysis

All available unblinded preliminary safety, PK, and PD results will be comprehensively reviewed during 2 interim analysis timepoints:

- The first interim analysis will be performed at the end of the Safety Run-in Period, after the last of the 24 patients randomized in Part A has completed Day 28 (Week 4). It is anticipated that at the time of the first interim analysis, approximately 10 patients will have completed Day 84 (Week 12) of Part A.
- A second interim analysis will be performed when 50% of patients in Part B have completed Day 56 (Week 8).

The interim analyses will be performed on all available primary and secondary endpoints according to the DSMC charter. The conclusions and recommendations of the DSMC will be shared blindly with the Sponsor and clinical sites.

10.2.7 Data and Safety Monitoring Committee

An external, independent DSMC will review all available unblinded preliminary safety, PK, and PD results when any stopping rules are met and in accordance with the interim analysis timepoints described in Section 10.2.6. In Part B, the DSMC will be promptly notified for further review if any patients experience ALT, AST, or bilirubin elevations 2 × above baseline values.

The interim analyses will be performed on all available primary and secondary endpoints according to the DSMC charter, which describes the overall guidelines, composition, roles, and responsibilities of the independent DSMC for this study, including the selection of DSMC members, timing of meetings, methods of providing information to and from the DSMC, frequency and format of meetings, data analysis recommendations, and DSMC relationships with other parties participating in the conduct of this study. Patient accrual will continue throughout the period of DSMC review. The DSMC will advise on the accrual of the remaining patients per protocol or on any amendments that are necessary for safety reasons.

10.2.8 Sample Size Determination

The sample size of 114 randomized patients (n = 24 patients in Part A and n = 90 in Part B [n = 30 patients per treatment group]) is based on the efficacy endpoint: absolute change in LFC as measured by MRI-PDFF from baseline to Week 12, assuming that the treatment difference between each active treatment group with placebo is at least 5.1% with a common standard deviation of 5.8%.

With a 2-sample Z-test with the power of 0.8 and an overall family-wise 1-sided alpha of 0.025 (or each active versus placebo alpha = 0.0125 after Bonferroni adjustment), 26 patients per treatment group will be needed to complete the Week 12 Visit. With the consideration of an approximately 13% dropout rate before Week 12, 30 patients will be randomized per treatment group in Part B.

A Lan-DeMets alpha spending function will be used for this group sequential design. Nonbinding O'Brien-Fleming efficacy boundaries and futility boundaries will be calculated using EAST 6.4 software. The efficacy and futility boundaries are described in Table 6.

At the time of the interim analysis, if the test-statistic is equal to or less than the futility boundary, the Sponsor can decide to stop the study due to lack of efficacy.

Table 6. Efficacy and Futility Boundaries for Part B

Look	Week 8 Number of Patients	Week 12 Number of Patients	Information Fraction	Cumulative Alpha Spent	Cumulative Beta Spent	Z Efficacy Boundary	Z Futility Boundary	p-value Efficacy Boundary	p-value Futility Boundary
#1 (interim analysis)	45	23	0.25	<0.0001	0.0113	-4.7604	0.6966	<0.0001	0.7570
#2 (final analysis)	90		1	0.0125	0.1962	-2.2414	-2.2414	0.0125	0.0125

11 DATA MANAGEMENT AND RECORD KEEPING

11.1 Data Management

11.1.1 Data Handling

Data will be recorded at the clinical site on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents for completeness and accuracy. Data reported in the eCRFs that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. All corrections or changes made to any study data in the EDC system will be appropriately tracked in an audit trail. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

11.1.2 Computer Systems

Data will be processed using a validated computer system that adheres to Title 21 of the US Code of Federal Regulations (21 CFR Part 11) compliance.

11.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All clinical site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with 21 CFR Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

11.1.4 Medical Information Coding

For medical information, the latest versions of the following thesauri will be used:

- MedDRA for medical history and adverse events
- WHO Drug Dictionary for prior and concomitant medications

11.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the clinical site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

11.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study drug, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the clinical site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer

or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last patient in the study.

12 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

12.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

12.2 Institutional Review Board/Independent Ethics Committee

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at clinical sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and ICH Guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

No drug will be released to a clinical site for dosing until written IRB/IEC authorization has been received by the Sponsor.

12.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator or designee (where locally permitted) will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

12.4 Patient Card

On enrollment in the study, the patient will receive a patient card to be carried at all times. The patient card will state that the patient is participating in a clinical research study and contact details in case of an emergency.

12.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC for clinical sites in the European Union, applicable regulatory requirements, and the Declaration of Helsinki and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the Investigator and clinical site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the clinical site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the clinical site by signature and date on the study-specific monitoring log.

12.6 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

12.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

12.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

12.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under US 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out patient liability insurance for all patients who give their consent to the clinical study.

12.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (ie, initiation of study centers) when the CTA and favorable ethics opinion have been received.

13 STUDY ADMINISTRATIVE INFORMATION

13.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by the Sponsor or their designee. All protocol amendments will undergo the same review and approval process as the original protocol.

Written verification of IRB/IEC and Competent Authority approval will be obtained before any amendment is implemented that affects patient safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC and Competent Authority approvals; however, the IRB/IEC and Competent Authority will be notified about an administrative change if required by local regulations.

A protocol amendment may be implemented after it has been approved by the IRB/IEC and Competent Authority, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported according to the local regulations.

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APPENDIX A: SCHEDULE OF PROCEDURES

Table 7. Schedule of Procedures – Part A

		Treatment Period								
	Screening[a]	Safety Run-In Period					Continued Treatment Period		EOS FUP Visit	ET Visit[b]
Study Week	-12 to -1	0	1	2	3	4	8	12	14	
Study Day[b]	-84 to -3	Day 1	Day 7	Day 14	Day 21	Day 28	Day 56	Day 84	Day 98	
Assessment										
Informed consent	X									
Eligibility criteria	X	X[c]								
Demographics	X									
Medical history	X									
Prior/concomitant medications[d]	X	X	X	X	X	X	X	X	X	X
Height and body weight[e]	X	X	X	X	X	X	X	X	X	X
BMI calculation[e]	X	X	X	X	X	X	X	X	X	X
Waist circumference[f]	X	X	X	X	X	X	X	X	X	X
Physical examination[g]	X	X	X	X	X	X	X	X	X	X
Vital signs[h]	X	X	X	X	X	X	X	X	X	X
AUDIT-C[i]	X			X	X	X	X	X		X
Randomization[j]		X								
Pruritus assessment[m]		X	X	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X
Viral serology[k]	X									
Chemistry, hematology, coagulation, and lipid and metabolic profile[l]	X	X	X	X	X	X	X	X	X	X
Urinalysis[n]	X	X	X	X	X	X	X	X	X	X
Pregnancy test[o]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[p]	X		X	X	X	X	X	X	X	X
FibroScan®[q]	X							X		X
MRI-PDFF and cT1 imaging[r]	X							X		X[s]
Diet/lifestyle counseling[t]	X	X	X	X	X	X	X	X	X	X
PD biomarker sampling[v]		X		X		X	X	X	X	X[s]
Liver fibrosis and inflammation sampling[w]		X	X		X	X	X		X	X

Table 7. Schedule of Procedures – Part A (Continued)

	Screening[a]	Treatment Period							EOS FUP Visit	ET Visit[c]
		Safety Run-In Period					Continued Treatment Period			
Study Week	**-12 to -1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**14**	
Study Day[b] **Assessment**	**-84 to -3**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56**	**Day 84**	**Day 98**	
PK sampling[y]		X[z]	X	X[z]	X	X	X	X	X	X[x]
Blood sampling for plasma storage[aa]	X						X	X	X	X
Dispense patient diary		X								
Dispense EYP001a or placebo		X[bb]		X[bb]		X	X			
Collect used/unused study drug and assess compliance				X		X	X	X		X

Blood sample collection will be prioritized starting with the safety sample. All blood samples should be collected while the patient is in a fasted state, defined as nothing by mouth except water for ≥6 hours. Additional details on fasting during PK and PD sampling are provided in footnotes w and z, respectively.

a. The Screening Period may be up to 12 weeks in duration. A patient who is first designated as a screen failure prior to being randomized may be rescreened upon Sponsor or designee approval. If the patient was screen failed after the MRI-PDFF was completed, the original MRI-PDFF scan may be utilized for rescreening, provided it was obtained within 1 month prior to rescreening. Patients will be prerandomized into the study once all eligibility criteria are confirmed.
b. A ±3-day window is acceptable for all visits during the Treatment Period, except for Days 1 and 14 of Part A, when the window is ±1 day.
c. Patients who discontinue early from the study for any reason prior to completion of the Treatment Period will be requested to return to the clinic for an ET Visit within a maximum of 48 hours after their last intake of study drug, regardless of how many days they participated in the study. Patients who discontinue early from the study for any reason after completion of the Treatment Period and before the EOS FUP Visit will be requested to return to the clinic for an ET Visit as soon as possible and no later than the planned EOS FUP Visit.
d. Perform prior to dosing.
e. Authorized medications per exception list and on a case-by-case basis, as documented by written approval from the Sponsor, are acceptable.
f. Height assessed only at screening.
g. Use screening height for BMI calculation.
h. Measure the waist circumference at the end of several consecutive natural breaths, at a level parallel to the floor, midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid axillary line. The tape should be placed around the abdomen at the level of this midway point and a reading taken when the tape is snug but does not compress the skin.
i. A complete physical examination (including general appearance; eyes, ears, nose, and throat; head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatological; neurological systems; mental status; and extremities) will be performed at screening. Brief, symptom-directed physical examinations will be performed on Days 1, 7, 14, 21, 28, 56, 84, and at the EOS and ET Visits.
j. Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature and will be performed with the patient in the sitting position after 5 minutes of rest and before any blood draws. Clinical site staff will use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery. Clinical site staff will record the arm used for the measurement and use the same arm throughout the study. Clinical site staff will measure and record the blood pressure. Blood pressure will be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device. A blood pressure reading will be repeated 1 to 2 minutes later, and the second reading will also be recorded to the nearest 2 mmHg mark.
k. Patients with AUDIT-C scores ≥3 points at screening will receive the full AUDIT and will be excluded if they score ≥8 points on the full AUDIT. Patients with AUDIT-C scores <3 points will not receive the full AUDIT.
l. Can occur after eligibility check on Day -3 at the earliest and prior to dosing on Day 1 at the latest.

m. Assess using a visual analog scale and 5-D questionnaire (degree, duration, direction, disability, and distribution) itch scale.
n. Anti-HCV, anti-HIV, and anti-HBV status will be assessed, and HCV RNA will be reflexively tested. Samples will be collected for central laboratory analysis except if viral serology data is already available in patient's medical history/records and obtained within 90 days prior to screening.
o. Collected after ≥6 hours of fasting. See Appendix B for the complete list of clinical laboratory parameters.
p. Urinalysis will be evaluated from samples collected after ≥6 hours of fasting. Further analysis of urine sediment or urine microscopy will be performed when there are any abnormalities on any of the following 3 dipstick results: leukocyte esterase, blood, or nitrite, and if judged clinically significant by the Investigator.
q. For women of childbearing potential, a serum hCG test will be performed at screening and the EOS and ET Visits. Urine hCG testing will be performed at all other visits. If a urine hCG test is positive, a serum hCG test will be performed. Follicle-stimulating hormone level will be measured at screening to confirm postmenopausal state in women ≤55 years of age.
r. Single 12-lead ECGs will be performed at screening; on Days 7, 14, 21, 28, 56, and 84; and at the EOS and ET Visits after the patient has been resting in the supine position for at least 10 minutes. In case of evident bad quality of the tracing (eg, muscle tremor), the ECG will be repeated. QT interval corrected for heart rate using Fridericia's formula will be measured.
s. FibroScan with the use of a probe appropriate for the patient's stature for VCTE assessment of LSM for fibrosis and CAP for steatosis with cut-off values LSM ≥8.5 kPa and CAP >300 dB/m, respectively. Patients do not need to undergo a CAP assessment if their medical records indicate an MRI-PDFF LFC ≥10% within the 12 months prior to screening. Assessments at Day 84 and ET Visits are optional.
t. Perform if FibroScan values (LSM and CAP) are within eligibility range; MRI-PDFF using standardized imaging acquisition calibration protocol and central reading to be performed at screening (as baseline value) and Week 12 or ET.
u. Perform only for patients on study drug for ≥4 weeks.
v. Diet/lifestyle counseling will occur as per standard of care at each study visit. High-level dietary and physical activity guidelines will be provided and documented in the eCRF.
w. Intense PD sampling will occur on Day 1 (±1 day) and Day 14 (±1 day) of Part A at the following timepoints: 0 (predose, fasting), 4 (fasting), 6, 10, 12, and 24 hours postdose. Sparse PD sampling will also occur predose (fasting) and 2 hours postdose at the following visits: Days 28, 56, and 84. A sample will also be collected at the EOS and ET Visits. For BID dosing, PD sampling timepoints will be based on the time of morning dosing. Pharmacodynamic sampling will assess plasma levels of C4; FGF19; and total, primary, and secondary bile acids (such as CDCA, DCA, LCA, and/or others as appropriate).
x. At the ET Visit (if applicable), a PK/PD sample should be collected, preferably within 24 to 48 hours of last intake of study drug. The date and time of the PK/PD draw and the last dose of study drug must be recorded in the eCRF.
y. Liver fibrosis and inflammation parameters include ALT, AST, AST/ALT ratio, adiponectin, high sensitivity C-reactive protein, interleukin 6, tumor necrosis factor alpha, cytokeratin-18, fibronectin, hyaluronic acid, procollagen type III N-terminal peptide, tissue inhibitor of metalloproteinases-1 (and derived enhanced liver fibrosis score), Pro-C3, and chitinase-3-like protein 1 (also known as YKL-40).
z. Intense PK sampling will occur on Day 1 (±1 day) and Day 14 (±1 day) of Part A at the following timepoints: 0 (predose), 1, 2, 4, 6, 8, 10, 12, and 24 hours postdose; samples will be collected in the fasted state predose to 4 hours postdose, inclusive. Sparse PK samples will be collected for all other visits. Plasma samples to assess trough concentrations of EYP001a will be collected predose (fasting) in the morning and 2 hours postdose (an optional sample may also be collected at 6 hours postdose) at the following visits: Days 7, 21, 28, 56, and 84. A sample will also be collected at the EOS and ET Visits. For BID dosing, PK timepoints will be based on the time of morning dosing.
aa. Plasma from blood samples will be stored for protocol-related safety testing or exploratory analyses.
bb. During intense PK/PD sampling on Days 1 and 14 of Part A, dosing will occur with water only; blood sampling timepoints are fixed during this period. The start of meal times must be captured and can vary with meal times in the morning and evening – limited up to 3 main meals per 24 hours with ±2-hour variability.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUDIT = Alcohol Use Disorders Identification Test; AUDIT-C = Alcohol Use Disorders Identification Test-Concise; BID = twice daily; BMI = body mass index; C4 = 7αhydroxy-4-cholesten-3-one; CAP = controlled attenuation parameter; CDCA = chenodeoxycholic acid; cT1 = iron-corrected T1; DCA = deoxycholic acid; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End of Study; ET = Early Termination; FGF19 = fibroblast growth factor 19; FUP = Follow-up; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LCA = lithocholic acid; LFC = liver fat content; LSM = liver stiffness measurement; MRI-PDFF = magnetic resonance imaging proton density fat fraction; PD = pharmacodynamic; PK = pharmacokinetic; RNA = ribonucleic acid; VCTE = vibration-controlled transient elastography.

Table 8. Schedule of Procedures – Part B

	Screening[a]	Treatment Period							EOS FUP Visit	ET Visit[c]
Study Week	**-12 to -1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	
Study Day[b] **Assessment**	**-84 to -3**	**Day 1**	**Day 14**	**Day 28**	**Day 42**	**Day 56**	**Day 70**	**Day 84**	**Day 98**	
Informed consent	X									
Eligibility criteria	X	X[d]								
Demographics	X									
Medical history	X[e]									
Prior/concomitant medications[f]	X	X	X	X	X	X	X	X	X	X
Height and body weight[g]	X	X	X	X		X		X	X	X
BMI calculation[h]	X	X	X	X		X		X	X	X
Waist and hip circumference[i]	X	X	X	X		X		X	X	X
WHR and WHtR calculations[h]	X	X	X	X		X		X	X	X
Physical examination[j]	X	X	X	X		X		X	X	X
Vital signs[k]	X	X	X	X		X		X	X	X
AUDIT-C[l]	X			X		X		X		X
Randomization[m]		X								
Adverse event monitoring[e]	X	X	X	X	X	X	X	X	X	X
Viral serology[n]	X									
Chemistry, hematology, and coagulation[o]	X	X	X	X	X[p]	X	X[q]	X	X	X
Lipid and metabolic profile[o]	X	X	X	X		X		X	X	X
Urinalysis[r]	X	X	X	X		X		X	X	X
Pregnancy test[s]	X	X	X	X		X		X	X	X
12-Lead ECG[t]	X		X	X		X		X	X	X
FibroScan®[u]	X							X		X
MRI-PDFF and cT1 imaging[u]	X							X		X[v]
Diet/lifestyle counseling[w]	X	X	X	X		X		X	X	X
PD biomarker sampling[x]		X	X	X		X		X	X	X[y]
Liver fibrosis and inflammation sampling[z]		X		X		X			X	X
PK sampling[aa]		X	X	X		X		X	X	X[y]

Table 8. Schedule of Procedures – Part B (Continued)

	Screening[a]	Treatment Period							EOS FUP Visit	ET Visit[c]
Study Week	**-12 to -1**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	
Study Day[b] **Assessment**	**-84 to -3**	**Day 1**	**Day 14**	**Day 28**	**Day 42**	**Day 56**	**Day 70**	**Day 84**	**Day 98**	
Blood sampling for plasma storage[bt]	X	X	X	X		X		X	X	X
Dispense EYP001a or placebo		X	X	X	X	X	X			
Collect used/unused study drug and assess compliance			X[cc]	X[cc]	X	X[cc]	X[cc]	X[cc]		X

Blood sample collection will be prioritized starting with the safety sample. All blood samples should be collected while the patient is in a fasted state, defined as nothing by mouth except water for ≥6 hours.

a. The Screening Period may be up to 12 weeks in duration. A patient who is first designated as a screen failure prior to being randomized may be rescreened upon Sponsor or designee approval. If the patient was screen failed after the MRI-PDFF was completed, the original MRI-PDFF scan may be utilized for rescreening, provided it was obtained within 1 month prior to rescreening.
b. A ±3-day window is acceptable for all visits during the Treatment Period.
c. Patients who discontinue early from the study for any reason prior to completion of the Treatment Period will be requested to return to the clinic for an ET Visit within a maximum of 48 hours after their last intake of study drug, regardless of how many days they participated in the study. Patients who discontinue early from the study for any reason after completion of the Treatment Period and before the EOS FUP Visit will be requested to return to the clinic for an ET Visit as soon as possible and no later than the planned EOS FUP Visit.
d. Perform prior to dosing.
e. If pruritus is reported, assess using a visual analog scale and 5-D questionnaire (degree, duration, direction, disability, and distribution) itch scale.
f. Authorized medications per exception list and on a case-by-case basis, as documented by written approval from the Sponsor, are acceptable.
g. Height assessed only at screening.
h. Use screening height for BMI and WHtR calculations.
i. Measure the waist circumference at the end of several consecutive natural breaths, at a level parallel to the floor, midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid axillary line. The tape should be placed around the abdomen at the level of this midway point and a reading taken when the tape is snug but does not compress the skin. Measure the hip circumference at a level parallel to the floor, at the largest circumference of the buttocks. The tape should be placed around the hips and a reading taken when the tape is snug but does not compress the skin. Waist to hip ratio (WHR) and (WHtR) will be calculated at each visit in which assessed.
j. A complete physical examination (including general appearance; eyes, ears, nose, and throat; head and neck; chest and lungs; cardiovascular; abdomen; musculoskeletal; lymphatic; dermatological; neurological systems; mental status; and extremities) will be performed at screening. Brief, symptom-directed physical examinations will be performed on Days 1, 14, 28, 56, 84, and at the EOS and ET Visits.
k. Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature and will be performed with the patient in the sitting position after 5 minutes of rest and before any blood draws. Clinical site staff will use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery. Clinical site staff will record the arm used for the measurement and use the same arm throughout the study. Clinical site staff will measure and record the blood pressure. Blood pressure will be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device. A blood pressure reading will be repeated 1 to 2 minutes later, and the second reading will also be recorded to the nearest 2 mmHg mark.
l. Patients with AUDIT-C scores ≥3 points at screening will receive the full AUDIT and will be excluded if they score ≥8 points on the full AUDIT. Patients with AUDIT-C scores <3 points will not receive the full AUDIT.
m. Can occur after eligibility check on Day -3 at the earliest and prior to dosing on Day 1 at the latest.

n. Anti-HCV, anti-HIV, and anti-HBV status will be assessed, and HCV RNA will be reflexively tested. Samples will be collected for central laboratory analysis except if viral serology data is already available in patient's medical history/records and obtained within 90 days prior to screening.
o. Collected after ≥6 hours of fasting. See Appendix B for the complete list of clinical laboratory parameters.
p. On Days 42 and 70 only ALT, AST, ALP, GGT, and total bilirubin will be measured.
q. Urinalysis will be evaluated from samples collected after ≥6 hours of fasting. Further analysis of urine sediment or urine microscopy will be performed when there are any abnormalities on any of the following 3 dipstick results: leukocyte esterase, blood, or nitrite, and if judged clinically significant by the Investigator.
r. For women of childbearing potential, a serum hCG test will be performed at screening and the EOS and ET Visits. Urine hCG testing will be performed at all other visits. If a urine hCG test is positive, a serum hCG test will be performed. Follicle-stimulating hormone level will be measured at screening to confirm postmenopausal state in women ≤55 years of age.
s. Single 12-lead ECGs will be performed at screening; on Days 14, 28, 56, and 84; and at the EOS and ET Visits after the patient has been resting in the supine position for at least 10 minutes. In case of evident bad quality of the tracing (eg, muscle tremor), the ECG will be repeated. QT interval corrected for heart rate using Fridericia's formula will be measured.
t. FibroScan with the use of a probe appropriate for the patient's stature for VCTE assessment of LSM for fibrosis and CAP for steatosis with cut-off values LSM ≥8.5 kPa and CAP >300 dB/m, respectively. Patients do not need to undergo a CAP assessment if their medical records indicate an MRI-PDFF LFC ≥10% within the 12 months prior to screening. Assessments at Day 84 and ET Visits are optional.
u. Perform if FibroScan values (LSM and CAP) are within eligibility range; MRI-PDFF using standardized imaging acquisition calibration protocol and central reading to be performed at screening (as baseline value) and Week 12 or ET.
v. Perform only for patients on study drug for ≥4 weeks.
w. Diet/lifestyle counseling will occur as per standard of care at screening and on Days 1, 14, 28, 56, and 84; and at the EOS and ET Visits. High-level dietary and physical activity guidelines will be provided and documented in the eCRF.
x. Sparse PD sampling will occur predose (fasting) at the following visits: Days 1, 14, 28, 56, and 84. A sample will also be collected at the EOS and ET Visits. Pharmacodynamic sampling will assess plasma levels of C4; FGF19; and total, primary, and secondary bile acids (such as CDCA, DCA, LCA, and/or others as appropriate).
y. At the ET Visit (if applicable), a PK/PD sample should be collected, preferably within 24 to 48 hours of last intake of study drug. The date and time of the PK/PD draw and the last dose of study drug must be recorded in the eCRF.
z. Liver fibrosis and inflammation parameters include ALT, AST, AST/ALT ratio, adiponectin, high sensitivity C-reactive protein, interleukin 6, tumor necrosis factor alpha, cytokeratin-18, fibronectin, hyaluronic acid, procollagen type III N-terminal peptide, tissue inhibitor of metalloproteinases-1 (and derived enhanced liver fibrosis score), Pro-C3, and chitinase-3-like protein 1 (also known as YKL-40).
aa. Sparse PK sampling will occur predose (fasting) at the following visits: Days 1, 14, 28, 56, and 84. A sample will also be collected at the EOS and ET Visits.
bb. At screening and on Days 1, 14, 28, 56, and 84; and at the EOS and ET Visits, plasma from blood samples will be stored for protocol-related safety testing or exploratory analyses.
cc. On Days 14, 28, 42, 56, 70, and 84, compliance will be assessed and study drug will be returned. In addition, on Days 14, 28, 42, 56, and 70 new study drug will be dispensed and dosing instructions provided.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUDIT = Alcohol Use Disorders Identification Test; AUDIT-C = Alcohol Use Disorders Identification Test-Concise; BMI = body mass index; C4 = 7αhydroxy-4-cholesten-3-one; CAP = controlled attenuation parameter; CDCA = chenodeoxycholic acid; cT1 = iron-corrected T1; DCA = deoxycholic acid; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End of Study; ET = Early Termination; FGF19 = fibroblast growth factor 19; FUP = Follow-up; HBV = hepatitis B virus; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LCA = lithocholic acid; LFC = liver fat content; LSM = liver stiffness measurement; MRI-PDFF = magnetic resonance imaging proton density fat fraction; PD = pharmacodynamic; PK = pharmacokinetic; RNA = ribonucleic acid; VCTE = vibration-controlled transient elastography; WHR = waist to hip ratio; WHtR = waist to height ratio.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Serum Chemistry Panel

- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase
- Amylase
- Aspartate aminotransferase (AST)
- Blood urea nitrogen
- Calcium
- Creatine kinase (CK)
- Creatinine
- CK-muscle/brain
- Estimation of glomerular filtration rate by the Modification of Diet in Renal Disease formula
- Gamma-glutamyl transferase
- Glucose
- Lactate dehydrogenase
- Potassium
- Sodium
- Total bilirubin [1]
- Total protein
- Uric acid

1. If >upper limit of normal, add conjugated (direct) bilirubin.

Additional Chemistry Parameters

- Alpha 2 macroglobulin
- Autotaxin
- Cardiac troponin I
- Ferritin
- Phosphate

Efficacy Parameters

- ALT
- AST
- AST/ALT ratio
- Iron-corrected T1
- High sensitivity C-reactive protein
- Tumor necrosis factor alpha
- Chitinase-3-like protein 1 (also known as YKL-40)
- Hyaluronic acid
- Adiponectin
- Cytokeratin-18
- Interleukin 6
- Fibronectin
- Procollagen type III N-terminal peptide
- Pro-C3
- Tissue inhibitor of metalloproteinases-1 (and derived enhanced liver fibrosis score)

Pharmacodynamic Parameters

- 7αhydroxy-4-cholesten-3-one
- Total bile acids
- Deoxycholic acid [1]
- Fibroblast growth factor 19
- Chenodeoxycholic acid [1]
- Lithocholic acid [1]

1. Plasma levels of total, primary, and secondary bile acids may be assessed as appropriate.

Lipid and Metabolic Profile

Branched-chain amino acid concentrations [1]
Hemoglobin A1c
Homeostatic model assessment for insulin resistance (morning fasting glucose and insulin)
Lipoprotein insulin resistance index by nuclear magnetic resonance based on serum cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, apolipoprotein B, small dense-LDL, and lipoprotein(a)
Lipoprotein particle size
Small LDL particle number
Small very low-density lipoprotein (VLDL) particle number
VLDL size

1. Liver function test.

Endocrinology

Human chorionic gonadotropin (hCG) [1]
Thyroid-stimulating hormone
Free thyroxine
Free triiodothyronine
Follicle-stimulating hormone (FSH) [2]

1. Serum hCG pregnancy test at screening and at study exit (whether at the End of Study or Early Termination Visit). Only urine hCG tests will be performed at all other study visits. If the urine hCG test is positive, pregnancy will be confirmed by a serum hCG test.
2. FSH level will be measured at screening to confirm postmenopausal state in women ≤55 years of age.

Coagulation

Activated partial thromboplastin time
International normalized ratio
Fibrinogen
Prothrombin time

Hematology

Basophils [1]
Erythrocytes [2]
Hemoglobin [2]
Lymphocytes [1]
Neutrophils [1]
Red blood cell count
White blood cell count and differential [3]
Eosinophils [1]
Hematocrit [2]
Leukocytes [2]
Monocytes [1]
Platelets
Thrombocytes [1]

1. Partial automated differentiation.
2. Blood quantitatively.
3. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis [1]

Bilirubin
Blood [2]
Glucose
Hemoglobin
Ketones
Leukocytes
Nitrite
pH
Protein
Specific gravity
Urobilinogen

1. Dipstick urine qualitatively. Further analysis of urine sediment or urine microscopy will be performed when there are any abnormalities on any of the following 3 dipstick results: leukocyte esterase, blood, or nitrite, and if judged clinically significant by the Investigator.
2. Microscopy is performed only as needed based on positive dipstick test results.

Serology

Hepatitis B virus
Hepatitis C virus (and polymerase chain reaction ribonucleic acid for positive antibody samples)
Human immunodeficiency virus

APPENDIX C: 5-D PRURITUS SCALE

5-D Pruritus Scale

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

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

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

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

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

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

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

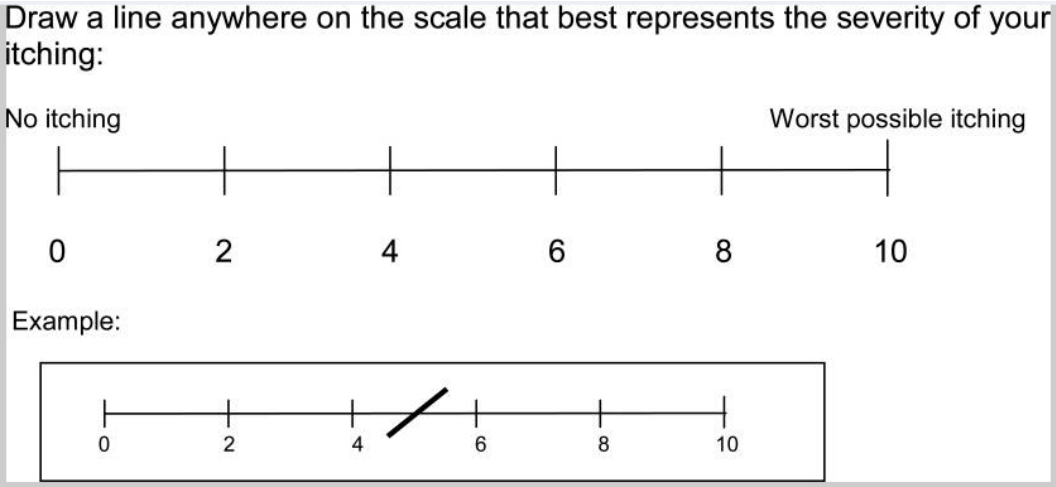
	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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

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

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

APPENDIX D: PRURITUS VISUAL ANALOG SCALE

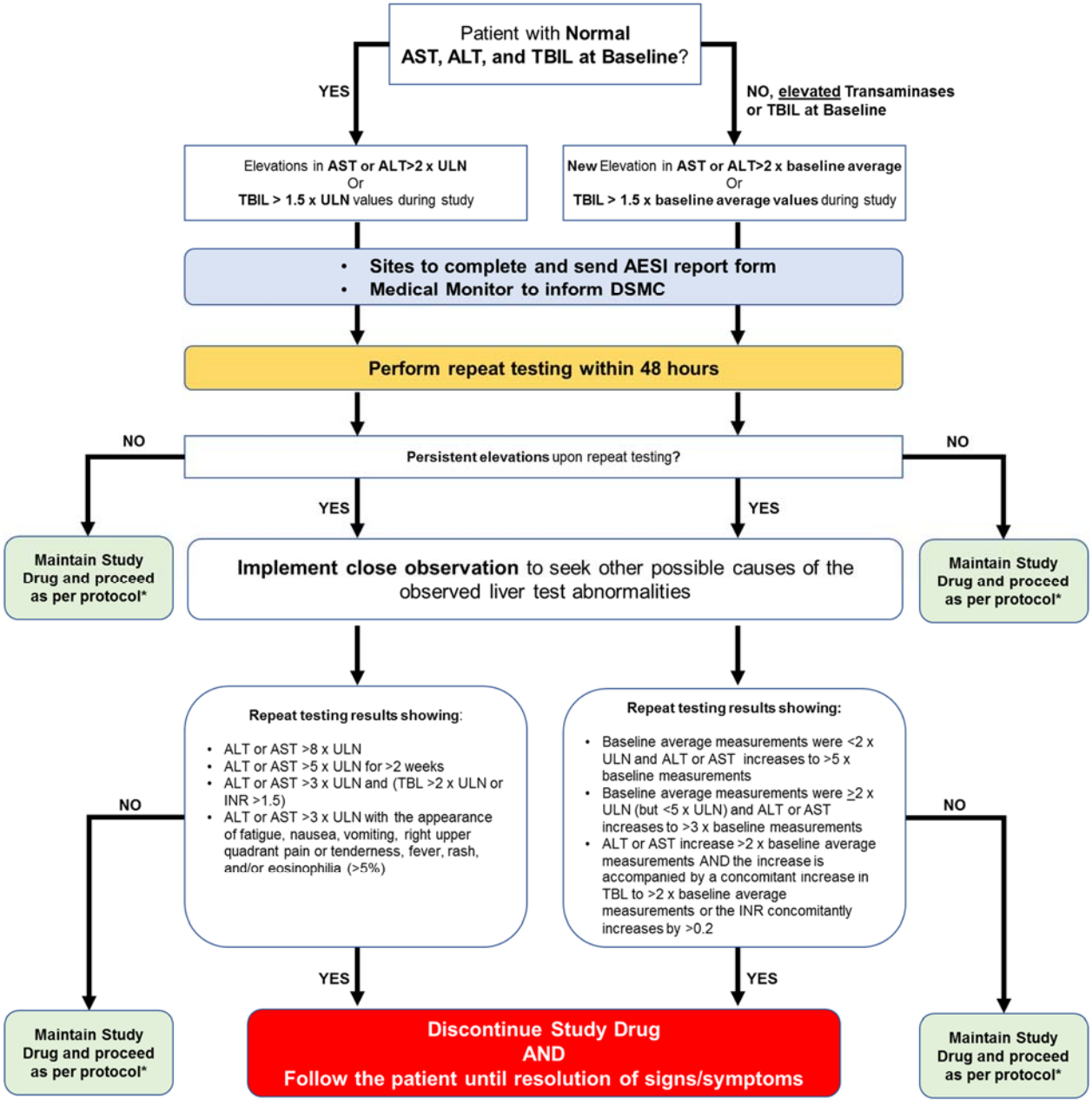


APPENDIX E: CLINICAL SAFETY MONITORING PLAN

Throughout the study, all treatment-emergent adverse events, clinical assessments, and clinical laboratory parameters will be closely monitored against the criteria for drug-induced liver injury and muscle toxicity as detailed in this Clinical Safety Monitoring Plan.

DRUG-INDUCED LIVER INJURY MONITORING

Drug-induced liver injury monitoring in patients with normal liver transaminases and bilirubin at baseline should be performed throughout the study according to the procedures summarized in the below diagram and text.



**In case of questions or if unclear how to proceed, seek advice from Medical Monitor*

AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DSMC = Data Safety Monitoring Committee; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

1. Patients with normal liver transaminases and bilirubin at baseline.

- If patients with normal baseline liver indices develop elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 × upper limit of normal (ULN) or total bilirubin (TBL) >1.5 × ULN values during the study, repeat testing should be performed within 48 hours.
    - If there are persistent elevations (ALT or AST >2 × ULN or TBL >1.5 × ULN) upon repeat testing, close observation (testing and physical examination 2 to 3 times per week) should be implemented. The Investigator will assess and record these events on an adverse event of special interest (AESI) form and send it to the ENYO safety designee via fax or email within 24 hours.
- Study drug should be discontinued, and the patient should be followed until resolution of signs or symptoms, in the following situations:
    - ALT or AST >8 × ULN.
    - ALT or AST >5 × ULN for more than 2 weeks.
    - ALT or AST >3 × ULN and (TBL >2 × ULN or international normalized ratio [INR] >1.5).
    - ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

For any patients who present with a constellation of syndromes indicative of liver disease as per the Investigator's overall assessment (ie, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]), perform liver function tests to determine if liver disease is worsening.

Reinitiation of study drug may be considered after consultation with the Medical Monitor.

In Part B, the Data Safety Monitoring Committee (DSMC) will be promptly notified for further review if any patients experience ALT, AST, or bilirubin elevations 2 × above baseline values.

2. Patients with elevations in liver transaminases or bilirubin at baseline.

Drug-induced liver injury monitoring in patients with elevations in liver transaminases or bilirubin at baseline should be performed throughout the study according to the procedures summarized below.

- If patients with abnormal baseline liver indices develop elevations of AST or ALT >2 × baseline average or TBL >1.5 × baseline average values during the study, repeat testing should be performed within 48 hours.
    - If there are persistent elevations (ALT or AST >2 × baseline average or TBL >1.5 × baseline average values) upon repeat testing, then close observation (testing and physical examination 2 to 3 times per week) should be implemented and discontinuation of study drug should be considered. The Investigator will assess and record these events on an AESI form and send to the ENYO safety designee via fax or email within 24 hours.

- Discontinue the study drug if any of the following occur:
    - Baseline average measurements were <2 × ULN and ALT or AST increases to >5 × baseline measurements.
    - Baseline average measurements were ≥2 × ULN (but <5 × ULN as per eligibility requirements) and ALT or AST increases to >3 × baseline measurements.
    - Baseline average measurements were ≥5 × ULN and ALT or AST increases to >2 × baseline measurements.
    - ALT or AST increase >2 × baseline average measurements AND the increase is accompanied by a concomitant increase in TBL to >2 × baseline average measurements or the INR concomitantly increases by >0.2.

For any patients who present with a constellation of syndromes indicative of liver disease as per the Investigator's overall assessment (ie, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]), perform liver function tests to determine if liver disease is worsening.

Reinitiation of study drug may be considered after consultation with the Medical Monitor.

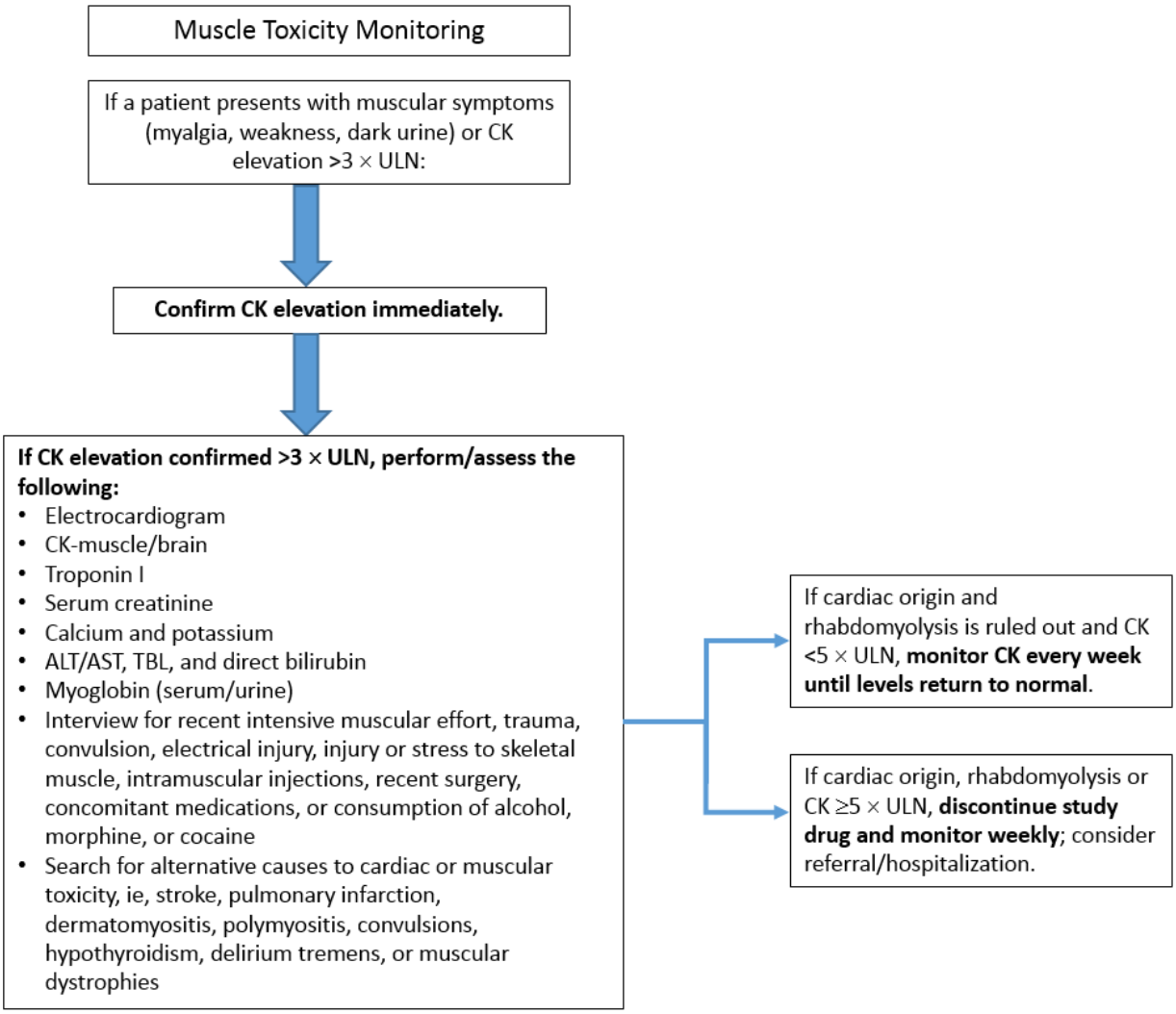
In Part B, the DSMC will be promptly notified for further review if any patients experience ALT, AST, or bilirubin elevations 2 × above baseline values.

3. For all patients (with normal or elevated AST, ALT, and TBL at baseline), persistent elevations upon repeated testing should prompt close observation for suspected drug-induced liver injury.

Close observation includes the following:

- Repeating liver enzyme (ALT, AST, and alkaline phosphatase) and serum bilirubin tests 2 or 3 times weekly.
- The frequency of repeat testing can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy due to cardiovascular causes; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (eg, INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

MUSCLE TOXICITY MONITORING



ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

If a patient presents with muscular symptoms (ie, myalgia, weakness, dark urine) or creatine kinase (CK) elevation >3 × ULN, the following actions should be taken:

- Confirm CK elevation immediately.
- If CK elevation is confirmed to be >3 × ULN, perform/assess the following:
    - Electrocardiogram.
    - CK-muscle/brain.
    - Troponin I.
    - Serum creatinine.
    - Calcium and potassium.
    - ALT/AST, TBL, and direct bilirubin.

  - Myoglobin (serum/urine).
  - Interview for recent intensive muscular effort, trauma, convulsion, electrical injury, injury or stress to skeletal muscle, intramuscular injections, recent surgery, concomitant medications, or consumption of alcohol, morphine, or cocaine.
  - Search for alternative causes to cardiac or muscular toxicity, ie, stroke, pulmonary infarction, dermatomyositis, polymyositis, convulsions, hypothyroidism, delirium tremens, or muscular dystrophies.
- If cardiac origin and rhabdomyolysis is ruled out and CK <5 × ULN, monitor CK every week until levels return to normal.
- If cardiac origin, rhabdomyolysis, or CK ≥5 × ULN, discontinue the study drug and monitor weekly; consider referral/hospitalization.

For patients who experience a statin-related serious adverse event, collect pharmacokinetic blood samples for statin plasma concentration.

Causality of muscular adverse events will be adjudicated by the Sponsor or designee using the Statin-Associated Muscle Symptom Clinical Index.[1]

[1] Rosenson RS, Miller K, Bayliss M, et al. The Statin-Associated Muscle Symptom Clinical Index (SAMS-CI): revision for clinical use, content validation, and inter-rater reliability. *Cardiovasc Drugs Ther*. 2017;31(2):179-186. DOI: 10.1007/s10557-017-6723-4.

APPENDIX F: ALCOHOL USE DISORDERS IDENTIFICATION TEST-CONCISE

The Alcohol Use Disorders Identification Test-Concise (AUDIT-C) has 3 questions and is scored on a scale of 0 to 12. Read the questions as written and circle the letter that corresponds to the answer. Each AUDIT-C question has 5 answer choices valued from 0 to 4 points. In men, a score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. In women, a score of 3 or more is considered positive. Generally the higher the score, the more likely it is that a person's drinking is affecting his or her safety.

AUDIT-C Questionnaire

Patient ID _____ Visit date _____

1. **How often do you have a drink containing alcohol?**
   a. Never
   b. Monthly or less
   c. 2-4 times a month
   d. 2-3 times a week
   e. 4 or more times a week

2. **How many standard drinks containing alcohol do you have on a typical day?**
   a. 1 or 2
   b. 3 or 4
   c. 5 or 6
   d. 7 to 9
   e. 10 or more

3. **How often do you have six or more drinks on one occasion?**
   a. Never
   b. Less than monthly
   c. Monthly
   d. Weekly
   e. Daily or almost daily

See answer module on the next page.

Answer Module

Question 1: How often do you have a drink containing alcohol?

Valid Values

Value	Value Meaning	Description	Display Order
Never	Never	Not ever; at no time in the past (or future).	0
Monthly or less	Monthly or less	Monthly or less	1
2 to 4 times a month	Two To Four Instance Per Month	A natural number greater than 1 and less than 3 and the quantity that it denotes: the sum of one and one.: Used as a function word to indicate direction, purpose, or movement.: A natural number greater than 3 and less than 5 and the quantity that it denotes: the sum of three and one.: An occurrence of something.: For each, generally denoting a ratio.: One of the 12 divisions of a year as determined by a calendar. It corresponds to the unit of time of approximately to one cycle of the moon's phases, about 30 days or 4 weeks.	2
2 to 3 times a week	Two To Three Instance Per Week	A natural number greater than 1 and less than 3 and the quantity that it denotes: the sum of one and one.: Used as a function word to indicate direction, purpose, or movement.: A natural number greater than 2 and less than 4 and the quantity that it denotes: the sum of two and one.: An occurrence of something.: For each, generally denoting a ratio.: Any period of seven consecutive days.	3
4 or more times a week	Four Or Greater Than Integer::4 Instance Per Week	A natural number greater than 3 and less than 5 and the quantity that it denotes: the sum of three and one.: An article used to connect words, phrases, or clauses representing alternatives; used to connect alternative terms for the same thing; used in correlation; used to correct or rephrase what was previously said; otherwise.: A statement about the relative size or order of two objects specifying that an object of interest exceeds another object in quantity or measure or value or status.: A number with no fractional part.::4: An occurrence of something.: For each, generally denoting a ratio.: Any period of seven consecutive days.	4

Question 2: How many standard drinks containing alcohol do you have on a typical day?

Valid Values

Value	Value Meaning	Description	Display Order
1 or 2	1 or 2	1 or 2	0
3 to 4	3 to 4	3 to 4	1
5 to 6	5 to 6	5 to 6	2
7 to 9	7 to 9	7 to 9	3
10 or more	10 or more	10 or more	4

Question 3: How often do you have six or more drinks on one occasion?

Valid Values

Value	Value Meaning	Description	Display Order
Never	Never	Not ever; at no time in the past (or future).	0
Less than monthly	Less Than Monthly	A statement about the relative size or order of two objects specifying that an object of interest is smaller than another object in quantity or measure or value or status.: Every month.	1
Monthly	Monthly	Every month.	2
Weekly	Weekly	Every week.	3
Daily or almost daily	Daily	Occurring or done each day.	4

APPENDIX G: THE ALCOHOL USE DISORDERS IDENTIFICATION TEST: INTERVIEW VERSION

Read questions as written. Read answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks." Place the correct answer number in the box at the right. Total scores of ≥8 are recommended as indicators of hazardous and harmful alcohol use.

1. How often do you have a drink containing alcohol? (0) Never [Skip to Qs 9-10] (1) Monthly or less (2) 2 to 4 times a month (3) 2 to 3 times a week (4) 4 or more times a week ☐	6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐
2. How many drinks containing alcohol do you have on a typical day when you are drinking? (0) 1 or 2 (1) 3 or 4 (2) 5 or 6 (3) 7, 8, or 9 (4) 10 or more ☐	7. How often during the last year have you had a feeling of guilt or remorse after drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐
3. How often do you have six or more drinks on one occasion? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily *Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0* ☐	8. How often during the last year have you been unable to remember what happened the night before because you had been drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐
4. How often during the last year have you found that you were not able to stop drinking once you had started? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐	9. Have you or someone else been injured as a result of your drinking? (0) No (2) Yes, but not in the last year (4) Yes, during the last year ☐
5. How often during the last year have you failed to do what was normally expected from you because of drinking? (0) Never (1) Less than monthly (2) Monthly (3) Weekly (4) Daily or almost daily ☐	10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down? (0) No (2) Yes, but not in the last year (4) Yes, during the last year ☐
If total is greater than recommended cut-off, consult User's Manual.	Record total of specific items here ☐

APPENDIX H: WORLD ALLERGY ORGANIZATION GRADING SYSTEM

Table 9. World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/ sign(s) of one organ system present[i] Cutaneous Generalized pruritus, urticaria, flushing or sensation of heat or warmth[ii] or Angioedema (not laryngeal, tongue or uvular) or Upper respiratory Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) or Throat-clearing (itchy throat) or Cough perceived to come from the upper airway, not the lung, larynx, or trachea or Conjunctival Conjunctival erythema, pruritus or tearing Other Nausea, metallic taste, or headache	*Symptom(s)/ sign(s) of more than one organ system present* or Lower respiratory Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) or Gastrointestinal Abdominal cramps, vomiting, or diarrhea or Other Uterine cramps	Lower respiratory Asthma (e.g., 40% PEF or FEV1 drop, NOT responding to an inhaled bronchodilator) or Upper respiratory Laryngeal, uvula or tongue edema with or without stridor	Lower or Upper respiratory Respiratory failure with or without loss of consciousness or Cardiovascular Hypotension with or without loss of consciousness	Death

Table 9. World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (Continued)

Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4. **Note:** children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis, e.g., becoming very quiet or irritable and cranky.
Scoring includes a suffix that denotes if and when epinephrine is or is not administered in relationship to symptom(s)/sign(s) of the SR: a, ≤ 5 minutes; b, >5 minutes to ≤10 minutes; c, >10 to ≤ 20 minutes; d, >20 minutes; z, epinephrine not administered.
The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the subcutaneous allergen immunotherapy injection [iii] and a suffix reflecting if and when epinephrine was or was not administered, **e.g., Grade 2a; rhinitis:10 minutes.**
Final report: Grade [a-d,or z] **_____ First symptom _____ Time of onset of first symptom _____**
Comments[iv]

i. Each Grade is based on organ system involved and severity. Organ systems are defined as: cutaneous, conjunctival, upper respiratory, lower respiratory, gastrointestinal, cardiovascular and other. A reaction from a single organ system such as cutaneous, conjunctival, or upper respiratory, but not asthma, gastrointestinal, or cardiovascular is classified as a Grade 1. Symptom(s)/sign(s) from more than one organ system or asthma, gastrointestinal, or cardiovascular are classified as Grades 2 or 3. Respiratory failure or hypotension, with or without loss of consciousness, defines Grade 4 and death Grade 5.The Grade is determined by the physician's clinical judgment.

ii. This constellation of symptoms may rapidly progress to a more severe reaction.

iii. Symptoms occurring within the first minutes after the injection may be a sign of severe anaphylaxis. Mild symptoms may progress rapidly to severe anaphylaxis and death.

iv. If signs or symptoms are not included in the Table or the differentiation between an SR and vasovagal (vasodepressor) reaction, which may occur with any medical intervention, is difficult, please include comment, as appropriate.

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APPENDIX I: CENTRAL LABORATORY REFERENCE RANGES

Reference Ranges, Notable Values, Critical Values, and Methodology

Sponsor: ENYO Pharma SA
Protocol: EYP001-202

Lab Director — 20/04/2019 Date(dd/mmm/yyyy)

Test Name	Subject Characteristics	Unit	Reference Range	Notable Values	Critical Values	Methodology
Chemistry						
Alkaline Phosphatase	Adult	U/L	41 - 146	> 348	---	Photometry
ALT/SGPT	Adult	U/L	10 - 53	> 123	> 164	Photometry
AST/SGOT	Adult	U/L	14 - 43	> 102	> 136	Photometry
Bilirubin (Direct)	Adult	µmol/L	0.0 - 3.4	---	---	Photometry
Bilirubin (Total)	Adult	µmol/L	1.7 - 18.8	> 34.2	---	Photometry
Gamma Glutamyl Transferase (GGT)	Adult Male	U/L	11 - 52	> 156	---	Photometry
	Adult Female	U/L	7 - 38	> 114	---	
Coagulation						
International Normalized Ratio (INR)	All	(None)	0.8 - 1.2	---	> 2.5	Calculation
Hematology						
Platelet	Adult	10^9/L	140 - 400	---	< 40 or > 999	Impedence

Reference Ranges, Notable Values, Critical Values, and Methodology

Sponsor: ENYO Pharma SA
Protocol: EYP001-202

Lab Director

Date(dd/mmm/yyyy)

Test Name	Subject Characteristics	Unit	Reference Range	Notable Values	Critical Values	Methodology
Chemistry						
Alkaline Phosphatase	Adult	U/L	41 - 146	> 348	---	Photometry
ALT/SGPT	Adult	U/L	10 - 53	> 123	> 164	Photometry
AST/SGOT	Adult	U/L	14 - 43	> 102	> 136	Photometry
Bilirubin (Direct)	Adult	mg/dL	0.00 - 0.20	---	---	Photometry
Bilirubin (Total)	Adult	mg/dL	0.10 - 1.10	> 2.00	---	Photometry
Gamma Glutamyl Transferase (GGT)	Adult Male	U/L	11 - 52	> 156	---	Photometry
	Adult Female	U/L	7 - 38	> 114	---	
Coagulation						
International Normalized Ratio (INR)	All	(None)	0.8 - 1.2	---	> 2.5	Calculation
Hematology						
Platelet	Adult	10^3/µL	140 - 400	---	< 40 or > 999	Impedence