# CLINICAL STUDY PROTOCOL A3309-012

## A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH)

| | |
|---|---|
| IND number: | 141078 |
| Test product: | Elobixibat |
| Indication: | Nonalcoholic Fatty Liver Disease or Nonalcoholic Steatohepatitis |
| Sponsor: | Elobix AB |
| Development phase: | Phase 2 |
| Sponsor medical monitor: | [redacted] |
| Principal investigator: | [redacted] |
| Date of the protocol: | 10 September 2019 |
| Version of the protocol: | Version 3.0 |

| Version No. | Previous Version Number | Effective Date |
|---|---|---|
| 1.0 | N/A | 25 February 2019 |
| 2.0 | 1.0 | 22 March 2019 |
| 3.0 | 2.0 | 10 September 2019 |

## SPONSOR SIGNATURE PAGE

**PROTOCOL TITLE: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH)**

PROTOCOL NUMBER: A3309-012

**Elobix AB**

## INVESTIGATOR SIGNATURE PAGE

**PROTOCOL TITLE: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH)**

PROTOCOL NUMBER: A3309-012

I have read this protocol and agree that it contains all necessary details for performing this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practice (GCP), local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

I will use only the informed consent approved by the Institutional Review Board (IRB) and will fulfill all responsibilities for submitting pertinent information to the IRB responsible for this study.

I agree that the Sponsor (Elobix AB) shall have access to any source documents from which case report form (CRF) information may have been generated.

I further agree not to originate or use the name of Elobix AB or elobixibat (A3309) in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to this protocol, to any amendment to the protocol, or to the performance of this protocol without the prior written consent of Elobix AB.

_____

Name of Investigator

_____ _____

Signature Date (day/month/year)

## 1. ADMINISTRATIVE INFORMATION

| | |
|---|---|
| **Protocol no.:** | A3309-012 |
| **Date of initial protocol:** | 25 February 2019, Version 1.0 |
| **Date and no. of amendments:** | 22 March 2019, Version 2.0<br>10 September 2019, Version 3.0 |
| **Sponsor:** | Elobix AB<br>Arvid Wallgrens backe 20<br>413 46 Göteborg<br>Sweden |
| **Clinical research organization:** | [redacted] |
| **Sponsor Medical Monitor:** | [redacted] |
| **Principal Investigator:** | [redacted] |

## 2. STUDY SYNOPSIS

| **Name of Sponsor/Company:** Elobix AB | **Name of Product:** Elobixibat | **Name of Active Ingredient:** Elobixibat |
|---|---|---|
| **Title of Study:** A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH) | | |
| **Principal Investigator:** [redacted] | | |
| **Study Centers:** Up to 15 sites will be initiated for this study in the United States (US) | | |
| **Publication(s):** Not applicable | | |
| **Planned Study Period:** Q2 2019 to Q2 2020 | **Development Phase:** Phase 2 | |

**Objectives:**

*Primary Objective*

The primary objective is to evaluate the efficacy of repeated once-daily doses of 5 mg elobixibat on serum levels of low-density lipoprotein cholesterol (LDL-C) in patients with NAFLD or NASH.

*Secondary Objectives*

- To assess the safety and tolerability of elobixibat in patients with NAFLD or NASH
- To evaluate the effect of elobixibat on liver steatosis as measured by magnetic resonance imaging (MRI) for (i) liver fat fraction (using proton density fat fraction [PDFF]) and (ii) total liver fat (using whole liver fat volume)
- To evaluate the effect of elobixibat on liver function using alanine aminotransferase (ALT)
- To evaluate the effect of elobixibat on lipids and total bile acids (BA) in patients with NAFLD or NASH

**Methodology:**

This is a double-blind, randomized, placebo-controlled, Phase 2 study to explore the efficacy and safety of elobixibat (oral dose of 5 mg) once daily for 16 weeks in patients with NAFLD or NASH. The study includes a 6-week Screening period, followed by a 16-week Treatment period, and a Follow-Up visit 2 weeks after the last dose of study drug.

After completing the Screening period, eligible patients will be randomized on Day 1 (Visit 2) in a 1:1 fashion to either 5 mg/day elobixibat or matching placebo. There will be a total of 7 scheduled visits during the study. Additional unscheduled visits may be required for patients who need direct site assistance (e.g., due to adverse event [AE] monitoring, in order to fulfill screening requirements, and/or for safety maintenance). Patients who screen fail may be rescreened if approved by Sponsor's Medical Monitor.

**Number of Patients:** Approximately 46 patients diagnosed with NAFLD/NASH and in accordance with the inclusion/exclusion criteria will be randomized.

**Inclusion Criteria:**

Patients must meet all of the following criteria to be included in the study:

1. Be willing to participate in the study and provide written informed consent
2. Be a man or woman ≥18 years of age
3. Have a current biopsy-confirmed NASH within 6 months of screening or a suspected diagnosis of NAFLD/NASH based on the criteria outlined below:

a. Biopsy-confirmed NASH is defined as histological NASH diagnosis with fibrosis stage F1 through F3 and a NAFLD activity score (NAS) of ≥4 with a score of ≥1 in each of the NAS components below as assessed by a pathologist using the NASH Clinical Research Network criteria (Kleiner 2005):
   i. Steatosis (scored 0 to 3)
   ii. Ballooning degeneration (scored 0 to 2)
   iii. Lobular inflammation (scored 0 to 3)

**OR**

b. The suspected diagnosis of NAFLD/NASH is based on the diagnosis of metabolic syndrome as having any 3 of the following 5 risk factors at Screening:
   i. Fasting plasma glucose ≥100 mg/dL or undergoing drug treatment for elevated glucose
   ii. High-density lipoprotein-cholesterol (HDL-C) <40 mg/dL in males or <50 mg/dL in females or undergoing drug treatment for reduced HDL-C
   iii. Triglycerides ≥150 mg/dL or undergoing drug treatment for elevated triglycerides
   iv. Waist circumference >102 cm in males or >88 cm in females
   v. Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or undergoing drug treatment for hypertension, or antihypertensive drug treatment in a patient with a history of hypertension

4. Screening MRI-PDFF with ≥10% liver steatosis
5. Fasting serum LDL-C >100 mg/dL at screening
6. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (beta human chorionic gonadotropin) at Screening and must agree to use highly effective birth control throughout the study and up to 30 days after the last dose of study drug. Highly effective contraception measures include combined estrogen- and progestogen-containing hormonal contraception (oral, intravaginal, and transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, and implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner (only in the event that the vasectomized partner is the sole sexual partner of the WOCBP), and sexual abstinence (defined as refraining from heterosexual intercourse) only in the event that this is the preferred lifestyle of the patient.

   Childbearing potential is defined as being fertile following menarche and until becoming postmenopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)

   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

   Men with partners who are WOCBP must either be surgically sterile or agree to use a barrier contraceptive for the duration of the study and up to 30 days after the last dose of study drug
7. Be willing to maintain a stable diet and physical activity throughout the course of the study

**Exclusion Criteria:**

1. Women who are pregnant, breastfeeding, or plan to become pregnant during the study
2. Body mass index (BMI) <25 kg/m$^2$
3. Fibrosis-4 Index (Fib-4) >2.6
4. Any of the following laboratory abnormalities:

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|---|---|---|

a. ALT >5 × upper limit normal (ULN) or AST >5 × ULN
b. International normalized ratio (INR) ≥1.3, unless on anticoagulant therapy
c. Total bilirubin > ULN, except with an established diagnosis of Gilbert's syndrome
d. Platelet count less than the lower limit of normal (LLN)
e. Creatinine clearance as calculated by the modification of diet in renal disease (MDRD) estimated glomerular filtration rate (eGFR) equation <60 mL/min

NOTE: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor.

5. Acute or chronic liver disease other than NAFLD/NASH including but not limited to the following:
   a. Hepatitis B (as defined by the presence of hepatitis B surface antigen at Screening) or hepatitis C (as defined by the presence of hepatitis C virus [HCV] antibody [anti-HCV]. Patients with positive anti-HCV who test negative for HCV ribonucleic acid at Screening will be allowed to participate in the study as long as there is evidence of viral negativity for a minimum of 12 months prior to Screening)
   b. Evidence of autoimmune hepatitis
   c. History of primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, homozygous alpha-1-anti-trypsin deficiency, hemochromatosis or iron overload, drug-induced or alcoholic liver disease, or known bile duct obstruction
   d. Suspected or proven hepatocellular carcinoma
6. Known history of human immunodeficiency virus
7. Medical history of liver cirrhosis
8. Clinical evidence of portal hypertension to include any history of ascites, hepatic encephalopathy, or presence of esophageal varices
9. Use of drugs historically associated with NAFLD (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 for >2 weeks in the year prior to Screening
10. Use of the following medications:
    a. Glucagon-like peptide-1 (GLP-1) agonists unless on a stable dose 3 months prior to liver biopsy or Screening
    b. Ursodeoxycholic acid, thiazolidinediones, or obeticholic acid within 3 months prior to Screening
    c. Statins and other lipid-modifying therapies must have been stable for ≥3 months prior to Screening
    d. Oral antidiabetic drugs (other than those specifically excluded) must have been stable for ≥3 months prior to Screening
    e. Agents (including herbal over-the-counter weight loss preparations) or medications known to significantly impact body weight within 3 months prior to screening (e.g., sibutramine, phenetamine, and orlistat)
11. History of significant alcohol consumption, defined as an average of >20 g/day in female patients and >30 g/day in male patients, for a period of >3 consecutive months within 1 year prior to Screening, hazardous alcohol use (Alcohol Use Disorders Identification Test score ≥8), or an inability to reliably quantify alcohol consumption based upon judgment of the Investigator

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|---|---|---|

12. Weight change ≥10% within the 6 months prior to Screening or ≥5% within the 3 months prior to Screening
13. Prior or planned (during the study period) bariatric surgery (e.g., gastroplasty, sleeve gastrectomy and roux-en-Y gastric bypass)
14. Type 1 diabetes by medical history
15. Uncontrolled Type 2 diabetes defined as hemoglobin A1c (HbA1c) >9.5% at Screening (patients with HbA1c >9.5% may be rescreened) or requiring oral diabetic medication dose adjustment >10% within 2 months prior to Screening
16. Clinical hyperthyroidism or hypothyroidism or Screening hormone results pointing to thyroid dysfunction. Patients receiving dose-stable thyroid replacement therapy for ≥3 months prior to Screening will be allowed to participate as long as thyroid tests (thyroid-stimulating hormone/triiodothyronine/thyroxine) show that the patient is euthyroid
17. History of any condition causing malabsorption such as chronic pancreatitis, extensive bowel/small intestine surgery, celiac disease, or bile flow obstruction
18. History of any condition associated with acute or chronic diarrhea such as inflammatory bowel disease (IBD), functional diarrhea, irritable bowel syndrome (IBS) with predominant diarrhea, IBS with mixed bowel habits, or unclassified IBS
19. History of ischemic colitis
20. Uncontrolled hypertension (either treated or untreated) defined as systolic blood pressure >160 mmHg or a diastolic blood pressure >100 mmHg at Screening. A retest of blood pressure, (after establishing good blood pressure control within a reasonable period of time and up to the Baseline visit) is permissible at the discretion of the Investigator
21. History of New York Heart Association Class III or IV heart failure, or known left ventricular ejection fraction <30%
22. History of myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke or major surgery within 6 months prior to Screening
23. Active substance abuse, within 1 year prior to Screening
24. Participation in an investigational new drug trial in the 30 days prior to Screening or within 5 half-lives of an investigational agent, whichever is longer
25. Malignancy within 5 years, except for basal- or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated. Patients with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor's Medical Monitor. Patients under evaluation for malignancy are not eligible
26. Patients with known intolerance to MRI or with conditions contraindicated for MRI procedures
27. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, compromise the well-being of the patient, or interfere with the study outcomes

**Test Product, Dose, and Mode of Administration:** Elobixibat, 5 mg once a day, orally administered

**Reference Therapy, Dose and Duration of Administration:** Matching placebo, orally administered

**Duration of Treatment:** Up to 16 weeks

**Variables**

**Efficacy:**

*Primary Efficacy Endpoint*

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The primary efficacy endpoint is the change from baseline in serum LDL-C at Week 16.

*Secondary Efficacy Endpoints*

Secondary efficacy endpoints include the following:

- Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
- Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI
- Change from Baseline to Week 16, and Follow-Up in the following:
  - Serum ALT, AST, and gamma-glutamyl transferase
  - HDL-C, non-HDL-C, LDL-C/HDL-C ratio and triglycerides
  - Total bile acids

*Exploratory Efficacy Endpoints*

The following exploratory efficacy endpoints will be assessed:

- Change from Baseline (unless otherwise specified) to Week 4, Week 8, Week 12, Week 16, and Follow-Up in the following:
  - Fasting glucose, insulin, homeostatic model assessment-insulin resistance, HbA1c, free fatty acids
  - GLP-1, fibroblast growth factor-19 (FGF-19), and C4 levels
  - High-sensitivity C-reactive protein (CRP)
  - Lanosterol and beta-sitosterol
  - Body weight, BMI, waist circumference, and waist-to-hip ratio
  - Apolipoprotein A1 and Apolipoprotein B

**Safety:**

Safety criteria are as follows:

- Occurrence of treatment-emergent adverse events categorized by causality, severity, and seriousness assessments made by Investigator by comparing study-drug exposure to placebo
- Trends in safety evaluated for the following assessments:
  - Physical examinations
  - Concomitant medications
  - Vital signs
  - 12-lead ECG
  - Laboratory test results (including clinical chemistry, hematology/coagulation, and urinalysis)

**Statistical Methods**
**Analysis Populations:**

- The intent-to-treat (ITT) population will include all patients who are randomized in the study and receive at least 1 dose of study drug. The ITT population will be used for all efficacy analyses based on the treatment randomized unless otherwise specified
- The per protocol (PP) population will include all ITT patients who finish Visit 7/End of Treatment (EOT) with valid LDL-C measurements and do not have any major protocol deviations. Allocation of patients to the PP analysis set will be performed before unblinding of the study
- The safety population will include all patients who are randomized and receive at least 1 dose of study drug and will be used for all safety analyses based on the treatment received
- Summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) at all visits and change or percent change from Baseline will be provided for efficacy and safety continuous variables. Count and frequency will be used to tabulate categorical variables
- Demographics, disposition, and study populations will be summarized descriptively

**Efficacy:**

- The primary efficacy endpoint is the change from Baseline in serum LDL-C at Week 16. Baseline is defined as the last non-missing LDL-C value prior to the first dose of study drug
- An analysis of covariance (ANCOVA) will be used to analyze the primary efficacy endpoint. The model will include treatment arm and baseline LDL-C scores
- Least square (LS) mean (SE), LS mean difference (SE), 95% confidence intervals, and *P*-values between elobixibat 5 mg and placebo will be provided. The model assumptions will be checked before the analysis. If there are concerns on model assumptions, i.e., normality and homogeneity of variances, a non-parametric ANCOVA based on the rank scores can be used as a sensitivity analysis
- Exploratory comparisons between elobixibat 5 mg and placebo will be performed for the following secondary efficacy endpoints:
    - Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
    - Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI
- The analysis methods for the other secondary endpoints and exploratory endpoints will be detailed in the Statistical Analysis Plan for the study.

**Safety:**

- The safety endpoints for this study include clinical laboratory assessments, vital signs, AEs, ECGs, physical examinations, and concomitant medications
- AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedRA). TEAEs will be defined as AEs that are new or worsening after the first dose of study drug. A general summary of patients with TEAEs and serious adverse events (SAEs)/adverse event of special interest (AESI) will be tabulated with numbers and percentages of patients and repeated for severity and relationship to study drug per treatment group. The number of AEs leading to withdrawal and SAEs leading to death will also be summarized. The incidence of TEAEs will be summarized by body system and treatment group

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- The safety laboratory data will be summarized by visit and by treatment group, along with changes from Baseline. Values outside of the reference range will be flagged and laboratory abnormalities of special interest will be summarized

**Sample Size Determination:**

Due to the exploratory nature of this study, no formal power calculations were used to determine the sample size. The number of subjects (46 patients in total, 23 patients per treatment group) was chosen based on clinical experience with other similar proof-of-concept studies.

**Date of the Protocol:** 10 September 2019

## 3. TABLE OF CONTENTS

## 3.1 List of Tables

## 4. LIST OF ABBREVIATIONS, ACRONYMS, AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| A3309 | elobixibat |
| AE(s) | adverse event(s) |
| AESI(s) | adverse event(s) of special interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| Anti-HCV | hepatitis C antibody |
| APRI | AST to platelet ratio index |
| ASBT | apical sodium-dependent bile acid transporter (also known as IBAT) |
| AST | aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BA | bile acid(s) |
| BMI | body mass index |
| C4 | 7α-hydroxy-4-cholesten-3-one |
| CRA | clinical research associate |
| CRF | case report form |
| CRP | C-reactive protein |
| ECG(s) | electrocardiogram(s) |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| EOT | End of Treatment |
| FDA | US Food and Drug Administration |
| FGF-19 | fibroblast growth factor-19 |
| Fib-4 | fibrosis-4 |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| GLP-1 | glucagon-like peptide-1 |
| H&E | hematoxylin and eosin |

| Abbreviation | Definition |
|---|---|
| HbA1c | hemoglobin A1c |
| HCV | hepatitis C virus |
| HDL-C | high-density lipoprotein-cholesterol |
| IBAT | ileal bile acid transporter (also known as ASBT) |
| IBD | inflammatory bowel disease |
| IBS | irritable bowel syndrome |
| ICF(s) | informed consent form(s) |
| ICH | International Council on Harmonisation |
| INR | international normalized ratio |
| IRB | institutional review board |
| ITT | intent to treat |
| IWRS | Interactive Web Response System |
| LDL | low-density lipoprotein |
| LDL-C | low density lipoprotein-cholesterol |
| LLN | lower limit of normal |
| LPLV | last patient last visit |
| LS | least square |
| MDRD | modification of diet in renal disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MRI-PDFF | magnetic resonance imaging—proton density fat fraction |
| N/A | not applicable |
| NAFLD | nonalcoholic fatty liver disease |
| NAS | NAFLD activity score |
| NASH | nonalcoholic steatohepatitis |
| ob/ob (mice) | leptin-deficient mice |
| PCS | potentially clinically significant |
| PDFF | proton density fat fraction |
| PP | per protocol |
| PVM | pharmacovigilance manager |

| Abbreviation | Definition |
|---|---|
| RNA | ribonucleic acid |
| SAE(s) | serious adverse event(s) |
| SAP | statistical analysis plan |
| SE | standard error |
| SOC | system organ class |
| SOP(s) | standard operating procedure(s) |
| Sponsor | Elobix AB |
| SUSAR | suspected unexpected serious adverse reaction(s) |
| TEAE(s) | treatment-emergent adverse event(s) |
| ULN | upper limit of normal |
| US | United States |
| VLDL | very low-density lipoprotein |
| WHO | World Health Organization |
| WOCBP | Women (woman) of childbearing potential |
| α-SMA | alpha-smooth muscle actin |

# 5. INTRODUCTION

## 5.1 Investigational Medicinal Product

Elobixibat is a potent inhibitor of the ileal bile acid transporter (IBAT; also known as the apical sodium bile acid transporter [ASBT]). The IBAT, expressed mainly in the distal ileum, is a key element in the enterohepatic circulation of bile acids because it facilitates the very efficient process of bile acid reabsorption. Elobixibat is orally administered and acts locally in the gut where it binds reversibly to the IBAT to decrease the reuptake of bile acids to the liver. Elobixibat has minimal systemic exposure at expected therapeutic dose ranges.

## 5.2 Background

### 5.2.1 Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

Recent data suggest that bile acids may play an important role in NASH pathogenesis (Ferslew 2015; Aranha 2008; Puri 2018). Bile acids are signaling molecules involved in lipid, glucose, and energy homeostasis, which are metabolic pathways linked to NAFLD/NASH and comorbidities such as metabolic syndrome, obesity, and diabetes. Bile acids as well as free cholesterol, which is the precursor from which bile acids are synthesized, can act as lipotoxic agents that drive inflammation and fibrosis. Studies have shown that both serum and liver bile acids are increased in patients with NASH, and recent data have suggested that the presence and severity of NASH is associated with specific changes in circulating bile acids (Puri 2018). Thus, targeting of bile acid pathways has therapeutic potential in patients with NASH.

The enterohepatic circulation of bile acids plays a crucial role in whole body sterol balance. Bile acids are secreted to the intestine via the bile duct and then reabsorbed, mainly by a specific bile acid transporter located in the ileum (IBAT or ASBT) and delivered back to the liver, completing the enterohepatic circulation (Prawitt 2011).

Bile acid reabsorption from the intestine is a very efficient process where 95% of the secreted bile acids are reabsorbed and IBAT appears to be the major regulator of the bile acid pool in animals and humans. IBAT inhibitors reduce the reabsorption of bile acids from the ileum and prevent their return to the liver. The liver compensates for the decrease in bile acid levels by upregulating cholesterol 7α-hydroxylase, the rate-limiting

enzyme for bile acid synthesis. This results in lower hepatic cholesterol levels and an increased number of low-density lipoprotein (LDL) receptors in the liver leading to reduced plasma low-density lipoprotein cholesterol (LDL-C; [Bertolotti 2003; Naoumova 1999]). Bile acids also positively regulate glucagon-like peptide-1 (GLP-1) levels via activation of TGR5 (Prawitt 2011; Schaap 2014). GLP-1 is an insulinotropic hormone but has many other roles, e.g., slowing gastric emptying and increasing satiety signals leading to weight loss (Andersen 2018).

Inhibition of bile acid absorption locally in the intestine has the potential to positively influence NASH, cardiovascular disease, and metabolic disease by targeting multiple mechanisms, as follows: lowering of LDL-C by increased bile acid synthesis; improving metabolic status and weight loss by increasing GLP-1 levels; and reducing hepatic cell damage by lowering toxic bile acid and free cholesterol in the liver.

### 5.2.2 Summary of Nonclinical Studies in NASH

One nonclinical study with elobixibat in a NASH model has been completed. The study evaluated the effects of elobixibat in leptin-deficient ob/ob mice treated with a diet high in trans fats, fructose, and cholesterol. Although elobixibat did not reduce liver NAFLD activity score or fibrosis stage, there were indicators of relevant effects, including reduction in liver alpha-smooth muscle actin (α-SMA), which is a marker of stellate cell activation and thereby an indirect marker for fibrosis formation. Administration of 10 and 30 mg/kg/day elobixibat decreased liver steatosis as quantified by lipid fractional area in hematoxylin and eosin (H&E)-stained liver sections in a dose-dependent fashion. This was further evident in animals treated with 30 mg/kg elobixibat that showed reduced liver triglycerides and liver total cholesterol as determined by biochemical analyses. Analysis of liver gene expression by next generation RNA sequencing revealed pronounced and dose-dependent effects of elobixibat. It affected the expression of genes in key pathways associated with NASH pathology.

Additional nonclinical studies with elobixibat are summarized in the Investigator's Brochure (M1.14.4.1).

## 5.3 Rationale

Bile acids act as signaling molecules in lipid, glucose, and energy homeostasis. Studies have shown that both serum and liver bile acids are increased in patients with NASH

(Ferslew 2015), and recent data have suggested that the presence and severity of NASH is associated with specific changes in circulating bile acids (Puri 2018; Sanyal 2018). Inhibition of bile acid absorption from the intestine has the potential to improve the pathophysiology in NASH, including the related cardiovascular and metabolic disease due to impingement on multiple key metabolic feedback mechanisms, as follows: lowering of LDL-C by increased bile acid synthesis, and improving insulin sensitivity by increasing GLP-1 levels. A reduction of cardiovascular risk is particularly desirable for any pharmacological NASH treatment, because cardiovascular complications contribute to a significant amount of mortality in patients with NAFLD/NASH, with their annual risk being 2-fold increased (Mahfood Haddad 2017; Younossi 2018). IBAT inhibition reduces the levels of bile acid that circulate to the liver, and triggers increased hepatic bile acid synthesis from cholesterol. Thus, besides having a positive impact on cardiovascular health, IBAT inhibition might also reduce hepatic cell damage by lowering free cholesterol and changing the composition of toxic bile acids in the liver.

### 5.4 Risk/Benefit

Elobixibat is orally administered and acts locally in the gut where it binds reversibly to the IBAT to decrease the reuptake of bile acids into the liver, thereby increasing the concentration of bile acids in the colon. Due to its mechanism of action, most adverse events (AEs) are gastrointestinal (GI) tract disorders, such as abdominal pain, diarrhea, abdominal distention, flatulence, and nausea; the incidence of these has increased with increasing dose levels. Diarrhea has been the most prominent dose-limiting side effect. No clinically significant findings in laboratory measures or electrocardiograms (ECGs) have been reported. Based on postmarketing case reporting, ischemic colitis will be monitored as an adverse event of special interest for elobixibat.

There is no established benefit for subjects participating in this Phase 2 study. Based upon these data, the risk/benefit for subjects participating in this trial is acceptable.

This study will be conducted in compliance with the protocol and with the International Council on Harmonisation (ICH) guidelines on GCP.

# 6. STUDY OBJECTIVES

## 6.1 Primary Objective

The primary objective is to evaluate the efficacy of repeated once-daily doses of 5 mg elobixibat on serum levels of LDL-C in patients with NAFLD or NASH.

## 6.2 Secondary Objectives

- To assess the safety and tolerability of elobixibat in patients with NAFLD or NASH
- To evaluate the effect of elobixibat on liver steatosis as measured by magnetic resonance imaging (MRI) for (i) liver fat fraction (using proton density fat fraction [PDFF]) and (ii) total liver fat (using whole liver fat volume)
- To evaluate the effect of elobixibat on liver function using alanine aminotransferase (ALT)
- To evaluate the effect of elobixibat on lipids and total bile acids (BA) in patients with NAFLD or NASH

# 7. INVESTIGATIONAL PLAN

## 7.1 Overall Study Design and Plan

### 7.1.1 Description

This is a double-blind, randomized, placebo-controlled, Phase 2 study to explore the efficacy and safety of elobixibat (oral dose of 5 mg) once daily for 16 weeks in patients with NAFLD or NASH. The study includes a 6-week Screening Period, followed by a 16-week Treatment Period, and a Follow-Up Visit 2 weeks after the last dose of study drug.

After completing the Screening Period, eligible patients will be randomized on Day 1 (Visit 2) in a 1:1 fashion to either 5 mg/day elobixibat or matching placebo. Visit windows applicable to each visit are presented in the schedule of assessments (Table 1). There will be up to 7 clinic visits during the study, as follows:

- Visit 1: Screening period (Week -6 through Day -1)
- Visit 2: Day 1/Randomization visit
- Visit 3: Week 4
- Visit 4: Week 8
- Visit 5: Week 12
- Visit 6: Week 16/End of Treatment (EOT). Any patient that discontinues treatment prematurely should complete this visit at the time of discontinuation
- Visit 7: Follow-Up period. The Follow-Up visit will occur 2 weeks after the last dose of study drug whether the patient completes the study or discontinues prematurely

Additional unscheduled visits may be required for patients who need direct site assistance (due to AE monitoring, in order to fulfill screening requirements, and/or for safety maintenance).

Patients who screen fail may be rescreened if approved by Sponsor's Medical Monitor.

#### 7.1.1.1 Screening Period

Informed consent must be obtained at Visit 1 prior to performing any study procedures. After signing the informed consent form (ICF), patients will be considered enrolled and evaluated for study eligibility.

#### 7.1.1.2 Treatment Period

Eligibility for randomization will be determined at Visit 2 using the assessment of eligibility in accordance to the inclusion/exclusion criteria.

The patient will return to the clinic at Visits 3-6 for assessments. Patients will be requested to return study drug bottles as part of drug accountability during the Treatment period.

#### 7.1.1.3 Follow-Up Period

The patient will return to the clinic for Visit 7 approximately 2 weeks after the last dose of study drug. This visit will be completed for patients that discontinue treatment prematurely.

#### 7.1.1.4 End of Study

The end of the study is defined as last patient last visit (LPLV) and all sites are closed.

### 7.1.2 Schedule of Assessments

The schedule of assessments is presented in Table 1.

**Table 1 Schedule of Assessments**

| Visit | Screening Period | Treatment Period | | | | | Follow-Up Period |
|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2/ Randomization | Visit 3 | Visit 4 | Visit 5 | Visit 6/ End of Treatment | Visit 7 |
| Study Week | Week -6 to Day -1 | Day 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 18 |
| Visit Window | | | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days |
| Informed consent | X | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | |
| Medical/surgical history[f] | X | | | | | | |
| Demographics | X | | | | | | |
| Serology[a] | X | | | | | | |
| 12-lead ECG | X | | | | | X | |
| Physical examination[b] | X | X | | | | X | |
| Vital signs[c] | X | X | X | X | X | X | X |
| Pregnancy test[d] | X | X | X | X | X | X | X |
| MRI[e] | X | | | | | X | |
| Randomization[g] | | X | | | | | |
| Clinical safety laboratory tests[h] | X | X | X | X | X | X | X |

*(Continued on next page)*

| VISIT | SCREENING PERIOD | TREATMENT PERIOD | | | | | FOLLOW-UP PERIOD |
|---|---|---|---|---|---|---|---|
| | VISIT 1 | VISIT 2/ RANDOMIZA-TION | VISIT 3 | VISIT 4 | VISIT 5 | VISIT 6/ END OF TREATMENT | VISIT 7 |
| STUDY WEEK | WEEK -6 TO DAY -1 | DAY 1 | WEEK 4 | WEEK 8 | WEEK 12 | WEEK 16 | WEEK 18 |
| VISIT WINDOW | | | ±3 DAYS | ±3 DAYS | ±3 DAYS | ±3 DAYS | ±3 DAYS |
| Endocrinology[h] | X | X | X | | | X | |
| GLP-1, FGF-19, C4[h] | X | X | X | X | X | X | X |
| Total bile acids[h] | X | X | X | X | X | X | X |
| Lipid profile[h] | X | X | X | X | X | X | X |
| Fibrosis and inflammation markers[h] | | X | X | | | X | |
| High-sensitivity CRP | X | | X | | | X | |
| Stored blood sample for future testing[i] | X | X | X | X | X | X | X |
| Dispense study drug | | X | X | X | X | | |
| Review alcohol consumption[j] | X | | | | | | |
| Review concomitant medications | X | X | X | X | X | X | X |
| Review adverse events | X | X | X | X | X | X | X |

[a] Includes hepatitis B virus surface antigen and hepatitis C virus antibody and RNA

[b] Includes height (at Screening only), weight, waist circumference, and waist-to-hip ratio. Body mass index will be calculated based on height and weight. A full physical examination will be performed at Screening and at Visits 2 and 6.

[c] Vital signs include blood pressure, heart rate, respiratory rate, and oral body temperature.

*(Continued on next page)*

[d] For women of childbearing potential, a serum pregnancy test will be performed at Screening, and a urine pregnancy test will be performed at each visit at which study drug is dispensed.

[e] Patients will have MRI to measure liver fat (PDFF), and total liver volume. Patients who discontinue before Visit 6 (Week 16) should have an MRI performed at End of Treatment if they completed at least 4 weeks of treatment.

[f] Liver biopsy results for confirmed NASH within 6 months of Screening to confirm patient eligibility will be collected in the eCRF, if available.

[g] Randomization will occur at Visit 2 to assign patients to either 5 mg/day elobixibat or placebo in 1:1 ratio.

[h] See Table 2, Laboratory Parameters. Clinical safety laboratory tests include clinical chemistry, hematology/coagulation, and urinalysis

[i] See Section 9.2.4.

[j] History of alcohol consumption will be obtained at Screening.

Abbreviations: C4: 7α-hydroxy-4-cholesten-3-one; CRF: case report form; CRP: C-reactive protein; ECG: electrocardiogram; EOT: End of Treatment; FGF-19: fibroblast growth factor-19; GLP-1: glucagon-like peptide-1; INR: international normalized ratio; MRI: magnetic resonance imaging; NASH: nonalcoholic steatohepatitis; PDFF: proton density fat fraction

### 7.1.3 Study Procedures and Assessments

#### 7.1.3.1 Screening Period (-6 Weeks to Day -1)

##### 7.1.3.1.1 Visit 1

Patients will undergo a Screening visit up to 6 weeks prior to the planned first day of study treatment. Screening procedures and assessments are as follows:

- Obtain written informed consent
- Assess inclusion/exclusion criteria (Sections 7.2.1 and 7.2.2, respectively)
- Medical and surgical history (date of diagnosis of NAFLD/NASH including liver biopsy results for biopsy-confirmed NASH patients within 6 months of screening; any surgery performed; any other diagnosis)
- Record demographics (age, full date of birth, gender, race, and ethnicity)
- Serology
- 12-lead ECG (Section 10.2.6)
- Physical examination (Section 10.2.4)
- Vital signs (Section 10.2.5)
- Pregnancy test
- MRI (Section 9.2.2)
- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)
- Fibrosis and inflammation markers (Section 10.2.1)

- High-sensitivity CRP
- Stored sample for future testing (Section 10.2.1)
- Review of alcohol consumption
- Document concomitant medications
- AE monitoring

#### 7.1.3.2 Treatment Period (Day 1 to Week 16)

##### 7.1.3.2.1 Study Day 1/Visit 2 (Randomization)

At the randomization visit, the following assessments will be conducted:

- Review inclusion/exclusion criteria (Sections 7.2.1 and 7.2.2, respectively)
- Physical examination (Section 10.2.4)
- Vital signs (Section 10.2.5)
- Pregnancy test
- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)
- Fibrosis and inflammation markers (Section 10.2.1)
- Stored sample for future testing (Section 10.2.1)
- Study drug is dispensed and patients are instructed to administer daily from Day 1
- Review of concomitant medications
- AE monitoring

#### 7.1.3.2.2 Study Weeks 4-12/Visits 3-5

The following procedures and assessments will be conducted:

- Vital signs (Section 10.2.5)
- Pregnancy test
- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Visit 3 only; Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)
- Fibrosis and inflammation markers (Visit 3 only; Section 10.2.1)
- High-sensitivity CRP (Visit 3 only; Section 10.2.1)
- Stored sample for future testing (Section 10.2.1)
- Study drug is dispensed; review of compliance
- Review of concomitant medications
- AE monitoring

#### 7.1.3.2.3 Study Week 16/Visit 6/EOT

The last dose of study drug will be taken in the morning the day before Visit 6 and the following procedures and assessments will be conducted (also conducted at the time a patient prematurely withdraws):

- 12-lead ECG (Section 10.2.6)
- Physical examination (Section 10.2.4)
- Vital signs (Section 10.2.5)
- Pregnancy test
- MRI (Section 9.2.2)

- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)
- Fibrosis and inflammation markers (Section 10.2.1)
- High-sensitivity CRP
- Stored sample for future testing (Section 10.2.1)
- Review of concomitant medications
- AE monitoring

#### 7.1.3.3 Follow-Up Period

##### 7.1.3.3.1 Study Week 18/ Visit 7

All patients will complete a Follow-Up visit approximately 2 weeks after the last dose of study drug for the following assessments:

- Vital signs (Section 10.2.5)
- Pregnancy test
- Clinical safety laboratory tests (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total BA (Section 9.2.3)
- Lipid profile (Section 10.2.1)
- Stored sample for future testing (Section 10.2.1)
- Review of concomitant medications
- AE monitoring

## 7.2 Study Population

A total of approximately 46 patients with a clinical diagnosis of NAFLD/NASH (in accordance with the protocol definition) will be randomized.

### 7.2.1 Inclusion Criteria

Patients must meet all the following criteria to be included in the study:

1. Be willing to participate in the study and provide written informed consent
2. Be a man or woman ≥18 years of age
3. Have a current biopsy-confirmed NASH within 6 months of screening **or** a suspected diagnosis of NAFLD/NASH based on the criteria outlined below:

    a. Biopsy-confirmed NASH is defined as histological NASH diagnosis with fibrosis stage F1 through F3 and a NAFLD activity score (NAS) of ≥4 with a score of ≥1 in each of the NAS components below as assessed by the central pathologist using the NASH Clinical Research Network criteria (Kleiner 2005)

        i. Steatosis (scored 0 to 3)

        ii. Ballooning degeneration (scored 0 to 2)

        iii. Lobular inflammation (scored 0 to 3)

    **OR**

    b. The suspected diagnosis of NAFLD/NASH is based on the diagnosis of metabolic syndrome as having any 3 of the following 5 risk factors at Screening:

        i. Fasting plasma glucose ≥100 mg/dL or undergoing drug treatment for elevated glucose

        ii. High-density lipoprotein-cholesterol (HDL-C) <40 mg/dL in males or <50 mg/dL in females or undergoing drug treatment for reduced HDL-C

iii. Triglycerides ≥150 mg/dL or undergoing drug treatment for elevated triglycerides

iv. Waist circumference >102 cm in males or >88 cm in females

v. Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or undergoing drug treatment for hypertension, or antihypertensive drug treatment in a patient with a history of hypertension

4. Screening MRI-PDFF with ≥10% liver steatosis

5. Fasting serum LDL-C >100 mg/dL at Screening

6. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (beta human chorionic gonadotropin) at Screening and must agree to use highly effective birth control throughout the study and up to 30 days after the last dose of study drug. Highly effective contraception measures include combined estrogen- and progestogen-containing hormonal contraception (oral, intravaginal, and transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, and implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner (only in the event that the vasectomized partner is the sole sexual partner of the WOCBP), and sexual abstinence (defined as refraining from heterosexual intercourse) only in the event that this is the preferred lifestyle of the patient.

   Childbearing potential is defined as being fertile following menarche and until becoming postmenopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

   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.

Men with partners who are WOCBP must either be surgically sterile or agree to use a barrier contraceptive for the duration of the study and up to 30 days after the last dose of study drug.

7. Be willing to maintain a stable diet and physical activity throughout the course of the study

### 7.2.2 Exclusion Criteria

Patients who meet any of the following criteria will not be included in the study:

1. Women who are pregnant, breastfeeding, or plan to become pregnant during the study
2. Body mass index (BMI) <25 kg/$m^2$
3. Fibrosis-4 index (Fib-4) >2.6
4. Any of the following laboratory abnormalities:
    a. ALT >5 × upper limit of normal (ULN) or AST >5 × ULN
    b. International normalized ratio (INR) ≥1.3, unless on anticoagulant therapy
    c. Total bilirubin >ULN, except with an established diagnosis of Gilbert's syndrome
    d. Platelet count less than the lower limit of normal (LLN)
    e. Creatinine clearance as calculated by the modification of diet in renal disease (MDRD) estimated glomerular filtration rate (eGFR) equation <60 mL/min

    NOTE: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor.
5. Acute or chronic liver disease other than NAFLD/NASH including but not limited to the following:
    a. Hepatitis B (as defined by the presence of hepatitis B surface antigen at screening) or hepatitis C (as defined by the presence of hepatitis C virus [HCV] antibody [anti-HCV]). Patients with positive anti-HCV who test

negative for HCV ribonucleic acid at screening will be allowed to participate in the study as long as there is evidence of viral negativity for a minimum of 12 months prior to screening)

b. Evidence of autoimmune hepatitis

c. History of primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, homozygous alpha-1-anti-trypsin deficiency, hemochromatosis or iron overload, drug-induced or alcoholic liver disease, or known bile duct obstruction

d. Suspected or proven hepatocellular carcinoma

6. Known history of human immunodeficiency virus
7. Medical history of liver cirrhosis
8. Clinical evidence of portal hypertension to include any history of ascites, hepatic encephalopathy, or presence of esophageal varices
9. Use of drugs historically associated with NAFLD (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 for >2 weeks in the year prior to screening
10. Use of the following medications:

    a. GLP-1 agonists unless on a stable dose 3 months prior to liver biopsy or Screening

    b. Ursodeoxycholic acid, thiazolidinediones, or obeticholic acid within 3 months prior to Screening

    c. Statins and other lipid-modifying therapies must have been stable for ≥3 months prior to Screening

    d. Oral antidiabetic drugs (other than those specifically excluded) must have been stable for ≥3 months prior to Screening

e. Agents (including herbal over-the-counter weight-loss preparations) or medications known to significantly impact body weight within 3 months prior to Screening (e.g., sibutramine, phenetamine, and orlistat)

11. History of significant alcohol consumption, defined as an average of >20 g/day in female patients and >30 g/day in male patients, for a period of >3 consecutive months within 1 year prior to Screening, hazardous alcohol use (Alcohol Use Disorders Identification Test score ≥8), or an inability to reliably quantify alcohol consumption based upon judgment of the Investigator
12. Weight change ≥10% within the 6 months prior to Screening or ≥5% within the 3 months prior to Screening
13. Prior or planned (during the study period) bariatric surgery (e.g., gastroplasty, sleeve gastrectomy and roux-en-Y gastric bypass)
14. Type 1 diabetes by medical history
15. Uncontrolled Type 2 diabetes defined as hemoglobin A1c (HbA1c) >9.5% at Screening (patients with HbA1c >9.5% may be rescreened) or requiring oral diabetes medication dose adjustment >10% within 2 months prior to Screening
16. Clinical hyperthyroidism or hypothyroidism or screening hormone results pointing to thyroid dysfunction. Patients receiving dose-stable thyroid replacement therapy for ≥3 months prior to Screening will be allowed to participate as long as thyroid tests (thyroid-stimulating hormone/triiodothyronine/thyroxine) show that the patient is euthyroid
17. History of any condition causing malabsorption such as chronic pancreatitis, extensive bowel/small intestine surgery, celiac disease, or bile flow obstruction
18. History of any condition associated with acute or chronic diarrhea such as inflammatory bowel disease (IBD), functional diarrhea, irritable bowel syndrome (IBS) with predominant diarrhea, IBS with mixed bowel habits, or unclassified IBS
19. History of ischemic colitis

20. Uncontrolled hypertension (either treated or untreated) defined as systolic blood pressure >160 mmHg or a diastolic blood pressure >100 mmHg at Screening. A retest of blood pressure, (after establishing good blood pressure control within a reasonable period of time and up to the Baseline visit) is permissible at the discretion of the Investigator

21. History of New York Heart Association Class III or IV heart failure, or known left ventricular ejection fraction <30%

22. History of myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke or major surgery within 6 months prior to Screening

23. Active substance abuse within 1 year prior to Screening

24. Participation in an investigational new drug trial in the 30 days prior to Screening or within 5 half-lives of an investigational agent, whichever is longer

25. Malignancy within 5 years, except for basal- or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated. Patients with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor's Medical Monitor. Patients under evaluation for malignancy are not eligible

26. Patients with known intolerance to MRI or with conditions contraindicated for MRI procedures

27. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, compromise the well-being of the patient, or interfere with the study outcomes

### 7.2.3 Withdrawal of Patients

Patients will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and that they are not obliged to state their reasons.

Any withdrawal, and reasons for withdrawal, must be fully documented in the electronic case report form (eCRF) and source documents and the patient followed by the investigator/investigative staff. Even after the study is completed at the Follow-Up visit, the investigator/investigative staff will, regardless of reason for withdrawal, record any patient data they receive concerning serious adverse events (SAEs), and all drug-related non-serious AEs, and report these in the eCRF. Withdrawn patients will not be replaced.

Patients will be withdrawn in the following circumstances:

- A patient's desire for withdrawal for any reason
- Lost to follow-up (every effort must be made to contact the patient; a certified letter must be sent)
- An AE that, in the opinion of the Investigator, necessitates withdrawal
- Death
- A patient's substantial noncompliance (study drug compliance) or protocol violation
- An Investigator's opinion that continuing the patient in the study is not appropriate. The Investigator may withdraw a patient at any time if it is considered to be in the patient's best interest

A patient who withdraws from treatment prematurely will have EOT (Visit 6) assessments at the time of withdrawal and a Follow-Up assessment (Visit 7) approximately 2 weeks following the last dose of study drug, and the patient will be recorded as withdrawn.

### 7.2.4 Study Termination by Sponsor

This study may be terminated at any time by the Sponsor if serious side effects should occur, if the Investigator does not adhere to the protocol, or if, in the Sponsor's judgment, there are no further benefits to be achieved from the study. In this event, the Sponsor or its designee will inform the study investigators, institutions, and all regulatory authorities.

The Sponsor may temporarily or permanently discontinue the study at an investigative site at any time for safety, ethical, compliance, or other reasons. If this is necessary, the Sponsor will endeavor to provide advance notification to the site. If a site or the study is

suspended or discontinued, the Investigator/investigative staff will be responsible for promptly informing the IRB. If required by local regulations, the Sponsor or its designee will be responsible for informing the IRB and the regulatory authority of study or site discontinuation. In such an event, all study data and unused study drug must be returned to the Sponsor or its designee.

# 8. TREATMENT OF PATIENTS

## 8.1 Identity of Study Drug

Elobixibat and placebo will be supplied as tablets for oral administration during the Treatment phase of the study. White tablets containing elobixibat or placebo will be provided.

The elobixibat and placebo tablets will be identical in appearance. Tablet filling weight will also be identical for elobixibat and placebo. Bottles containing 34 tablets will be given to the patient at each visit. Refer to the study reference manual.

## 8.2 Administration of Study Drug

Patients will be dosed with elobixibat at a dose of 5 mg or placebo once daily for 16 weeks. Study drug will be dispensed to the patient at Visits 2-5 together with instructions on how to store and take the drug. Study drug compliance will be evaluated at each study visit.

Elobixibat should be taken in the morning, prior to the first meal. On clinic visit days when laboratory assessments are conducted, study drug should be taken after the visit and after laboratory samples are taken.

## 8.3 Study Treatment Packaging and Labeling

### 8.3.1 Packaging and Labeling

The tablets will be packed in high-density polyethylene bottles, with child-proof polypropylene caps. Packaging and labeling will be prepared to comply with applicable regulatory requirements.

### 8.3.2 Storage

Treatment bottles containing elobixibat tablets should be stored and dispensed in accordance with regulations in their original containers. The storage facility at the investigative site should be locked and the storage temperature should be between 15°C and 25°C.

Caregivers should be informed of appropriate storage conditions (i.e., room temperature, between 15°C and 25°C).

Any deviations from the recommended storage conditions should be immediately reported to the Sponsor and the study drug should not be used until authorization has been given by the Sponsor.

### 8.3.3 Blinding and Randomization of Study Drug

A double-blind design is employed so that both the investigators and the patients will be unaware of the treatment assignment during the study.

After written informed consent is obtained from an eligible patient, a 6-digit patient number will be assigned. The first 3 digits will be the site number followed by a 3-digit patient sequence number. This number will be created and allocated by the site when the patient first enters at Screening. The randomization codes will be computer-generated by a statistician independent from the project team. The randomization will be done in blocks to ensure approximate balance between dose schemes (1:1). Randomization codes will be assigned sequentially as patients become eligible for randomization.

Patients who are eligible for randomization will be assigned a unique 4-digit randomization number by the Interactive Web Response System (IWRS). This randomization number identifies which treatment will be allocated to the patient. Patients who withdraw from the study after randomization visit are not to be replaced and their randomization number will not be reused.

To ensure blinding, the study drug and the matching placebo have the same shape and size. Labels on the treatment bottles will not identify the treatment to which a patient has been randomized. Traceability of the treatment is ensured by the bottle number.

The 5-digit bottle number will identify the study-drug bottle and will be detailed on the study-drug label. Dispensing of the study drug will be coordinated by IWRS.

The system will assign a study-drug number corresponding to the randomization arm. The randomization number will be used in the background only to ensure that there is no unblinding and will not be displayed to end-users in the IWRS.

## 8.4 Procedure for Breaking the Randomization Code

Should a situation arise where unblinding is urgently required, i.e., only where knowledge of the study drug is required to adequately manage a life-threatening situation,

the Investigator at that study site may perform immediate unblinding through IWRS. The responsibility to break the treatment code in emergency situations resides solely with the Investigator. The Investigator should make every effort to discuss the rationale (status and outcome) for emergency unblinding with the Sponsor's Medical Monitor as soon as possible to review the individual patient details.

The study-site Investigator and appropriate project team members will be authorized to access the emergency unblinding functionality within the IWRS. Once the randomization code is broken for a patient, he/she must be withdrawn from the study and all assessments and procedures for Visit 6/EOT should be performed. Once a randomization code has been broken, the Investigator must inform the project team and Sponsor's Medical Monitor in writing within 24 hours. In case of technical issues accessing the system online, please see the IWRS site user manual for contact telephone numbers for the help desk 24/7 system support.

## 8.5 Patient Compliance

Patients will return all unused study drug at Visits 3 through 6. The study-site staff will count all returned drug, assess compliance, and record details in the eCRF.

Any noncompliance will be documented and explained in the source documents.

Treatment compliance = 100 × ([number of study drug dispensed—number of study drug returned]/number of study drug that should be taken)

Treatment compliance between 80% and 120% is acceptable.

## 8.6 Study Drug Accountability

Records shall be maintained of the delivery of study treatment(s) to the study site(s), of the inventory at the study site(s), of each use of the study treatment(s) for each patient and the return or destruction of used and unused study treatment(s). Local destruction of used/unused study treatment(s) will follow institution standard operating procedures (SOPs) and will require Sponsor pre-approval.

These records shall include dates, quantities, batch numbers, expiry dates, and the unique code numbers assigned to the study drug and to the study patients.

The Investigator will be responsible for ensuring that the records adequately document that the patients were provided the quantities specified in the protocol and that all study drug received from the Sponsor or its designee is reconciled.

## 8.7 Concomitant Therapy and Prohibited Medications

The Investigator will note all ongoing medication and any medication recently stopped (within 3 months prior to Visit 2) in the eCRF. At Visits 2 through 6, all changes in medication (stopping or starting new medication or changes in dose) will be recorded in the eCRF.

All medications taken by a patient within 3 months prior to the first intake of study drug are regarded as prior medication.

All medications taken by a patient on or after the first intake of study drug, and which continue to be taken during the study, are regarded as concomitant medication.

# 9. ASSESSMENT OF EFFICACY

## 9.1 Efficacy Endpoints

### 9.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline in serum LDL-C at Week 16.

### 9.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
- Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI
- Change from Baseline to Week 16, and Follow-Up in the following:
    - Serum ALT, AST, and gamma-glutamyl transferase
    - HDL-C, non-HDL-C, LDL-C/HDL-C ratio, and triglycerides
    - Total bile acids

### 9.1.3 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be assessed:

- Change from Baseline (unless otherwise specified) to Week 4, Week 8, Week 12, Week 16, and Follow-Up in the following:
    - Fasting glucose, insulin, homeostatic model assessment-insulin resistance, HbA1c, free fatty acids
    - GLP-1, FGF-19, and C4 levels
    - High-sensitivity CRP
    - Lanosterol and beta-sitosterol
    - Body weight, BMI, waist circumference, and waist-to-hip ratio

- Apolipoprotein A1 and Apolipoprotein B

## 9.2 Efficacy Assessments

### 9.2.1 Lipid Profile

Fasting blood samples for analysis of LDL-C will be drawn at all visits, according to the schedule of assessments (Table 1). Fasting should be for at least 8 hours prior to the collection of the blood sample. Samples will be processed and transported to a central laboratory per instructions in the study reference manual.

### 9.2.2 Magnetic Resonance Imaging

Patients will have an MRI at Screening and EOT to assess liver fat by MRI-PDFF, and total liver volume. Details of the image acquisition and analysis can be found in the study reference manual.

### 9.2.3 Total Bile Acids

Fasting blood samples for analysis of total BA will be drawn at all visits, according to the schedule of assessments (Table 1). Fasting should be for at least 8 hours prior to the collection of the blood sample. All BA results during the treatment period will be blinded. Samples will be processed and transported to a central laboratory per instructions in the study reference manual.

### 9.2.4 Biomarkers and Blood Samples for Future Testing

Blood samples for analysis of additional markers of disease, fibrosis, inflammation, and cardiovascular risk factors, and other pharmacodynamic markers will be drawn at the appropriate visits, according to the schedule of assessments (Table 1). These include a bile acid profile, including primary and secondary bile acids, interleukin-6, Pro-C3, tumor necrosis factor alpha, and cytokeratine-18. Samples will be processed and transported to a central laboratory per instructions in the study reference manual.

# 10. ASSESSMENT OF SAFETY

The timing and frequency of safety assessments are described in Section 7.1.3 and in Table 1.

The primary safety analysis will include the occurrence of treatment emergent adverse events (TEAE) and TEAEs categorized by causality, severity, and seriousness assessments made by the Investigator by comparing study drug exposure to placebo.

Trends in safety will also be evaluated for the following assessments:

- AEs, including discontinuations due to AEs
- Physical examinations
- Concomitant medications
- Vital signs
- 12-lead ECG
- Laboratory test results (including clinical chemistry, hematology/coagulation, and urinalysis)

## 10.1 Adverse Events

### 10.1.1 Definitions and Investigator Assessments

An AE is defined as any untoward medical occurrence in an enrolled patient regardless of causal relationship with study drug. An AE can therefore be any clinically significant unfavorable and unintended sign, symptom, or disease that occurs once a patient is enrolled (ICF is signed) in the study until the patient is discharged from the study, whether or not related to the study drug.

#### 10.1.1.1 Clinical Significance

Clinical significance is defined as any abnormal finding that results in further clinical investigation(s), treatment(s), or the diagnosis of a new condition. Patient reported events and protocol mandated laboratory values, vital signs, and physical examination findings can be considered clinically significant (i.e., an AE) if there is a deterioration as compared to Baseline. Examples of clinically significant worsening from Baseline could

include, but is not limited to, events causing withdrawal from the study and events requiring medical intervention outside of the study causing apparent clinical manifestations or judged to be relevant by the Investigator.

#### 10.1.1.2 Serious Adverse Events

Serious criteria are applied by the investigator to each AE as specifically defined below. These criteria are used to determine whether an AE is serious or non-serious. The assessment is made independently of severity assessment (Section 10.1.1.3). For example, the development of a severe rash that occurs after signing of the ICF may not meet serious criteria as defined below and therefore would be considered a severe, non-serious AE.

Any AE that meets any 1 of the following 6 criteria is considered to be an SAE:

- The outcome of the AE is **death**
- The AE is immediately **life-threatening**. Life-threatening means that the patient is, in the opinion of the Investigator, at immediate risk of death from the reaction as it occurred. This does not include an AE that, if more severe, might have caused death
- The AE results in persistent or significant **disability/incapacity**. Disability means a substantial disruption of a person's ability to conduct normal life functions
- The AE requires or prolongs **hospitalization**
- The AE results in a **congenital anomaly/birth defect**
- **The AE is an important medical event**. Important medical events may meet serious criteria should the Investigator assess that they may significantly jeopardize the patient, represent a significant hazard, or require medical/surgical intervention to prevent one of the outcomes listed above. Examples of potential SAEs based on these criteria include, but are not limited to, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions even if they do not result in inpatient hospitalization, or the development of drug dependency and drug abuse.

#### 10.1.1.3 Adverse Events of Special Interest

An adverse event of special interest (AESI) should be recorded as an AE in the eCRF as outlined in Section 10.1.2 and reported using the SAE/AESI Report Form outlined in Section 10.1.3.

For this study, any occurrence of ischemic colitis should be reported as an AESI.

#### 10.1.1.4 Severity Assessment

Severity assessments are based on the intensity of the event in relation to expectation. The Investigator will assess the intensity of AEs based on the following definitions:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

Severity is a measure of intensity where seriousness is defined by the criteria outlined in Section 10.1.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not meet serious criteria, and therefore would be assessed as a severe AE but not an SAE.

#### 10.1.1.5 Causality Assessment

The Investigator determines the causality of all AEs to the study drug using medical judgment and considering all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study drug, and de-challenge or re-challenge. The causality assessment of the AE/SAE is to be made as follows:

**Related to Study Drug (Possibly, Probably, or Definitely Related)**

Based on medical judgment, there is at least a reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug

- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The event follows a known pattern of response to study drug
- The event disappears or decreases on cessation or reduction in dose of the study drug. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon discontinuation of study drug despite other clear indications of relatedness)
- The event reappears or worsens when the study drug is re-administered

**Unrelated to Study Drug (Unlikely or Unrelated)**

Based on medical judgment there is no reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of study drug
- The event could be reasonably attributed to the known characteristics of the patient's clinical state, concurrent illness, environment or toxic factors, or other modes of therapy administered to the patient
- The event does not follow a known pattern of response to study drug
- The event does not disappear or decrease on cessation or reduction in dose of the study drug, and it does not reappear or worsen when the study drug is re-administered

### 10.1.2 Recording of Adverse Events

It is the Investigator's responsibility to assess whether each untoward event is a clinically significant worsening from Baseline, thereby considered an AE. For all AEs, the severity, seriousness, and causality to study drug for each AE as outlined in Section 10.1.1 will be assessed and recorded in the eCRF.

All serious and non-serious AEs are collected once the patient has signed the ICF and until the post-treatment follow-up (Visit 7) or 14 days after the last dose of study drug.

Any AEs or SAEs that are unresolved at the patient's last AE assessment are followed up by the Investigator until resolution or stabilization up to the database lock and recorded in the eCRF. The Sponsor retains the right to request additional information for any patient with ongoing AE(s) or SAE(s) at the end of the study.

TEAEs are defined as any AE that occurs after first dose of study drug. All AEs that occur in the Screening period, i.e., after enrollment and prior to randomization, will be collected on the eCRF as non-TEAEs.

If there is a clinically significant deterioration of a laboratory value/vital sign or other routine study assessment that is associated with a diagnosis, the clinical diagnosis will be reported as an AE and the associated signs and symptoms will be considered additional information unless the sign or symptom is more severe than expected given the diagnosis. For example, if an Investigator diagnoses a study patient with hepatitis during the study period, hepatitis would be considered the AE and the concomitant signs and symptoms of abdominal pain, vomiting, and elevated ALT and AST would not be reported separately unless, in the opinion of the Investigator, one of these signs or symptoms is more severe than expected and therefore a separate AE assessment is indicated.

### 10.1.3 Recording and Reporting of Serious Adverse Events and Adverse Events of Special Interest

Every SAE/AESI (regardless of severity and causality) that occurs once the patient has signed the ICF and through 14 days after the final dose of study drug, should immediately and not later than within 24 hours of knowledge of the event, be reported by the Investigator or delegate using the SAE/AESI report form.

Report of a SAE/AESI must include at least the following information:

- Patient identification information (study number, site number, and date of birth [as per local country requirements for data protection])
- The last study drug administration date
- The diagnosis of the event with the description (or a brief description of signs/symptoms/clinical course if the diagnosis is not available) and the date of onset

- The action used to treat the event (i.e., treatment medications, temporary discontinuation)
- The reason(s) for considering the event serious
- The relationship of the event to the study drug or to the study procedure (i.e., the Investigator's assessment of causality)
- A brief narrative of the SAE/AESI

Follow-up reports including all new information obtained of the subsequent course of the SAE/AESI must be prepared and the information collected in the SAE/AESI report form submitted to the CRA, and [redacted] by e-mail within 24 hours of knowledge of the event.

The pharmacovigilance manager (PVM) or the CRA may contact the Investigator to obtain further information on a reported SAE/AESI. The investigator/investigative staff must respond to any request for follow-up information or answers to questions regarding the SAE/AESI within the same timelines as for initial reports.

The PVM reports the occurrence of the SAE/AESI and follow-up to the Sponsor's Medical Monitor for medical assessment of the case.

Should an outcome of death occur within the study period or within 14 days after the last administration of study drug, an SAE/AESI report form should be completed including the main and contributory causes of death.

All SAE/AESI reports must be e-mailed to the following e-mail address within **24 hours**: [redacted]

If email is unavailable, SAEs/AESIs may be transmitted via fax to the following number: [redacted]

### 10.1.4 Notification of Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that occurs in a patient, the nature or severity of which is not expected per the applicable product information. The elobixibat Investigator's Brochure will serve as the reference safety information for this study.

Reporting and tracking of SUSARs will be in accordance with all applicable competent authority regulations. The IRBs and all Investigators involved in this study will be informed according to local requirements.

## 10.2 Laboratory Values, Vital Signs, Physical Examinations, and Other Safety Assessments

### 10.2.1 Laboratory Assessments

Samples will be collected for clinical chemistry, hematology, urinalysis, and other lab assessments at the time points specified in Table 1. The parameters assessed are presented in Table 2. All samples will be processed and transported to a central laboratory per instructions in the study reference manual.

The observed values will be recorded and assessed as “normal” or “abnormal not clinically significant” or “abnormal clinically significant.”

Additional blood samples may be needed due to follow-up of an abnormal value or analysis failure. The blood samples collected for safety laboratory analysis will be destroyed after the analyses have been completed.

Stored blood samples for future testing are detailed in Section 9.2.4.

**Table 2: Laboratory Parameters**

| CLINICAL CHEMISTRY (FASTING) | HEMATOLOGY/COAGULATION | URINALYSIS |
|---|---|---|
| • Albumin<br>• ALT<br>• Alkaline phosphatase<br>• Amylase<br>• AST<br>• Bicarbonate<br>• Blood urea nitrogen<br>• Calcium<br>• Chloride<br>• Creatine kinase<br>• eGFR by MDRD (screening only)<br>• Gamma-glutamyl transferase<br>• Glucose<br>• Hemoglobin HbA1C<br>• Inorganic phosphorus<br>• Lactate dehydrogenase<br>• Lipase<br>• Potassium<br>• Sodium<br>• Total bilirubin<br>• Total protein<br>• Uric acid | • Hematocrit<br>• Hemoglobin<br>• Platelet count<br>• Red blood cell count<br>• White blood cell count and differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)<br>Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.<br>• International normalized ratio (INR)<br>• Prothrombin time (PT) | • Bilirubin<br>• Blood<br>• Glucose<br>• Ketones<br>• Leukocyte esterase<br>• Microscopy including leukocytes (performed only as needed based on positive dipstick test results)<br>• Nitrites<br>• pH<br>• Protein<br>• Specific gravity<br>• Urobilinogen |

*(Continued on next page)*

| LIPID PROFILE (FASTING) | OTHER TESTS | ENDOCRINOLOGY |
|---|---|---|
| • Apolipoprotein A1<br>• Apolipoprotein B<br>• Chylomicron cholesterol<br>• Chylomicron triglycerides<br>• High-density lipoprotein (HDL) cholesterol<br>• Lipoprotein(a) cholesterol<br>• Low-density lipoprotein (LDL) cholesterol[1]<br>• LDL triglyceride<br>• Non-high-density lipoprotein cholesterol<br>• Total cholesterol<br>• Triglycerides<br>• Very low-density lipoprotein (VLDL) cholesterol<br>• VLDL triglyceride<br>• Lanosterol<br>• Beta-sitosterol | • High-sensitivity C-reactive protein (CRP)<br>• C4<br>• Fibroblast growth factor-19 (FGF-19)<br>• Fibrosis and inflammation markers: FIB-4, APRI, and NAS<br>• Glucagon-like peptide-1 (GLP-1) | • Follicle-stimulating hormone[2]<br>• Homeostatic model assessment-insulin resistance<br>• Insulin<br>• Thyroxine[3]<br>• Triiodothyronine[3]<br>• Thyroid-stimulating hormone[3]<br>• Free fatty acids<br>• Adipose tissue insulin resistance<br>• Adiponectin |
| **BILE ACIDS (FASTING)** | **PREGNANCY** | **SEROLOGY** |
| • Total bile acids | • Serum<br>• Urine | • Hepatitis B virus surface antigen<br>• Hepatitis C virus antibody and ribonucleic acid |

[1] LDL-cholesterol will be determined by calculation when triglyceride levels are less than or equal to 400 mg/dL, LDL-C will be determined by preparative ultracentrifugation (PUC) when triglyceride levels are greater than 400 mg/dL.

[2] A postmenopausal state is defined as no menses for ≥12 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, performed at Screening visit only.

[3] Thyroid function test will be performed during Screening visit only.

### 10.2.2 Individual Patient Safety Monitoring

#### 10.2.2.1 Liver Monitoring

Strategies to monitor markers of liver disease throughout the study are outlined below where the ULN will be based on central laboratory reference values for age and gender. Patients will be monitored as described below for drug-induced liver injury from randomization to 2 weeks following the last administration of study drug.

**Elevated ALT**

- ALT >5 × ULN or >3 × Baseline (if ALT elevated at Baseline): repeat AST, ALT, total bilirubin, alkaline phosphatase (ALP), and INR within 72 hours of receipt of the result and closely monitor the patient. If liver enzyme elevation is confirmed, interrupt the study drug. The study drug can be restarted only if a competing etiology is identified or liver tests return to Baseline.

**Elevated AST**

- AST >5 × ULN or 3 × baseline (if AST elevated at baseline): repeat AST, ALT, total bilirubin, ALP, and INR within 72 hours of receipt of the result and closely monitor the patient. If liver enzyme elevation confirmed, interrupt the study drug. The study drug can be restarted only if a competing etiology is identified or liver tests return to Baseline.

**Elevated Total Bilirubin**

- Total bilirubin >2 × ULN or >1.5 × Baseline (if total bilirubin elevated at Baseline), regardless of ALT or AST levels: repeat AST, ALT, total bilirubin, ALP, and INR within 72 hours of receipt of the result and closely monitor the patient. If liver enzyme elevation confirmed, interrupt the study drug. The study drug can be restarted only if a competing etiology is identified or liver tests return to Baseline.

**Other Clinical Symptoms**

- Clinical signs of hepatitis or indicators of immunological reaction (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, jaundice, rash,

eosinophilia >5% or symptoms/signs of hepatic decompensation): discontinue the study drug and repeat AST, ALT, total bilirubin, ALP, and INR within 72 hours and closely monitor. Other causes of hepatitis should be excluded.

When close monitoring of a patient is not possible while the patient is on study drug, interrupt the study drug and closely monitor the patient.

### 10.2.3 Demographics/Medical and Surgical History

Demographic information per country regulations (age, full date of birth, gender, race, and ethnicity), along with medical and surgical history, will be obtained and recorded in the eCRF at Visit 1.

Medical and surgical history will be entered in the eCRF at Visit 1. This includes date of diagnosis of NASH/NAFLD including liver biopsy results for biopsy-confirmed NASH patients within 6 months of screening, ongoing medication, any surgery performed, and any other diagnoses.

### 10.2.4 Physical Examination

A physician or suitably trained qualified assistant will perform a complete physical examination at Screening, at Visit 2, and at Visit 6. Height (Screening only), weight, waist circumference, and waist-to-hip ratio will also be collected. BMI will be calculated based on height and weight.

A complete physical examination will include assessment of general appearance, eyes, ears, nose, throat, head/neck/thyroid, lymph nodes, cardiovascular, lungs/chest, abdomen, genitourinary, extremities, skin, musculoskeletal, neurologic, and other.

### 10.2.5 Vital Signs

Evaluation of vital signs will be performed at all visits. This includes blood pressure (systolic and diastolic), pulse, respiratory rate, and oral temperature.

### 10.2.6 12-Lead ECG

A 12-lead ECG will be performed at the Screening visit and the EOT visits.

### 10.2.7 Overdose

Elobixibat is minimally absorbed and has a very low systemic availability. It is not known whether elobixibat can be removed from the systemic circulation by dialysis. There are no known antidotes for elobixibat overdoses. If an overdose occurs, the patient should be carefully monitored and treated with supportive therapy.

### 10.2.8 Pregnancy

If a pregnancy is discovered in a female patient enrolled in the study, the patient will be immediately discontinued from the study drug, if applicable, and will attend the same visits as a prematurely withdrawn patient. If the pregnancy is discovered after completion of the treatment period, the patient will continue in the study per protocol. If a pregnancy occurs in a male patient's partner at any time during the study, the pregnancy should also be reported and followed.

If the patient has been dosed with the study drug, the pregnancy must be recorded on the appropriate form and submitted to the PVM (Section 10.1.3) within 24 hours of learning of the pregnancy.

The pregnancy should be followed to determine outcome, including spontaneous termination, details of birth and presence of any birth defects, congenital anomalies or newborn or maternal complication. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported as described in Section 10.1.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

# 11. STATISTICAL EVALUATION

All personnel involved with the analysis of the study will remain blinded until database lock for the double-blind treatment period and until major protocol violations have been identified.

All statistical analyses will be performed using SAS version 9.3 or higher.

## 11.1 Sample Size and Power

Due to the exploratory nature of this study, no formal power calculations were used to determine the sample size. The number of subjects (46 patients in total, 23 patients per treatment group) was chosen based on clinical experience with other similar proof-of-concept studies.

## 11.2 Statistical Methods

### 11.2.1 Statistical Analysis Populations

**ITT Population**

The intent-to-treat (ITT) population will include all patients who are randomized in the study and receive at least 1 dose of study drug. The ITT population will be used for all efficacy analyses based on the treatment randomized unless otherwise specified.

**Per Protocol Population**

The per protocol (PP) population will include all ITT patients who finish Visit 7/EOT with valid LDL-C measurements and do not have any major protocol deviations. Allocation of patients to the PP analysis set will be performed before unblinding of the study.

**Safety Population**

The safety population will include all patients who are randomized and receive at least 1 dose of study drug and will be used for all safety analyses based on the treatment received.

### 11.2.2 Methods of Statistical Analyses

#### 11.2.2.1 General Principles

Summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) at all visits and change or percent change from Baseline will be provided for efficacy and safety continuous variables. Count and frequency will be used to tabulate categorical variables.

##### 11.2.2.1.1 Efficacy

The primary efficacy endpoint is the change from Baseline in serum LDL-C at Week 16. Baseline is defined as the last non-missing LDL-C value prior to the first dose of study drug.

Exploratory comparisons between elobixibat 5 mg and placebo will be performed for the following secondary efficacy endpoints:

- Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
- Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI

The analysis methods for the other secondary and exploratory endpoints will be detailed in the statistical analysis plan (SAP).

##### 11.2.2.1.2 Safety

The safety endpoints for this study include clinical laboratory assessments, vital signs, AEs, ECGs, physical examinations, and concomitant medications.

AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedRA). TEAEs will be defined as AEs that are new or worsening after the first dose of study drug. A general summary of patients with TEAEs and serious adverse events (SAEs) will be tabulated with numbers and percentages of patients and repeated for severity and relationship to study drug per treatment group. The number of AEs leading to withdrawal and SAEs leading to death will also be summarized. The incidence of TEAEs will be summarized by body system and treatment group.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from Baseline. Values outside of the reference range will be flagged and laboratory abnormalities of special interest will be summarized.

#### 11.2.2.2 Missing Data

Missing data handling for the primary efficacy endpoint will be specified in the SAP.

#### 11.2.2.3 Demographic and Baseline Characteristics

Descriptive summaries of demographics and other baseline characteristics (including medical and surgical history) will be presented by treatment group and overall using the ITT population.

Prior medication will be summarized by treatment group and overall using the ITT population.

#### 11.2.2.4 Subject Disposition

The following will be summarized descriptively (by treatment group and overall where applicable):

- Patients enrolled (who signed the informed consent)
- Patients randomized
- Patients treated
- Patients completing the study
- Patients withdrawing early (including withdrawal reason)

#### 11.2.2.5 Evaluation of Primary Efficacy Endpoints

An analysis of covariance (ANCOVA) will be used to analyze the primary efficacy endpoint. The model will include treatment arm and Baseline LDL-C scores.

Least square (LS) mean (SE), LS mean difference (SE), 95% confidence intervals, and *P*-values between elobixibat 5 mg and placebo will be provided. The model assumptions will be checked before the analysis. If there are concerns on model assumptions, i.e.,

normality and homogeneity of variances, a non-parametric ANCOVA based on the rank scores can be used as a sensitivity analysis.

Sensitivity analyses may be performed and will be detailed in the SAP.

#### 11.2.2.6 Evaluation of Secondary and Exploratory Efficacy Endpoints

Descriptive statistics will be provided for secondary and exploratory endpoints listed in Sections 9.1.2 and 9.1.3, respectively, unless otherwise specified.

#### 11.2.2.7 Evaluation of Safety Endpoints

Safety data will be analyzed using descriptive statistics and summaries by treatment group of SAEs, AEs, vital signs, clinical safety laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis), and concomitant medication. Analyses will be performed using the safety analysis set.

Summaries of AEs (coded according to the MedDRA system organ class [SOC] and MedDRA preferred term) will include the following:

- Overview of the incidence of TEAEs (TEAEs, drug-related TEAEs, TEAEs leading to study discontinuation, and treatment-emergent SAEs)
- TEAEs by SOC and preferred term
- Intensity of TEAEs by SOC and preferred term
- Drug-related TEAEs by SOC and preferred term
- TEAEs leading to study discontinuation by SOC and preferred term
- Treatment-emergent SAEs by SOC and preferred term

Concomitant medication use during the treatment period will be summarized by Anatomical Therapeutic Chemical (ATC) class and World Health Organization (WHO) preferred name.

Summaries of vital signs will be presented. For each visit, the actual results, the change from Baseline, and the observed post-baseline value will be presented.

Summaries of clinical safety laboratory data will be presented. For each visit, the actual result, the change from Baseline, and the observed post-baseline value will be presented.

Data listings will be provided for each patient for all safety parameters.

#### 11.2.2.8 Compliance and Exposure

Exposure will be analyzed by calculating the number of days with exposure to study drug. Results will be presented by treatment group using the safety analysis set.

The percentage compliance will be described by treatment group and the number of patients with a compliance <80%, between 80% and 120%, and >120% will be presented based on the safety analysis set.

## 12. DIRECT ACCESS TO SOURCE DATA/NOTES

The Investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, IRB review, and regulatory inspection.

# 13. QUALITY CONTROL AND QUALITY ASSURANCE

## 13.1 Conduct of the Study

The study team shall implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with US Food and Drug Administration (FDA) regulations (Code of Federal Regulations, Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95).

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate competent authority and IRB, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the patient having to be withdrawn from the study and render that patient non-evaluable.

## 13.2 Study Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative or designee will review the protocol and eCRF with the Investigators and the investigative staff. During the study, the clinical monitor (the CRA) will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The investigator must ensure that eCRFs are completed within a timely period of patient visits, as per individual site agreements, and must allow the CRA and the Sponsor representative or designee periodic access to patient records and all study-related materials, including relevant hospital or clinical records, to confirm their consistency with the eCRF entries. No information in these records about the identity of the patients will leave the study center. The Sponsor monitoring standards require full verification for the presence of the signed ICF, adherence to the inclusion/exclusion criteria,

documentation of SAEs, and recording of primary efficacy and safety variables. The CRA will review source data compared with the eCRFs and will verify source data according to the study-specific monitoring plan. The design of the study, the frequency of patient visits, and the site enrollment rate will determine the frequency of monitoring visits. Upon study completion, the CRA will visit the site to conduct a study termination visit, which will include collection of any outstanding documentation.

It is recommended that the Investigator/investigative staff log into the eCRF system every working day or at minimum twice weekly in order to provide a prompt response to queries. The Investigator/investigative staff should respond to queries and make any relevant changes to the study data within 3 working days.

# 14. ETHICS

## 14.1 Institutional Review Board

Prior to the start of the study, the Investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IRB. The IRB shall be appropriately constituted and perform its functions in accordance with FDA, ICH, GCP, and local requirements as applicable.

The IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, patient recruitment procedures (e.g., advertisements), written information to be provided to the patients and caregivers, the Investigator's Brochure, available safety information, information about payment and compensation available to patients, the Investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IRB and regulatory authority (competent authority) as applicable.

## 14.2 Written Informed Consents

The Investigator (physician) or investigative staff, in accordance with local regulations, will explain to each patient (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, alternative treatment, the potential risks and benefits involved, and any discomfort that may occur. Each patient will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

If written consent is not possible, oral consent can be obtained if witnessed and followed by a signed statement from one or more persons not involved in the study, indicating why the patient was unable to sign the form. No patient can enter the study before his/her informed consent has been obtained, as required by country regulations.

The ICF is part of the protocol and must be submitted by the Investigator/investigative staff with the protocol for IRB approval. The Sponsor will supply an ICF which complies with regulatory requirements and country laws and is considered appropriate for the study. Any changes to the ICF suggested by the Investigator must be agreed to by the Sponsor before submission to the IRB and a copy of the approved version must be provided to the clinical monitor after IRB approval.

# 15. DATA HANDLING AND RECORDKEEPING

## 15.1 Electronic Case Report Forms/Source Data Handling

The investigator shall be provided with standardized eCRFs and shall ensure that all data from patient visits are promptly entered into the eCRFs in accordance with the specific instructions given. The Investigator must sign each eCRF to verify the integrity of the data recorded.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to the start of the study. As a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analyzed at that laboratory.

The Investigator must maintain source documents such as laboratory reports, consultation reports, and complete medical history and physical examination reports.

## 15.2 Retention of Essential Documents

Essential documents, as defined by ICH GCP, include the signed protocol and any amendment(s); copies of the completed eCRFs (for site archiving of eCRF data for specific patients will be provided); signed ICFs; hospital records and other source documents; IRB approvals and all related correspondence including approved documents; drug accountability records; study correspondence; and a list of patients' names and addresses.

The Investigator/investigative staff must retain copies of these essential documents for the period specified by ICH GCP and by applicable regulatory requirements. The Investigator/investigative staff will inform the Sponsor of the location where the essential documents are stored and must contact the Sponsor for approval before disposing of any essential documents. The Investigator/investigative staff should take measures to prevent accidental or premature destruction of these documents.

## 16. FINANCING AND INSURANCE

Financing and insurance are addressed in a separate agreement.

## 17. PUBLICATION POLICY

The Sponsor will retain ownership of all data. When the study is complete, the Sponsor will arrange the analysis, tabulation of data, and preparation of a clinical study report. The Sponsor may also use the data for publication, presentation at scientific meetings, and submission to regulatory authorities. All proposed publications based on this study must be subject to the Sponsor's approval requirements.

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# CLINICAL STUDY PROTOCOL A3309-012

## A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH)

| | |
|---|---|
| IND number: | 141078 |
| Test product: | Elobixibat |
| Indication: | Nonalcoholic Fatty Liver Disease or Nonalcoholic Steatohepatitis |
| Sponsor: | Elobix AB |
| Development phase: | Phase 2 |
| Sponsor medical monitor: | [redacted] |
| Principal investigator: | [redacted] |
| Date of the protocol: | 22 March 2019 |
| Version of the protocol: | Version 2.0 |

| Version No. | Previous Version Number | Effective Date |
|---|---|---|
| 1.0 | N/A | 25 February 2019 |
| 2.0 | 1.0 | 22 March 2019 |

## SPONSOR SIGNATURE PAGE

**PROTOCOL TITLE: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH)**

PROTOCOL NUMBER: A3309-012

**Elobix AB**

[redacted]

## INVESTIGATOR SIGNATURE PAGE

**PROTOCOL TITLE: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH)**

PROTOCOL NUMBER: A3309-012

I have read this protocol and agree that it contains all necessary details for performing this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practice (GCP), local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

I will use only the informed consent approved by the Institutional Review Board (IRB) and will fulfill all responsibilities for submitting pertinent information to the IRB responsible for this study.

I agree that the Sponsor (Elobix AB) shall have access to any source documents from which case report form (CRF) information may have been generated.

I further agree not to originate or use the name of Elobix AB or elobixibat (A3309) in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to this protocol, to any amendment to the protocol, or to the performance of this protocol without the prior written consent of Elobix AB.

_____

Name of Investigator

_____ _____

Signature Date (day/month/year)

# 1. ADMINISTRATIVE INFORMATION

| | |
|---|---|
| **Protocol no.:** | A3309-012 |
| **Date of initial protocol:** | 25 February 2019, Version 1.0 |
| **Date and no. of amendments:** | 22 March 2019, Version 2.0 |
| **Sponsor:** | Elobix AB<br>Arvid Wallgrens backe 20<br>413 46 Göteborg<br>Sweden |
| **Clinical research organization:** | [redacted] |
| **Sponsor Medical Monitor:** | [redacted] |
| **Principal Investigator:** | [redacted] |

## 2. STUDY SYNOPSIS

| **Name of Sponsor/Company:** Elobix AB | **Name of Product:** Elobixibat | **Name of Active Ingredient:** Elobixibat |
|---|---|---|

**Title of Study:**
A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH)

**Principal Investigator:** [redacted]

**Study Centers:** Up to 15 sites will be initiated for this study in the United States (US)

**Publication(s):** Not applicable

| **Planned Study Period:** Q2 2019 to Q2 2020 | **Development Phase:** Phase 2 |
|---|---|

**Objectives:**

*Primary Objective*

The primary objective is to evaluate the efficacy of repeated once-daily doses of 5 mg elobixibat on serum levels of low-density lipoprotein cholesterol (LDL-C) in patients with NAFLD or NASH.

*Secondary Objectives*

- To assess the safety and tolerability of elobixibat in patients with NAFLD or NASH
- To evaluate the effect of elobixibat on liver steatosis as measured by magnetic resonance imaging (MRI) for (i) liver fat fraction (using proton density fat fraction [PDFF]) and (ii) total liver fat (using whole liver fat volume)
- To evaluate the effect of elobixibat on liver function using alanine aminotransferase (ALT)
- To evaluate the effect of elobixibat on lipids and serum bile acids (s-BA) in patients with NAFLD or NASH

**Methodology:**

This is a double-blind, randomized, placebo-controlled, Phase 2 study to explore the efficacy and safety of elobixibat (oral dose of 5 mg) once daily for 16 weeks in patients with NAFLD or NASH. The study includes a 6-week Screening period, followed by a 16-week Treatment period, and a Follow-Up visit 2 weeks after the last dose of study drug. Continued collection of efficacy data for patients who discontinue treatment will be made for as long as possible per the schedule of assessments.

After completing the Screening period, eligible patients will be randomized on Day 1 (Visit 2) in a 1:1 fashion to either 5 mg/day elobixibat or matching placebo. There will be a total of 7 scheduled visits during the study. Additional unscheduled visits may be required for patients who need direct site assistance (e.g., due to adverse event [AE] monitoring, in order to fulfill screening requirements, and/or for safety maintenance).

**Number of Patients:** Approximately 46 patients diagnosed with NAFLD/NASH and in accordance with the inclusion/exclusion criteria will be randomized.

**Inclusion Criteria:**

Patients must meet all of the following criteria to be included in the study:

1. Be willing to participate in the study and provide written informed consent
2. Be a man or woman ≥18 years of age
3. Have a current biopsy-confirmed NASH within 6 months of screening or a suspected diagnosis of NAFLD/NASH based on the criteria outlined below:

a. Biopsy-confirmed NASH is defined as histological NASH diagnosis with fibrosis stage F1 through F3 and a NAFLD activity score (NAS) of ≥4 with a score of ≥1 in each of the NAS components below as assessed by a pathologist using the NASH Clinical Research Network criteria (Kleiner 2005):
   i. Steatosis (scored 0 to 3)
   ii. Ballooning degeneration (scored 0 to 2)
   iii. Lobular inflammation (scored 0 to 3)

**OR**

b. The suspected diagnosis of NAFLD/NASH is based on each of the following criteria being met:
   i. Serum AST ≥20 U/L and ALT ≥40 U/L
   ii. Diagnosis of metabolic syndrome as having any 3 of the following 5 risk factors at Screening:
      - Fasting plasma glucose ≥100 mg/dL or undergoing drug treatment for elevated glucose
      - High-density lipoprotein-cholesterol (HDL-C) <40 mg/dL in males or <50 mg/dL in females or undergoing drug treatment for reduced HDL-C
      - Triglycerides ≥150 mg/dL or undergoing drug treatment for elevated triglycerides
      - Waist circumference >102 cm in males or >88 cm in females
      - Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or undergoing drug treatment for hypertension, or antihypertensive drug treatment in a patient with a history of hypertension

4. Screening MRI-PDFF with ≥10% liver steatosis
5. Fasting serum LDL-C >130 mg/dL at screening, >110 mg/dL on lipid-lowering medications
6. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (beta human chorionic gonadotropin) at Screening and must agree to use highly effective birth control throughout the study and up to 30 days after the last dose of study drug. Highly effective contraception measures include combined estrogen- and progestogen-containing hormonal contraception (oral, intravaginal, and transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, and implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner (only in the event that the vasectomized partner is the sole sexual partner of the WOCBP), and sexual abstinence (defined as refraining from heterosexual intercourse) only in the event that this is the preferred lifestyle of the patient.

   Childbearing potential is defined as being fertile following menarche and until becoming postmenopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)

   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

   Men with partners who are WOCBP must either be surgically sterile or agree to use a barrier contraceptive for the duration of the study and up to 30 days after the last dose of study drug
7. Be willing to maintain a stable diet and physical activity throughout the course of the study

| **Name of Sponsor/Company:** Elobix AB | **Name of Product:** Elobixibat | **Name of Active Ingredient:** Elobixibat |
|---|---|---|

**Exclusion Criteria:**

1. Women who are pregnant, breastfeeding, or plan to become pregnant during the study
2. Body mass index (BMI) <25 kg/m$^2$
3. Fibrosis-4 Index (Fib-4) >2.6
4. Any of the following laboratory abnormalities:
    a. ALT >5 × upper limit normal (ULN) or AST >5 × ULN
    b. International normalized ratio (INR) ≥1.3, unless on anticoagulant therapy
    c. Total bilirubin > ULN, except with an established diagnosis of Gilbert's syndrome
    d. Platelet count less than the lower limit of normal (LLN)
    e. Creatinine clearance as calculated by the modification of diet in renal disease (MDRD) estimated glomerular filtration rate (eGFR) equation <60 mL/min

    NOTE: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor.
5. Acute or chronic liver disease other than NAFLD/NASH including but not limited to the following:
    a. Hepatitis B (as defined by the presence of hepatitis B surface antigen at Screening) or hepatitis C (as defined by the presence of hepatitis C virus [HCV] antibody [anti-HCV]. Patients with positive anti-HCV who test negative for HCV ribonucleic acid at Screening will be allowed to participate in the study as long as there is evidence of viral negativity for a minimum of 12 months prior to Screening)
    b. Evidence of ongoing autoimmune hepatitis
    c. History of primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, homozygous alpha-1-anti-trypsin deficiency, hemochromatosis or iron overload, drug-induced or alcoholic liver disease, or known bile duct obstruction
    d. Suspected or proven hepatocellular carcinoma
6. Known history of human immunodeficiency virus
7. Medical history of liver cirrhosis
8. Clinical evidence of portal hypertension to include any history of ascites, hepatic encephalopathy, or presence of esophageal varices
9. Use of drugs historically associated with NAFLD (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 for >2 weeks in the year prior to Screening
10. Use of the following medications:
    a. Glucagon-like peptide-1 (GLP-1) agonists unless on a stable dose 3 months prior to liver biopsy or Screening
    b. Ursodeoxycholic acid, thiazolidinediones, or obeticholic acid within 3 months prior to Screening
    c. Statins and other lipid-modifying therapies must have been stable for ≥3 months prior to Screening
    d. Oral antidiabetic drugs (other than those specifically excluded) must have been stable for ≥3 months prior to Screening

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|---|---|---|

e. Agents (including herbal over-the-counter weight loss preparations) or medications known to significantly impact body weight within 3 months prior to screening (e.g., sibutramine, phenetamine, and orlistat)

11. History of significant alcohol consumption, defined as an average of >20 g/day in female patients and >30 g/day in male patients, for a period of >3 consecutive months within 1 year prior to Screening, hazardous alcohol use (Alcohol Use Disorders Identification Test score ≥8), or an inability to reliably quantify alcohol consumption based upon judgment of the Investigator
12. Weight change ≥10% within the 6 months prior to Screening or ≥5% within the 3 months prior to Screening
13. Prior or planned (during the study period) bariatric surgery (e.g., gastroplasty and roux-en-Y gastric bypass)
14. Type 1 diabetes by medical history
15. Uncontrolled Type 2 diabetes defined as hemoglobin A1c (HbA1c) >9.5% at Screening (patients with HbA1c >9.5% may be rescreened) or requiring insulin dose adjustment >10% within 2 months prior to Screening
16. Clinical hyperthyroidism or hypothyroidism or Screening hormone results pointing to thyroid dysfunction. Patients receiving dose-stable thyroid replacement therapy for ≥3 months prior to Screening will be allowed to participate as long as thyroid tests (thyroid-stimulating hormone/triiodothyronine/thyroxine) show that the patient is euthyroid
17. History of any condition causing malabsorption such as chronic pancreatitis, extensive bowel/small intestine surgery, celiac disease, or bile flow obstruction
18. History of any condition associated with acute or chronic diarrhea such as inflammatory bowel disease (IBD), functional diarrhea, irritable bowel syndrome (IBS) with predominant diarrhea, IBS with mixed bowel habits, or unclassified IBS
19. History of ischemic colitis
20. Uncontrolled hypertension (either treated or untreated) defined as systolic blood pressure >160 mmHg or a diastolic blood pressure >100 mmHg at Screening. A retest of blood pressure, (after establishing good blood pressure control within a reasonable period of time and up to the Baseline visit) is permissible at the discretion of the Investigator
21. History of New York Heart Association Class III or IV heart failure, or known left ventricular ejection fraction <30%
22. History of myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke or major surgery within 6 months prior to Screening
23. Active substance abuse, within 1 year prior to Screening
24. Participation in an investigational new drug trial in the 30 days prior to Screening or within 5 half-lives of an investigational agent, whichever is longer
25. Malignancy within 5 years, except for basal- or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated. Patients with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor's Medical Monitor. Patients under evaluation for malignancy are not eligible
26. Patients with known intolerance to MRI or with conditions contraindicated for MRI procedures
27. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, compromise the well-being of the patient, or interfere with the study outcomes

| **Name of Sponsor/Company:** Elobix AB | **Name of Product:** Elobixibat | **Name of Active Ingredient:** Elobixibat |
|---|---|---|
| **Test Product, Dose, and Mode of Administration:** Elobixibat, 5 mg once a day, orally administered | | |
| **Reference Therapy, Dose and Duration of Administration:** Matching placebo, orally administered | | |
| **Duration of Treatment:** Up to 16 weeks | | |

**Variables**

**Efficacy:**

*Primary Efficacy Endpoint*

The primary efficacy endpoint is the change from baseline in serum LDL-C at Week 16.

*Secondary Efficacy Endpoints*

Secondary efficacy endpoints include the following:

- Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
- Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI
- Change from Baseline to Week 16, and Follow-Up in the following:
    - Serum ALT, AST, and gamma-glutamyl transferase
    - HDL-C, non-HDL-C, LDL-C/HDL-C ratio and triglycerides
    - Serum total bile acids

*Exploratory Efficacy Endpoints*

The following exploratory efficacy endpoints will be assessed:

- Change from Baseline (unless otherwise specified) to Week 4, Week 8, Week 12, Week 16, and Follow-Up in the following:
    - Fasting glucose, insulin, homeostatic model assessment-insulin resistance, HbA1c, free fatty acids
    - GLP-1, fibroblast growth factor-19 (FGF-19), and C4 levels
    - High-sensitivity C-reactive protein (CRP)
    - Lanosterol and beta-sitosterol
    - Body weight, BMI, waist circumference, and waist-to-hip ratio
    - MRI-based measurement of pulse wave velocity to measure aortic stiffness
    - Apolipoprotein A1 and Apolipoprotein B

**Safety:**

Safety criteria are as follows:

- Occurrence of treatment-emergent adverse events categorized by causality, severity, and seriousness assessments made by Investigator by comparing study-drug exposure to placebo
- Trends in safety evaluated for the following assessments:
    - Physical examinations
    - Concomitant medications
    - Vital signs
    - 12-lead ECG
    - Laboratory test results (including clinical chemistry, hematology/coagulation, and urinalysis)

**Statistical Methods**
**Analysis Populations:**

- The intent-to-treat (ITT) population will include all patients who are randomized in the study and receive at least 1 dose of study drug. The ITT population will be used for all efficacy analyses based on the treatment randomized unless otherwise specified
- The per protocol (PP) population will include all ITT patients who finish Visit 7/End of Treatment (EOT) with valid LDL-C measurements and do not have any major protocol deviations. Allocation of patients to the PP analysis set will be performed before unblinding of the study
- The safety population will include all patients who are randomized and receive at least 1 dose of study drug and will be used for all safety analyses based on the treatment received
- Summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) at all visits and change or percent change from Baseline will be provided for efficacy and safety continuous variables. Count and frequency will be used to tabulate categorical variables
- Demographics, disposition, and study populations will be summarized descriptively

**Efficacy:**

- The primary efficacy endpoint is the change from Baseline in serum LDL-C at Week 16. Baseline is defined as the last non-missing LDL-C value prior to the first dose of study drug
- To address the potential missing data from patients who are lost to follow-up after treatment discontinuation, multiple imputation method will be used. Data from patients who discontinue the study drug but stay in the study with scheduled assessments collected will be used to impute missing values for patients lost to follow-up. This imputation will be done within each treatment group. Interim missing data will be handled as missing at random (predictable from observed data from subjects in the same treatment group)
- After the imputation is performed, an analysis of covariance (ANCOVA) will be used to analyze the primary efficacy endpoint. The model will include treatment arm and Baseline LDL-C scores
- Least square (LS) mean (SE), LS mean difference (SE), 95% confidence intervals, and *P*-values between elobixibat 5 mg and placebo will be provided. The model assumptions will be checked before the analysis. If there are concerns on model assumptions, i.e., normality and homogeneity of variances, a non-parametric ANCOVA based on the rank scores can be used as a sensitivity analysis
- Exploratory comparisons between elobixibat 5 mg and placebo will be performed for the following secondary efficacy endpoints:
    - Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
    - Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI
- The analysis methods for the other secondary endpoints and exploratory endpoints will be detailed in the Statistical Analysis Plan for the study.

**Safety:**

- The safety endpoints for this study include clinical laboratory assessments, vital signs, AEs, ECGs, physical examinations, and concomitant medications
- AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedRA). TEAEs will be defined as AEs that are new or worsening after the first dose of study drug. A general summary of patients with TEAEs and serious adverse events (SAEs)/adverse

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event of special interest (AESI) will be tabulated with numbers and percentages of patients and repeated for severity and relationship to study drug per treatment group. The number of AEs leading to withdrawal and SAEs leading to death will also be summarized. The incidence of TEAEs will be summarized by body system and treatment group

- The safety laboratory data will be summarized by visit and by treatment group, along with changes from Baseline. Values outside of the reference range will be flagged and laboratory abnormalities of special interest will be summarized

**Sample Size Determination:**

Due to the exploratory nature of this study, no formal power calculations were used to determine the sample size. The number of subjects (46 patients in total, 23 patients per treatment group) was chosen based on clinical experience with other similar proof-of-concept studies.

**Date of the Protocol:** 22 March 2019

## 3. TABLE OF CONTENTS

## 3.1 List of Tables

## 4. LIST OF ABBREVIATIONS, ACRONYMS, AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| A3309 | elobixibat |
| AE(s) | adverse event(s) |
| AESI(s) | adverse event(s) of special interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| Anti-HCV | hepatitis C antibody |
| APRI | AST to platelet ratio index |
| ASBT | apical sodium-dependent bile acid transporter (also known as IBAT) |
| AST | aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BMI | body mass index |
| C4 | 7α-hydroxy-4-cholesten-3-one |
| CRA | clinical research associate |
| CRF | case report form |
| CRP | C-reactive protein |
| ECG(s) | electrocardiogram(s) |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| EOT | End of Treatment |
| FDA | US Food and Drug Administration |
| FGF-19 | fibroblast growth factor-19 |
| Fib-4 | fibrosis-4 |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| GLP-1 | glucagon-like peptide-1 |
| H&E | hematoxylin and eosin |
| HbA1c | hemoglobin A1c |

| Abbreviation | Definition |
|---|---|
| HCV | hepatitis C virus |
| HDL-C | high-density lipoprotein-cholesterol |
| IBAT | ileal bile acid transporter (also known as ASBT) |
| IBD | inflammatory bowel disease |
| IBS | irritable bowel syndrome |
| ICF(s) | informed consent form(s) |
| ICH | International Council on Harmonisation |
| INR | international normalized ratio |
| IRB | institutional review board |
| ITT | intent to treat |
| IWRS | Interactive Web Response System |
| LDL | low-density lipoprotein |
| LDL-C | low density lipoprotein-cholesterol |
| LLN | lower limit of normal |
| LPLV | last patient last visit |
| LS | least square |
| MDRD | modification of diet in renal disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MRI-PDFF | magnetic resonance imaging—proton density fat fraction |
| N/A | not applicable |
| NAFLD | nonalcoholic fatty liver disease |
| NAS | NAFLD activity score |
| NASH | nonalcoholic steatohepatitis |
| ob/ob (mice) | leptin-deficient mice |
| PCS | potentially clinically significant |
| PDFF | proton density fat fraction |
| PP | per protocol |
| PVM | pharmacovigilance manager |
| RNA | ribonucleic acid |

| Abbreviation | Definition |
|---|---|
| s-BA | serum bile acid(s) |
| SAE(s) | serious adverse event(s) |
| SAP | statistical analysis plan |
| SE | standard error |
| SOC | system organ class |
| SOP(s) | standard operating procedure(s) |
| Sponsor | Elobix AB |
| SUSAR | suspected unexpected serious adverse reaction(s) |
| TEAE(s) | treatment-emergent adverse event(s) |
| ULN | upper limit of normal |
| US | United States |
| VLDL | very low-density lipoprotein |
| WHO | World Health Organization |
| WOCBP | Women (woman) of childbearing potential |
| α-SMA | alpha-smooth muscle actin |

# 5. INTRODUCTION

## 5.1 Investigational Medicinal Product

Elobixibat is a potent inhibitor of the ileal bile acid transporter (IBAT; also known as the apical sodium bile acid transporter [ASBT]). The IBAT, expressed mainly in the distal ileum, is a key element in the enterohepatic circulation of bile acids because it facilitates the very efficient process of bile acid reabsorption. Elobixibat is orally administered and acts locally in the gut where it binds reversibly to the IBAT to decrease the reuptake of bile acids to the liver. Elobixibat has minimal systemic exposure at expected therapeutic dose ranges.

## 5.2 Background

### 5.2.1 Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

Recent data suggest that bile acids may play an important role in NASH pathogenesis (Ferslew 2015; Aranha 2008; Puri 2018). Bile acids are signaling molecules involved in lipid, glucose, and energy homeostasis, which are metabolic pathways linked to NAFLD/NASH and comorbidities such as metabolic syndrome, obesity, and diabetes. Bile acids as well as free cholesterol, which is the precursor from which bile acids are synthesized, can act as lipotoxic agents that drive inflammation and fibrosis. Studies have shown that both serum and liver bile acids are increased in patients with NASH, and recent data have suggested that the presence and severity of NASH is associated with specific changes in circulating bile acids (Puri 2018). Thus, targeting of bile acid pathways has therapeutic potential in patients with NASH.

The enterohepatic circulation of bile acids plays a crucial role in whole body sterol balance. Bile acids are secreted to the intestine via the bile duct and then reabsorbed, mainly by a specific bile acid transporter located in the ileum (IBAT or ASBT) and delivered back to the liver, completing the enterohepatic circulation (Prawitt 2011).

Bile acid reabsorption from the intestine is a very efficient process where 95% of the secreted bile acids are reabsorbed and IBAT appears to be the major regulator of the bile acid pool in animals and humans. IBAT inhibitors reduce the reabsorption of bile acids from the ileum and prevent their return to the liver. The liver compensates for the decrease in bile acid levels by upregulating cholesterol 7α-hydroxylase, the rate-limiting

enzyme for bile acid synthesis. This results in lower hepatic cholesterol levels and an increased number of low-density lipoprotein (LDL) receptors in the liver leading to reduced plasma low-density lipoprotein cholesterol (LDL-C; [Bertolotti 2003; Naoumova 1999]). Bile acids also positively regulate glucagon-like peptide-1 (GLP-1) levels via activation of TGR5 (Prawitt 2011; Schaap 2014). GLP-1 is an insulinotropic hormone but has many other roles, e.g., slowing gastric emptying and increasing satiety signals leading to weight loss (Andersen 2018).

Inhibition of bile acid absorption locally in the intestine has the potential to positively influence NASH, cardiovascular disease, and metabolic disease by targeting multiple mechanisms, as follows: lowering of LDL-C by increased bile acid synthesis; improving metabolic status and weight loss by increasing GLP-1 levels; and reducing hepatic cell damage by lowering toxic bile acid and free cholesterol in the liver.

### 5.2.2 Summary of Nonclinical Studies in NASH

One nonclinical study with elobixibat in a NASH model has been completed. The study evaluated the effects of elobixibat in leptin-deficient ob/ob mice treated with a diet high in trans fats, fructose, and cholesterol. Although elobixibat did not reduce liver NAFLD activity score or fibrosis stage, there were indicators of relevant effects, including reduction in liver alpha-smooth muscle actin (α-SMA), which is a marker of stellate cell activation and thereby an indirect marker for fibrosis formation. Administration of 10 and 30 mg/kg/day elobixibat decreased liver steatosis as quantified by lipid fractional area in hematoxylin and eosin (H&E)-stained liver sections in a dose-dependent fashion. This was further evident in animals treated with 30 mg/kg elobixibat that showed reduced liver triglycerides and liver total cholesterol as determined by biochemical analyses. Analysis of liver gene expression by next generation RNA sequencing revealed pronounced and dose-dependent effects of elobixibat. It affected the expression of genes in key pathways associated with NASH pathology.

Additional nonclinical studies with elobixibat are summarized in the Investigator's Brochure (M1.14.4.1).

## 5.3 Rationale

Bile acids act as signaling molecules in lipid, glucose, and energy homeostasis. Studies have shown that both serum and liver bile acids are increased in patients with NASH

(Ferslew 2015), and recent data have suggested that the presence and severity of NASH is associated with specific changes in circulating bile acids (Puri 2018; Sanyal 2018). Inhibition of bile acid absorption from the intestine has the potential to improve the pathophysiology in NASH, including the related cardiovascular and metabolic disease due to impingement on multiple key metabolic feedback mechanisms, as follows: lowering of LDL-C by increased bile acid synthesis, and improving insulin sensitivity by increasing GLP-1 levels. A reduction of cardiovascular risk is particularly desirable for any pharmacological NASH treatment, because cardiovascular complications contribute to a significant amount of mortality in patients with NAFLD/NASH, with their annual risk being 2-fold increased (Mahfood Haddad 2017; Younossi 2018). IBAT inhibition reduces the levels of bile acid that circulate to the liver, and triggers increased hepatic bile acid synthesis from cholesterol. Thus, besides having a positive impact on cardiovascular health, IBAT inhibition might also reduce hepatic cell damage by lowering free cholesterol and changing the composition of toxic bile acids in the liver.

### 5.4 Risk/Benefit

Elobixibat is orally administered and acts locally in the gut where it binds reversibly to the IBAT to decrease the reuptake of bile acids into the liver, thereby increasing the concentration of bile acids in the colon. Due to its mechanism of action, most adverse events (AEs) are gastrointestinal (GI) tract disorders, such as abdominal pain, diarrhea, abdominal distention, flatulence, and nausea; the incidence of these has increased with increasing dose levels. Diarrhea has been the most prominent dose-limiting side effect. No clinically significant findings in laboratory measures or electrocardiograms (ECGs) have been reported. Based on postmarketing case reporting, ischemic colitis will be monitored as an adverse event of special interest for elobixibat.

There is no established benefit for subjects participating in this Phase 2 study. Based upon these data, the risk/benefit for subjects participating in this trial is acceptable.

This study will be conducted in compliance with the protocol and with the International Council on Harmonisation (ICH) guidelines on GCP.

# 6. STUDY OBJECTIVES

## 6.1 Primary Objective

The primary objective is to evaluate the efficacy of repeated once-daily doses of 5 mg elobixibat on serum levels of LDL-C in patients with NAFLD or NASH.

## 6.2 Secondary Objectives

- To assess the safety and tolerability of elobixibat in patients with NAFLD or NASH
- To evaluate the effect of elobixibat on liver steatosis as measured by magnetic resonance imaging (MRI) for (i) liver fat fraction (using proton density fat fraction [PDFF]) and (ii) total liver fat (using whole liver fat volume)
- To evaluate the effect of elobixibat on liver function using alanine aminotransferase (ALT)
- To evaluate the effect of elobixibat on lipids and serum bile acids (s-BA) in patients with NAFLD or NASH

# 7. INVESTIGATIONAL PLAN

## 7.1 Overall Study Design and Plan

### 7.1.1 Description

This is a double-blind, randomized, placebo-controlled, Phase 2 study to explore the efficacy and safety of elobixibat (oral dose of 5 mg) once daily for 16 weeks in patients with NAFLD or NASH. The study includes a 6-week Screening Period, followed by a 16-week Treatment Period, and a Follow-Up Visit 2 weeks after the last dose of study drug. Continued collection of efficacy data for patients who discontinue treatment will be made for as long as possible as per the schedule of assessments (Table 1).

After completing the Screening Period, eligible patients will be randomized on Day 1 (Visit 2) in a 1:1 fashion to either 5 mg/day elobixibat or matching placebo. Visit windows applicable to each visit are presented in the schedule of assessments (Table 1). There will be up to 7 clinic visits during the study, as follows:

- Visit 1: Screening period (Week -6 through Day -1)
- Visit 2: Day 1/Randomization visit
- Visit 3: Week 4
- Visit 4: Week 8
- Visit 5: Week 12
- Visit 6: Week 16/End of Treatment (EOT). Any patient that discontinues treatment prematurely should complete this visit at the time of discontinuation
- Visit 7: Follow-Up period. The Follow-Up visit will occur 2 weeks after the last dose of study drug whether the patient completes the study or discontinues prematurely

Additional unscheduled visits may be required for patients who need direct site assistance (due to AE monitoring, in order to fulfill screening requirements, and/or for safety maintenance).

#### 7.1.1.1 Screening Period

Informed consent must be obtained at Visit 1 prior to performing any study procedures. After signing the informed consent form (ICF), patients will be considered enrolled and evaluated for study eligibility.

#### 7.1.1.2 Treatment Period

Eligibility for randomization will be determined at Visit 2 using the assessment of eligibility in accordance to the inclusion/exclusion criteria.

The patient will return to the clinic at Visits 3-6 for assessments. Patients will be requested to return study drug bottles as part of drug accountability during the Treatment period.

#### 7.1.1.3 Follow-Up Period

The patient will return to the clinic for Visit 7 approximately 2 weeks after the last dose of study drug. This visit will be completed for patients that may discontinue the study prematurely.

#### 7.1.1.4 End of Study

The end of the study is defined as last patient last visit (LPLV) and all sites are closed.

### 7.1.2 Schedule of Assessments

The schedule of assessments is presented in Table 1.

**Table 1 Schedule of Assessments**

| Visit | Screening Period | Treatment Period | | | | | Follow-Up Period |
|---|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2/ Randomization | Visit 3 | Visit 4 | Visit 5 | Visit 6/ End of Treatment | Visit 7 |
| Study Week | Week -6 to Day -1 | Day 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 18 |
| Visit Window | | | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days |
| Informed consent | X | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | |
| Medical/surgical history | X | | | | | | |
| Demographics | X | | | | | | |
| Serology[a] | X | | | | | | |
| 12-lead ECG | X | | | | | X | |
| Physical examination[b] | X | X | | | | X | |
| Vital signs[c] | X | X | X | X | X | X | X |
| Pregnancy test[d] | X | X | X | X | X | X | X |
| MRI[e] | X | | | | | X | |
| Liver biopsy[f] | X | | | | | | |
| Randomization[g] | | X | | | | | |
| Clinical safety laboratory tests[h] | X | X | X | X | X | X | X |

*(Continued on next page)*

| VISIT | SCREENING PERIOD | TREATMENT PERIOD | | | | | FOLLOW-UP PERIOD |
|---|---|---|---|---|---|---|---|
| | VISIT 1 | VISIT 2/ RANDOMIZA-TION | VISIT 3 | VISIT 4 | VISIT 5 | VISIT 6/ END OF TREATMENT | VISIT 7 |
| STUDY WEEK | WEEK -6 TO DAY -1 | DAY 1 | WEEK 4 | WEEK 8 | WEEK 12 | WEEK 16 | WEEK 18 |
| VISIT WINDOW | | | ±3 DAYS | ±3 DAYS | ±3 DAYS | ±3 DAYS | ±3 DAYS |
| Endocrinology[h] | X | X | X | | | X | |
| GLP-1, FGF-19, C4[h] | X | X | X | X | X | X | X |
| Total serum bile acids[h] | X | X | X | X | X | X | X |
| Lipid profile[h] | X | X | X | X | X | X | X |
| Fibrosis and inflammation markers[h] | | X | X | | | X | |
| High-sensitivity CRP | X | | X | | | X | |
| Stored blood sample for future testing[i] | X | X | X | X | X | X | X |
| Dispense study drug | | X | X | X | X | | |
| Review alcohol consumption[j] | X | | | | | | |
| Review concomitant medications | X | X | X | X | X | X | X |
| Review adverse events | X | X | X | X | X | X | X |

[a] Includes hepatitis B virus surface antigen and hepatitis C virus antibody and RNA

[b] Includes height (at Screening only), weight, waist circumference, and waist-to-hip ratio. Body mass index will be calculated based on height and weight. A full physical examination will be performed at Screening and at Visits 2 and 6.

[c] Vital signs include blood pressure, heart rate, respiratory rate, and oral body temperature.

*(Continued on next page)*

[d] For women of childbearing potential, a serum pregnancy test will be performed at Screening, and a urine pregnancy test will be performed at each visit at which study drug is dispensed.

[e] Patients will have MRI to measure liver fat (PDFF), total liver volume, and pulse wave velocity. Patients who discontinue before Visit 6 (Week 16) should have an MRI performed at End of Treatment if they completed at least 4 weeks of treatment.

[f] Liver biopsy results for confirmed NASH within 6 months of Screening to confirm patient eligibility will be collected in the eCRF, if available.

[g] Randomization will occur at Visit 2 to assign patients to either 5 mg/day elobixibat or placebo in 1:1 ratio.

[h] See Table 2, Laboratory Parameters. Clinical safety laboratory tests include clinical chemistry, hematology/coagulation, and urinalysis

[i] See Section 9.2.4.

[j] History of alcohol consumption will be obtained at Screening.

Abbreviations: C4: 7α-hydroxy-4-cholesten-3-one; CRF: case report form; CRP: C-reactive protein; ECG: electrocardiogram; EOT: End of Treatment; FGF-19: fibroblast growth factor-19; GLP-1: glucagon-like peptide-1; INR: international normalized ratio; MRI: magnetic resonance imaging; NASH: nonalcoholic steatohepatitis; PDFF: proton density fat fraction

### 7.1.3 Study Procedures and Assessments

#### 7.1.3.1 Screening Period (-6 Weeks to Day -1)

##### 7.1.3.1.1 Visit 1

Patients will undergo a Screening visit up to 6 weeks prior to the planned first day of study treatment. Screening procedures and assessments are as follows:

- Obtain written informed consent
- Assess inclusion/exclusion criteria (Sections 7.2.1 and 7.2.2, respectively)
- Medical and surgical history (date of diagnosis of NAFLD/NASH; any surgery performed; any other diagnosis)
- Record demographics (age, full date of birth, gender, race, and ethnicity)
- Serology
- 12-lead ECG (Section 10.2.6)
- Physical examination (Section 10.2.4)
- Vital signs (Section 10.2.5)
- Pregnancy test
- MRI (Section 9.2.2)
- Liver biopsy (applicable for patients' biopsy-confirmed NASH within 6 months of Screening)
- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total s-BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)

- Fibrosis and inflammation markers (Section 10.2.1)
- High-sensitivity CRP
- Stored sample for future testing (Section 10.2.1)
- Review of alcohol consumption
- Document concomitant medications
- AE monitoring

#### 7.1.3.2 Treatment Period (Day 1 to Week 16)

##### 7.1.3.2.1 Study Day 1/Visit 2 (Randomization)

At the randomization visit, the following assessments will be conducted:

- Review inclusion/exclusion criteria (Sections 7.2.1 and 7.2.2, respectively)
- Physical examination (Section 10.2.4)
- Vital signs (Section 10.2.5)
- Pregnancy test
- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total s-BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)
- Fibrosis and inflammation markers (Section 10.2.1)
- Stored sample for future testing (Section 10.2.1)
- Study drug is dispensed and patients are instructed to administer daily from Day 1
- Review of concomitant medications
- AE monitoring

#### 7.1.3.2.2 Study Weeks 4-12/Visits 3-5

The following procedures and assessments will be conducted:

- Vital signs (Section 10.2.5)
- Pregnancy test
- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Visit 3 only; Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total s-BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)
- Fibrosis and inflammation markers (Visit 3 only; Section 10.2.1)
- High-sensitivity CRP (Visit 3 only; Section 10.2.1)
- Stored sample for future testing (Section 10.2.1)
- Study drug is dispensed; review of compliance
- Review of concomitant medications
- AE monitoring

#### 7.1.3.2.3 Study Week 16/Visit 6/EOT

The last dose of study drug will be taken in the morning the day before Visit 6 and the following procedures and assessments will be conducted (also conducted at the time a patient prematurely withdraws):

- 12-lead ECG (Section 10.2.6)
- Physical examination (Section 10.2.4)
- Vital signs (Section 10.2.5)
- Pregnancy test
- MRI (Section 9.2.2)

- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total s-BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)
- Fibrosis and inflammation markers (Section 10.2.1)
- High-sensitivity CRP
- Stored sample for future testing (Section 10.2.1)
- Review of concomitant medications
- AE monitoring

#### 7.1.3.3 Follow-Up Period

##### 7.1.3.3.1 Study Week 18/ Visit 7

All patients will complete a Follow-Up visit approximately 2 weeks after the last dose of study drug for the following assessments:

- Vital signs (Section 10.2.5)
- Pregnancy test
- Clinical safety laboratory tests (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total s-BA (Section 9.2.3)
- Lipid profile (Section 10.2.1)
- Stored sample for future testing (Section 10.2.1)
- Review of concomitant medications
- AE monitoring

## 7.2 Study Population

A total of approximately 46 patients with a clinical diagnosis of NAFLD/NASH (in accordance with the protocol definition) will be randomized.

### 7.2.1 Inclusion Criteria

Patients must meet all the following criteria to be included in the study:

1. Be willing to participate in the study and provide written informed consent
2. Be a man or woman ≥18 years of age
3. Have a current biopsy-confirmed NASH within 6 months of screening **or** a suspected diagnosis of NAFLD/NASH based on the criteria outlined below:
    a. Biopsy-confirmed NASH is defined as histological NASH diagnosis with fibrosis stage F1 through F3 and a NAFLD activity score (NAS) of ≥4 with a score of ≥1 in each of the NAS components below as assessed by the central pathologist using the NASH Clinical Research Network criteria (Kleiner 2005)
        i. Steatosis (scored 0 to 3)
        ii. Ballooning degeneration (scored 0 to 2)
        iii. Lobular inflammation (scored 0 to 3)

    **OR**

    b. The suspected diagnosis of NAFLD/NASH is based on each of the following criteria being met:
        i. Serum aspartate aminotransferase (AST) ≥20 U/L and ALT ≥40 U/L
        ii. Diagnosis of metabolic syndrome as having any 3 of the following 5 risk factors at Screening:
            - Fasting plasma glucose ≥100 mg/dL or undergoing drug treatment for elevated glucose

- High-density lipoprotein-cholesterol (HDL-C) <40 mg/dL in males or <50 mg/dL in females or undergoing drug treatment for reduced HDL-C
- Triglycerides ≥150 mg/dL or undergoing drug treatment for elevated triglycerides
- Waist circumference >102 cm in males or >88 cm in females
- Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or undergoing drug treatment for hypertension, or antihypertensive drug treatment in a patient with a history of hypertension

4. Screening MRI-PDFF with ≥10% liver steatosis
5. Fasting serum LDL-C >130 mg/dL at Screening, >110 mg/dL on lipid-lowering medications
6. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (beta human chorionic gonadotropin) at Screening and must agree to use highly effective birth control throughout the study and up to 30 days after the last dose of study drug. Highly effective contraception measures include combined estrogen- and progestogen-containing hormonal contraception (oral, intravaginal, and transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, and implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner (only in the event that the vasectomized partner is the sole sexual partner of the WOCBP), and sexual abstinence (defined as refraining from heterosexual intercourse) only in the event that this is the preferred lifestyle of the patient.

   Childbearing potential is defined as being fertile following menarche and until becoming postmenopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

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.

Men with partners who are WOCBP must either be surgically sterile or agree to use a barrier contraceptive for the duration of the study and up to 30 days after the last dose of study drug.

7. Be willing to maintain a stable diet and physical activity throughout the course of the study

### 7.2.2 Exclusion Criteria

Patients who meet any of the following criteria will not be included in the study:

1. Women who are pregnant, breastfeeding, or plan to become pregnant during the study
2. Body mass index (BMI) <25 kg/$m^2$
3. Fibrosis-4 index (Fib-4) >2.6
4. Any of the following laboratory abnormalities:
    a. ALT >5 × upper limit of normal (ULN) or AST >5 × ULN
    b. International normalized ratio (INR) ≥1.3, unless on anticoagulant therapy
    c. Total bilirubin >ULN, except with an established diagnosis of Gilbert's syndrome
    d. Platelet count less than the lower limit of normal (LLN)
    e. Creatinine clearance as calculated by the modification of diet in renal disease (MDRD) estimated glomerular filtration rate (eGFR) equation <60 mL/min

NOTE: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor.

5. Acute or chronic liver disease other than NAFLD/NASH including but not limited to the following:

    a. Hepatitis B (as defined by the presence of hepatitis B surface antigen at screening) or hepatitis C (as defined by the presence of hepatitis C virus [HCV] antibody [anti-HCV]). Patients with positive anti-HCV who test negative for HCV ribonucleic acid at screening will be allowed to participate in the study as long as there is evidence of viral negativity for a minimum of 12 months prior to screening)

    b. Evidence of ongoing autoimmune hepatitis

    c. History of primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, homozygous alpha-1-anti-trypsin deficiency, hemochromatosis or iron overload, drug-induced or alcoholic liver disease, or known bile duct obstruction

    d. Suspected or proven hepatocellular carcinoma

6. Known history of human immunodeficiency virus

7. Medical history of liver cirrhosis

8. Clinical evidence of portal hypertension to include any history of ascites, hepatic encephalopathy, or presence of esophageal varices

9. Use of drugs historically associated with NAFLD (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 for >2 weeks in the year prior to screening

10. Use of the following medications:

    a. GLP-1 agonists unless on a stable dose 3 months prior to liver biopsy or Screening

    b. Ursodeoxycholic acid, thiazolidinediones, or obeticholic acid within 3 months prior to Screening

c. Statins and other lipid-modifying therapies must have been stable for ≥3 months prior to Screening

d. Oral antidiabetic drugs (other than those specifically excluded) must have been stable for ≥3 months prior to Screening

e. Agents (including herbal over-the-counter weight-loss preparations) or medications known to significantly impact body weight within 3 months prior to Screening (e.g., sibutramine, phenetamine, and orlistat)

11. History of significant alcohol consumption, defined as an average of >20 g/day in female patients and >30 g/day in male patients, for a period of >3 consecutive months within 1 year prior to Screening, hazardous alcohol use (Alcohol Use Disorders Identification Test score ≥8), or an inability to reliably quantify alcohol consumption based upon judgment of the Investigator

12. Weight change ≥10% within the 6 months prior to Screening or ≥5% within the 3 months prior to Screening

13. Prior or planned (during the study period) bariatric surgery (e.g., gastroplasty and roux-en-Y gastric bypass)

14. Type 1 diabetes by medical history

15. Uncontrolled Type 2 diabetes defined as hemoglobin A1c (HbA1c) >9.5% at Screening (patients with HbA1c >9.5% may be rescreened) or requiring insulin dose adjustment >10% within 2 months prior to Screening

16. Clinical hyperthyroidism or hypothyroidism or screening hormone results pointing to thyroid dysfunction. Patients receiving dose-stable thyroid replacement therapy for ≥3 months prior to Screening will be allowed to participate as long as thyroid tests (thyroid-stimulating hormone/triiodothyronine/thyroxine) show that the patient is euthyroid

17. History of any condition causing malabsorption such as chronic pancreatitis, extensive bowel/small intestine surgery, celiac disease, or bile flow obstruction

18. History of any condition associated with acute or chronic diarrhea such as inflammatory bowel disease (IBD), functional diarrhea, irritable bowel syndrome

(IBS) with predominant diarrhea, IBS with mixed bowel habits, or unclassified IBS

19. History of ischemic colitis
20. Uncontrolled hypertension (either treated or untreated) defined as systolic blood pressure >160 mmHg or a diastolic blood pressure >100 mmHg at Screening. A retest of blood pressure, (after establishing good blood pressure control within a reasonable period of time and up to the Baseline visit) is permissible at the discretion of the Investigator
21. History of New York Heart Association Class III or IV heart failure, or known left ventricular ejection fraction <30%
22. History of myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke or major surgery within 6 months prior to Screening
23. Active substance abuse within 1 year prior to Screening
24. Participation in an investigational new drug trial in the 30 days prior to Screening or within 5 half-lives of an investigational agent, whichever is longer
25. Malignancy within 5 years, except for basal- or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated. Patients with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor's Medical Monitor. Patients under evaluation for malignancy are not eligible
26. Patients with known intolerance to MRI or with conditions contraindicated for MRI procedures
27. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, compromise the well-being of the patient, or interfere with the study outcomes

### 7.2.3 Withdrawal of Patients

Patients will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and that they are not obliged to state their reasons.

Any withdrawal, and reasons for withdrawal, must be fully documented in the electronic case report form (eCRF) and source documents and the patient followed by the investigator/investigative staff. Even after the study is completed at the Follow-Up visit, the investigator/investigative staff will, regardless of reason for withdrawal, record any patient data they receive concerning serious adverse events (SAEs), and all drug-related non-serious AEs, and report these in the eCRF. Withdrawn patients will not be replaced.

Patients will be withdrawn in the following circumstances:

- A patient's desire for withdrawal for any reason
- Lost to follow-up (every effort must be made to contact the patient; a certified letter must be sent)
- An AE that, in the opinion of the Investigator, necessitates withdrawal
- Death
- A patient's substantial noncompliance (study drug compliance) or protocol violation
- An Investigator's opinion that continuing the patient in the study is not appropriate. The Investigator may withdraw a patient at any time if it is considered to be in the patient's best interest

A patient who withdraws from treatment prematurely will have EOT (Visit 6) assessments at the time of withdrawal and a Follow-Up assessment (Visit 7) approximately 2 weeks following the last dose of study drug, and the patient will be recorded as withdrawn.

### 7.2.4 Study Termination by Sponsor

This study may be terminated at any time by the Sponsor if serious side effects should occur, if the Investigator does not adhere to the protocol, or if, in the Sponsor's judgment,

there are no further benefits to be achieved from the study. In this event, the Sponsor or its designee will inform the study investigators, institutions, and all regulatory authorities.

The Sponsor may temporarily or permanently discontinue the study at an investigative site at any time for safety, ethical, compliance, or other reasons. If this is necessary, the Sponsor will endeavor to provide advance notification to the site. If a site or the study is suspended or discontinued, the Investigator/investigative staff will be responsible for promptly informing the IRB. If required by local regulations, the Sponsor or its designee will be responsible for informing the IRB and the regulatory authority of study or site discontinuation. In such an event, all study data and unused study drug must be returned to the Sponsor or its designee.

# 8. TREATMENT OF PATIENTS

## 8.1 Identity of Study Drug

Elobixibat and placebo will be supplied as tablets for oral administration during the Treatment phase of the study. White tablets containing elobixibat or placebo will be provided.

The elobixibat and placebo tablets will be identical in appearance. Tablet filling weight will also be identical for elobixibat and placebo. Bottles containing 34 tablets will be given to the patient at each visit. Refer to the study reference manual.

## 8.2 Administration of Study Drug

Patients will be dosed with elobixibat at a dose of 5 mg or placebo once daily for 16 weeks. Study drug will be dispensed to the patient at Visits 2-5 together with instructions on how to store and take the drug. Study drug compliance will be evaluated at each study visit.

Elobixibat should be taken in the morning, prior to the first meal. On clinic visit days when laboratory assessments are conducted, study drug should be taken after the visit and after laboratory samples are taken.

## 8.3 Study Treatment Packaging and Labeling

### 8.3.1 Packaging and Labeling

The tablets will be packed in high-density polyethylene bottles, with child-proof polypropylene caps. Packaging and labeling will be prepared to comply with applicable regulatory requirements.

### 8.3.2 Storage

Treatment bottles containing elobixibat tablets should be stored and dispensed in accordance with regulations in their original containers. The storage facility at the investigative site should be locked and the storage temperature should be between 15°C and 25°C.

Caregivers should be informed of appropriate storage conditions (i.e., room temperature, between 15°C and 25°C).

Any deviations from the recommended storage conditions should be immediately reported to the Sponsor and the study drug should not be used until authorization has been given by the Sponsor.

### 8.3.3 Blinding and Randomization of Study Drug

A double-blind design is employed so that both the investigators and the patients will be unaware of the treatment assignment during the study.

After written informed consent is obtained from an eligible patient, a 6-digit patient number will be assigned. The first 3 digits will be the site number followed by a 3-digit patient sequence number. This number will be created and allocated by the Interactive Web Response System (IWRS), when the patient first enters the system at Screening. The randomization codes will be computer-generated by a statistician independent from the project team. The randomization will be done in blocks to ensure approximate balance between dose schemes (1:1). Randomization codes will be assigned sequentially as patients become eligible for randomization.

Patients who are eligible for randomization will be assigned a unique 4-digit randomization number by IWRS. This randomization number identifies which treatment will be allocated to the patient. Patients who withdraw from the study after randomization visit are not to be replaced and their randomization number will not be reused.

To ensure blinding, the study drug and the matching placebo have the same shape and size. Labels on the treatment bottles will not identify the treatment to which a patient has been randomized. Traceability of the treatment is ensured by the bottle number.

The 5-digit bottle number will identify the study-drug bottle and will be detailed on the study-drug label. Dispensing of the study drug will be coordinated by IWRS.

The system will assign a study-drug number corresponding to the randomization arm. The randomization number will be used in the background only to ensure that there is no unblinding and will not be displayed to end-users in the IWRS.

## 8.4 Procedure for Breaking the Randomization Code

Should a situation arise where unblinding is urgently required, i.e., only where knowledge of the study drug is required to adequately manage a life-threatening situation,

the Investigator at that study site may perform immediate unblinding through IWRS. The responsibility to break the treatment code in emergency situations resides solely with the Investigator. The Investigator should make every effort to discuss the rationale (status and outcome) for emergency unblinding with the Sponsor's Medical Monitor as soon as possible to review the individual patient details.

The study-site Investigator and appropriate project team members will be authorized to access the emergency unblinding functionality within the IWRS. Once the randomization code is broken for a patient, he/she must be withdrawn from the study and all assessments and procedures for Visit 6/EOT should be performed. Once a randomization code has been broken, the Investigator must inform the project team and Sponsor's Medical Monitor in writing within 24 hours. In case of technical issues accessing the system online, please see the IWRS site user manual for contact telephone numbers for the help desk 24/7 system support.

## 8.5 Patient Compliance

Patients will return all unused study drug at Visits 3 through 6. The study-site staff will count all returned drug, assess compliance, and record details in the eCRF.

Any noncompliance will be documented and explained in the source documents.

Treatment compliance = 100 × ([number of study drug dispensed—number of study drug returned]/number of study drug that should be taken)

Treatment compliance between 80% and 120% is acceptable.

## 8.6 Study Drug Accountability

Records shall be maintained of the delivery of study treatment(s) to the study site(s), of the inventory at the study site(s), of each use of the study treatment(s) for each patient and the return or destruction of used and unused study treatment(s). Local destruction of used/unused study treatment(s) will follow institution standard operating procedures (SOPs) and will require Sponsor pre-approval.

These records shall include dates, quantities, batch numbers, expiry dates, and the unique code numbers assigned to the study drug and to the study patients.

The Investigator will be responsible for ensuring that the records adequately document that the patients were provided the quantities specified in the protocol and that all study drug received from the Sponsor or its designee is reconciled.

## 8.7 Concomitant Therapy and Prohibited Medications

The Investigator will note all ongoing medication and any medication recently stopped (within 3 months prior to Visit 2) in the eCRF. At Visits 2 through 6, all changes in medication (stopping or starting new medication or changes in dose) will be recorded in the eCRF.

All medications taken by a patient within 3 months prior to the first intake of study drug are regarded as prior medication.

All medications taken by a patient on or after the first intake of study drug, and which continue to be taken during the study, are regarded as concomitant medication.

# 9. ASSESSMENT OF EFFICACY

## 9.1 Efficacy Endpoints

### 9.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline in serum LDL-C at Week 16.

### 9.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
- Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI
- Change from Baseline to Week 16, and Follow-Up in the following:
    - Serum ALT, AST, and gamma-glutamyl transferase
    - HDL-C, non-HDL-C, LDL-C/HDL-C ratio, and triglycerides
    - Serum total bile acids

### 9.1.3 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be assessed:

- Change from Baseline (unless otherwise specified) to Week 4, Week 8, Week 12, Week 16, and Follow-Up in the following:
    - Fasting glucose, insulin, homeostatic model assessment-insulin resistance, HbA1c, free fatty acids
    - GLP-1, FGF-19, and C4 levels
    - High-sensitivity CRP
    - Lanosterol and beta-sitosterol
    - Body weight, BMI, waist circumference, and waist-to-hip ratio

- MRI-based measurement of pulse wave velocity to measure aortic stiffness
- Apolipoprotein A1 and Apolipoprotein B

## 9.2 Efficacy Assessments

### 9.2.1 Lipid Profile

Fasting blood samples for analysis of LDL-C will be drawn at all visits, according to the schedule of assessments (Table 1). Fasting should be for at least 8 hours prior to the collection of the blood sample. Samples will be processed and transported to a central laboratory per instructions in the study reference manual.

### 9.2.2 Magnetic Resonance Imaging

Patients will have an MRI at Screening and EOT to assess liver fat by MRI-PDFF, total liver volume, and aortic pulse wave velocity. Details of the image acquisition and analysis can be found in the study reference manual.

### 9.2.3 Serum Bile Acids

Fasting blood samples for analysis of total s-BA will be drawn at all visits, according to the schedule of assessments (Table 1). Fasting should be for at least 8 hours prior to the collection of the blood sample. All s-BA results during the treatment period will be blinded. Samples will be processed and transported to a central laboratory per instructions in the study reference manual.

### 9.2.4 Biomarkers and Blood Samples for Future Testing

Blood samples for analysis of additional markers of disease, fibrosis, inflammation, and cardiovascular risk factors, and other pharmacodynamic markers will be drawn at the appropriate visits, according to the schedule of assessments (Table 1). These include a bile acid profile, including primary and secondary bile acids, interleukin-6, Pro-C3, tumor necrosis factor alpha, and cytokeratine-18. Samples will be processed and transported to a central laboratory per instructions in the study reference manual.

# 10. ASSESSMENT OF SAFETY

The timing and frequency of safety assessments are described in Section 7.1.3 and in Table 1.

The primary safety analysis will include the occurrence of treatment-emergent adverse events (TEAE) and TEAEs categorized by causality, severity, and seriousness assessments made by the Investigator by comparing study drug exposure to placebo.

Trends in safety will also be evaluated for the following assessments:

- AEs, including discontinuations due to AEs
- Physical examinations
- Concomitant medications
- Vital signs
- 12-lead ECG
- Laboratory test results (including clinical chemistry, hematology/coagulation, and urinalysis)

## 10.1 Adverse Events

### 10.1.1 Definitions and Investigator Assessments

An AE is defined as any untoward medical occurrence in an enrolled patient regardless of causal relationship with study drug. An AE can therefore be any clinically significant unfavorable and unintended sign, symptom, or disease that occurs once a patient is enrolled (ICF is signed) in the study until the patient is discharged from the study, whether or not related to the study drug.

#### 10.1.1.1 Clinical Significance

Clinical significance is defined as any abnormal finding that results in further clinical investigation(s), treatment(s), or the diagnosis of a new condition. Patient-reported events and protocol-mandated laboratory values, vital signs, and physical examination findings can be considered clinically significant (i.e., an AE) if there is a deterioration as compared to Baseline. Examples of clinically significant worsening from Baseline could

include, but is not limited to, events causing withdrawal from the study and events requiring medical intervention outside of the study causing apparent clinical manifestations or judged to be relevant by the Investigator.

#### 10.1.1.2 Serious Adverse Events

Serious criteria are applied by the investigator to each AE as specifically defined below. These criteria are used to determine whether an AE is serious or non-serious. The assessment is made independently of severity assessment (Section 10.1.1.3). For example, the development of a severe rash that occurs after signing of the ICF may not meet serious criteria as defined below and therefore would be considered a severe, non-serious AE.

Any AE that meets any 1 of the following 6 criteria is considered to be an SAE:

- The outcome of the AE is **death**
- The AE is immediately **life-threatening**. Life-threatening means that the patient is, in the opinion of the Investigator, at immediate risk of death from the reaction as it occurred. This does not include an AE that, if more severe, might have caused death
- The AE results in persistent or significant **disability/incapacity**. Disability means a substantial disruption of a person's ability to conduct normal life functions
- The AE requires or prolongs **hospitalization**
- The AE results in a **congenital anomaly/birth defect**
- **The AE is an important medical event**. Important medical events may meet serious criteria should the Investigator assess that they may significantly jeopardize the patient, represent a significant hazard, or require medical/surgical intervention to prevent one of the outcomes listed above. Examples of potential SAEs based on these criteria include, but are not limited to, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions even if they do not result in inpatient hospitalization, or the development of drug dependency and drug abuse.

#### 10.1.1.3 Adverse Events of Special Interest

An adverse event of special interest (AESI) should be recorded as an AE in the eCRF as outlined in Section 10.1.2 and reported using the SAE/AESI Report Form outlined in Section 10.1.3.

For this study, any occurrence of ischemic colitis should be reported as an AESI.

#### 10.1.1.4 Severity Assessment

Severity assessments are based on the intensity of the event in relation to expectation. The Investigator will assess the intensity of AEs based on the following definitions:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

Severity is a measure of intensity where seriousness is defined by the criteria outlined in Section 10.1.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not meet serious criteria, and therefore would be assessed as a severe AE but not an SAE.

#### 10.1.1.5 Causality Assessment

The Investigator determines the causality of all AEs to the study drug using medical judgment and considering all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study drug, and de-challenge or re-challenge. The causality assessment of the AE/SAE is to be made as follows:

**Related to Study Drug (Possibly, Probably, or Definitely Related)**

Based on medical judgment, there is at least a reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug

- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The event follows a known pattern of response to study drug
- The event disappears or decreases on cessation or reduction in dose of the study drug. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon discontinuation of study drug despite other clear indications of relatedness)
- The event reappears or worsens when the study drug is re-administered

**Unrelated to Study Drug (Unlikely or Unrelated)**

Based on medical judgment there is no reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of study drug
- The event could be reasonably attributed to the known characteristics of the patient's clinical state, concurrent illness, environment or toxic factors, or other modes of therapy administered to the patient
- The event does not follow a known pattern of response to study drug
- The event does not disappear or decrease on cessation or reduction in dose of the study drug, and it does not reappear or worsen when the study drug is re-administered

### 10.1.2 Recording of Adverse Events

It is the Investigator's responsibility to assess whether each untoward event is a clinically significant worsening from Baseline, thereby considered an AE. For all AEs, the severity, seriousness, and causality to study drug for each AE as outlined in Section 10.1.1 will be assessed and recorded in the eCRF.

All serious and non-serious AEs are collected once the caregiver/patient has signed the ICF and until the post-treatment follow-up (Visit 7) or 14 days after the last dose of study drug.

Any AEs or SAEs that are unresolved at the patient's last AE assessment are followed up by the Investigator until resolution or stabilization up to the database lock and recorded in the eCRF. The Sponsor retains the right to request additional information for any patient with ongoing AE(s) or SAE(s) at the end of the study.

TEAEs are defined as any AE that occurs after randomization (Day 1). All AEs that occur in the Screening period, i.e., after enrollment and prior to randomization, will be collected on the eCRF as non-TEAEs.

If there is a clinically significant deterioration of a laboratory value/vital sign or other routine study assessment that is associated with a diagnosis, the clinical diagnosis will be reported as an AE and the associated signs and symptoms will be considered additional information unless the sign or symptom is more severe than expected given the diagnosis. For example, if an Investigator diagnoses a study patient with hepatitis during the study period, hepatitis would be considered the AE and the concomitant signs and symptoms of abdominal pain, vomiting, and elevated ALT and AST would not be reported separately unless, in the opinion of the Investigator, one of these signs or symptoms is more severe than expected and therefore a separate AE assessment is indicated.

### 10.1.3 Recording and Reporting of Serious Adverse Events and Adverse Events of Special Interest

Every SAE/AESI (regardless of severity and causality) that occurs once the patient has signed the ICF and through 14 days after the final dose of study drug, should immediately and not later than within 24 hours of knowledge of the event, be reported by the Investigator or delegate in the SAE/AESI report form.

Report of a SAE/AESI must include at least the following information:

- Patient identification information (study number, site number, and date of birth [as per local country requirements for data protection])
- The last study drug administration date

- The diagnosis of the event with the description (or a brief description of signs/symptoms/clinical course if the diagnosis is not available) and the date of onset
- The action used to treat the event (i.e., treatment medications, temporary discontinuation)
- The reason(s) for considering the event serious
- The relationship of the event to the study drug or to the study procedure (i.e., the Investigator's assessment of causality)
- A brief narrative of the SAE/AESI

Follow-up reports including all new information obtained of the subsequent course of the SAE/AESI must be prepared and the information collected in the SAE/AESI report form submitted to the CRA, [redacted] by e-mail within 24 hours of knowledge of the event.

The pharmacovigilance manager (PVM) of the CRA may contact the Investigator to obtain further information on a reported SAE/AESI. The investigator/investigative staff must respond to any request for follow-up information or answers to questions regarding the SAE/AESI within the same timelines as for initial reports.

The PVM reports the occurrence of the SAE/AESI and follow-up to the Sponsor's Medical Monitor for medical assessment of the case.

Should an outcome of death occur within the study period or within 14 days after the last administration of study drug, an SAE/AESI report form should be completed including the main and contributory causes of death.

All SAE/AESI reports must be e-mailed to the following e-mail address within **24 hours**: [redacted]

If email is unavailable, SAEs/AESIs may be transmitted via fax to the following number: [redacted]

### 10.1.4 Reporting of Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reaction (SUSAR) is an SAE that occurs in a patient, the nature or severity of which is not expected per the applicable product information (e.g., the Investigator's Brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

Reporting and tracking of SUSARs will be in accordance with all applicable competent authority regulations. The IRBs and all Investigators involved in this study will be informed according to local requirements.

## 10.2 Laboratory Values, Vital Signs, Physical Examinations, and Other Safety Assessments

### 10.2.1 Laboratory Assessments

Samples will be collected for clinical chemistry, hematology, urinalysis, and other lab assessments at the time points specified in Table 1. The parameters assessed are presented in Table 2. All samples will be processed and transported to a central laboratory per instructions in the study reference manual.

The observed values will be recorded and assessed as "normal" or "abnormal not clinically significant" or "abnormal clinically significant."

Additional blood samples may be needed due to follow-up of an abnormal value or analysis failure. The blood samples collected for safety laboratory analysis will be destroyed after the analyses have been completed.

Stored blood sample for future testing are detailed in Section 9.2.4.

**Table 2: Laboratory Parameters**

| CLINICAL CHEMISTRY (FASTING) | HEMATOLOGY/COAGULATION | URINALYSIS |
|---|---|---|
| • Albumin<br>• ALT<br>• Alkaline phosphatase<br>• Amylase<br>• AST<br>• Bicarbonate<br>• Blood urea nitrogen<br>• Calcium<br>• Chloride<br>• Creatine kinase<br>• eGFR by MMRD (screening only)<br>• Gamma-glutamyl transferase<br>• Glucose<br>• Hemoglobin HbA1C<br>• Inorganic phosphorus<br>• Lactate dehydrogenase<br>• Lipase<br>• Potassium<br>• Sodium<br>• Total bilirubin<br>• Total protein<br>• Uric acid | • Hematocrit<br>• Hemoglobin<br>• Platelet count<br>• Red blood cell count<br>• White blood cell count and differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)<br>Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.<br>• International normalized ratio (INR)<br>• Prothrombin time (PT) | • Bilirubin<br>• Blood<br>• Glucose<br>• Ketones<br>• Leukocytes esterase<br>• Microscopy including leukocytes (performed only as needed based on positive dipstick test results)<br>• Nitrites<br>• pH<br>• Protein<br>• Specific gravity<br>• Urobilinogen |

*(Continued on next page)*

| LIPID PROFILE (FASTING) | OTHER TESTS | ENDOCRINOLOGY |
|---|---|---|
| • Apolipoprotein A1<br>• Apolipoprotein B<br>• Chylomicron cholesterol<br>• Chylomicron triglycerides<br>• High-density lipoprotein (HDL) cholesterol<br>• Lipoprotein(a) cholesterol<br>• Low-density lipoprotein (LDL) cholesterol by calculation<br>• LDL triglyceride<br>• Non-high-density lipoprotein cholesterol<br>• Total cholesterol<br>• Triglycerides<br>• Very low-density lipoprotein (VLDL) cholesterol<br>• VLDL triglyceride<br>• Lanosterol<br>• Beta-sitosterol | • High-sensitivity C-reactive protein (CRP)<br>• C4<br>• Fibroblast growth factor-19 (FGF-19)<br>• Fibrosis and inflammation markers: FIB-4, APRI, and NAS<br>• Glucagon-like peptide-1 (GLP-1) | • Follicle-stimulating hormone[1]<br>• Homeostatic model assessment-insulin resistance<br>• Insulin<br>• Thyroxine[2]<br>• Triiodothyronine[2]<br>• Thyroid-stimulating hormone[2]<br>• Free fatty acids<br>• Adipose tissue insulin resistance<br>• Adiponectin |
| **BILE ACIDS (FASTING)** | **PREGNANCY** | **SEROLOGY** |
| • Total serum bile acids | • Serum<br>• Urine | • Hepatitis B virus surface antigen<br>• Hepatitis C virus antibody and ribonucleic acid |

[1] A postmenopausal state is defined as no menses for ≥12 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, performed at Screening visit only.

[2] Thyroid function test will be performed during Screening visit only.

### 10.2.2 Individual Patient Safety Monitoring

#### 10.2.2.1 Liver Monitoring

Strategies to monitor markers of liver disease throughout the study are outlined below where the ULN will be based on central laboratory reference values for age and gender. Patients will be monitored as described below for drug-induced liver injury from randomization to 2 weeks following the last administration of study drug.

**Elevated ALT**

- ALT >5 × ULN or >3 × Baseline (if ALT elevated at Baseline): repeat AST, ALT, total bilirubin, alkaline phosphatase (ALP), and INR within 72 hours and closely monitor the patient. If liver enzyme elevation is confirmed, interrupt the study drug. The study drug can be restarted only if a competing etiology is identified or liver tests return to Baseline.

**Elevated AST**

- AST >5 × ULN or 3 × baseline (if AST elevated at baseline): repeat AST, ALT, total bilirubin, ALP, and INR within 72 hours and closely monitor the patient. If liver enzyme elevation confirmed, interrupt the study drug. The study drug can be restarted only if a competing etiology is identified or liver tests return to Baseline.

**Elevated Total Bilirubin**

- Total bilirubin >2 × ULN or >1.5 × Baseline (if total bilirubin elevated at Baseline), regardless of ALT or AST levels: repeat AST, ALT, total bilirubin, ALP, and INR within 72 hours and closely monitor the patient. If liver enzyme elevation confirmed, interrupt the study drug. The study drug can be restarted only if a competing etiology is identified or liver tests return to Baseline.

**Other Clinical Symptoms**

- Clinical signs of hepatitis or indicators of immunological reaction (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, jaundice, rash, eosinophilia >5% or symptoms/signs of hepatic decompensation): discontinue the

study drug and repeat AST, ALT, total bilirubin, ALP, and INR within 72 hours and closely monitor. Other causes of hepatitis should be excluded.

When close monitoring of a patient is not possible while the patient is on study drug, interrupt the study drug and closely monitor the patient.

### 10.2.3 Demographics/Medical and Surgical History

Demographic information per country regulations (age, full date of birth, gender, race, and ethnicity), along with medical and surgical history, will be obtained and recorded in the eCRF at Visit 1.

Medical and surgical history will be entered in the eCRF at Visit 1. This includes date of diagnosis of NASH/NAFLD, ongoing medication, any surgery performed, and any other diagnoses.

### 10.2.4 Physical Examination

A physician or suitably trained qualified assistant will perform a complete physical examination at Screening, at Visit 2, and at Visit 6. Height (Screening only), weight, waist circumference, and waist-to-hip ratio will also be collected. BMI will be calculated based on height and weight.

A complete physical examination will include assessment of general appearance, eyes, ears, nose, throat, head/neck/thyroid, lymph nodes, cardiovascular, lungs/chest, abdomen, genitourinary, extremities, skin, musculoskeletal, neurologic, and other.

### 10.2.5 Vital Signs

Evaluation of vital signs will be performed at all visits. This includes blood pressure (systolic and diastolic), pulse, respiratory rate, and oral temperature.

### 10.2.6 12-Lead ECG

A 12-lead ECG will be performed at the Screening visit and the EOT visits.

### 10.2.7 Overdose

Elobixibat is minimally absorbed and has a very low systemic availability. It is not known whether elobixibat can be removed from the systemic circulation by dialysis.

There are no known antidotes for elobixibat overdoses. If an overdose occurs, the patient should be carefully monitored and treated with supportive therapy.

### 10.2.8 Pregnancy

If a pregnancy is discovered in a female patient enrolled in the study, the patient will be immediately discontinued from the study drug, if applicable, and will attend the same visits as a prematurely withdrawn patient. If the pregnancy is discovered after completion of the treatment period, the patient will continue in the study per protocol. If a pregnancy occurs in a male patient's partner at any time during the study, the pregnancy should also be reported and followed.

If the patient has been dosed with the study drug, the pregnancy must be recorded on the appropriate form and submitted to the PVM (Section 10.1.3) within 24 hours of learning of the pregnancy.

The pregnancy should be followed to determine outcome, including spontaneous termination, details of birth and presence of any birth defects, congenital anomalies or newborn or maternal complication. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported as described in Section 10.1.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

# 11. STATISTICAL EVALUATION

All personnel involved with the analysis of the study will remain blinded until database lock for the double-blind treatment period and until major protocol violations have been identified.

All statistical analyses will be performed using SAS version 9.3 or higher.

## 11.1 Sample Size and Power

Due to the exploratory nature of this study, no formal power calculations were used to determine the sample size. The number of subjects (46 patients in total, 23 patients per treatment group) was chosen based on clinical experience with other similar proof-of-concept studies.

## 11.2 Statistical Methods

### 11.2.1 Statistical Analysis Populations

**ITT Population**

The intent-to-treat (ITT) population will include all patients who are randomized in the study and receive at least 1 dose of study drug. The ITT population will be used for all efficacy analyses based on the treatment randomized unless otherwise specified.

**Per Protocol Population**

The per protocol (PP) population will include all ITT patients who finish Visit 7/EOT with valid LDL-C measurements and do not have any major protocol deviations. Allocation of patients to the PP analysis set will be performed before unblinding of the study.

**Safety Population**

The safety population will include all patients who are randomized and receive at least 1 dose of study drug and will be used for all safety analyses based on the treatment received.

### 11.2.2 Methods of Statistical Analyses

#### 11.2.2.1 General Principles

Summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) at all visits and change or percent change from Baseline will be provided for efficacy and safety continuous variables. Count and frequency will be used to tabulate categorical variables.

##### 11.2.2.1.1 Efficacy

The primary efficacy endpoint is the change from Baseline in serum LDL-C at Week 16. Baseline is defined as the last non-missing LDL-C value prior to the first dose of study drug.

Exploratory comparisons between elobixibat 5 mg and placebo will be performed for the following secondary efficacy endpoints:

- Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
- Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI

The analysis methods for the other secondary and exploratory endpoints will be detailed in the statistical analysis plan (SAP).

##### 11.2.2.1.2 Safety

The safety endpoints for this study include clinical laboratory assessments, vital signs, AEs, ECGs, physical examinations, and concomitant medications.

AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedRA). TEAEs will be defined as AEs that are new or worsening after the first dose of study drug. A general summary of patients with TEAEs and serious adverse events (SAEs) will be tabulated with numbers and percentages of patients and repeated for severity and relationship to study drug per treatment group. The number of AEs leading to withdrawal and SAEs leading to death will also be summarized. The incidence of TEAEs will be summarized by body system and treatment group.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from Baseline. Values outside of the reference range will be flagged and laboratory abnormalities of special interest will be summarized.

#### 11.2.2.2 Missing Data

Continued collection of efficacy data for patients who discontinue treatment will be made for as long as possible as per the schedule of assessments (Table 1). Missing data handling for the primary efficacy endpoint is specified under Section 11.2.2.6. Details on missing data handling for secondary and exploratory endpoints will be specified in the SAP.

#### 11.2.2.3 Demographic and Baseline Characteristics

Descriptive summaries of demographics and other baseline characteristics (including medical and surgical history) will be presented by treatment group and overall using the ITT population.

Prior medication will be summarized by treatment group and overall using the ITT population.

#### 11.2.2.4 Subject Disposition

The following will be summarized descriptively (by treatment group and overall where applicable):

- Patients enrolled (who signed the informed consent)
- Patients randomized
- Patients treated
- Patients completing the study
- Patients withdrawing early (including withdrawal reason)

#### 11.2.2.5 Evaluation of Primary Efficacy Endpoints

To address the potential missing data from patients who are lost to follow-up after treatment discontinuation, multiple imputation method will be used. Data from patients who discontinue the study drug but stay in the study with scheduled assessments

collected will be used to impute missing values for patients lost to follow-up. This imputation will be done within each treatment group. Interim missing data will be handled as missing at random (predictable from observed data from subjects in the same treatment group).

After the imputation is performed, an analysis of covariance (ANCOVA) will be used to analyze the primary efficacy endpoint. The model will include treatment arm and Baseline LDL-C scores.

Least square (LS) mean (SE), LS mean difference (SE), 95% confidence intervals, and *P*-values between elobixibat 5 mg and placebo will be provided. The model assumptions will be checked before the analysis. If there are concerns on model assumptions, i.e., normality and homogeneity of variances, a non-parametric ANCOVA based on the rank scores can be used as a sensitivity analysis.

Sensitivity analyses may be performed and will be detailed in the SAP.

#### 11.2.2.6 Evaluation of Secondary and Exploratory Efficacy Endpoints

Descriptive statistics will be provided for secondary and exploratory endpoints listed in Sections 9.1.2 and 9.1.3, respectively, unless otherwise specified.

#### 11.2.2.7 Evaluation of Safety Endpoints

Safety data will be analyzed using descriptive statistics and summaries by treatment group of SAEs, AEs, vital signs, clinical safety laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis), and concomitant medication. Analyses will be performed using the safety analysis set.

Summaries of AEs (coded according to the MedDRA system organ class [SOC] and MedDRA preferred term) will include the following:

- Overview of the incidence of TEAEs (TEAEs, drug-related TEAEs, TEAEs leading to study discontinuation, and treatment-emergent SAEs)
- TEAEs by SOC and preferred term
- Intensity of TEAEs by SOC and preferred term
- Drug-related TEAEs by SOC and preferred term
- TEAEs leading to study discontinuation by SOC and preferred term
- Treatment-emergent SAEs by SOC and preferred term

Concomitant medication use during the treatment period will be summarized by Anatomical Therapeutic Chemical (ATC) class and World Health Organization (WHO) preferred name.

Summaries of vital signs will be presented. For each visit, the actual results and the change from Baseline, and the number and percentage of patients with potentially clinically significant (PCS) values as defined in the SAP, observed post-baseline will be presented.

Summaries of clinical safety laboratory data will be presented. For each visit, the actual result and the change from Baseline, and the number and percentage of patients with PCS values as defined in the SAP, observed post-baseline will be presented.

Data listings will be provided for each patient for all safety parameters.

#### 11.2.2.8 Compliance and Exposure

Exposure will be analyzed by calculating the number of days with exposure to study drug. Results will be presented by treatment group using the safety analysis set.

The percentage compliance will be described by treatment group and the number of patients with a compliance <80%, between 80% and 120%, and >120% will be presented based on the safety analysis set.

## 12. DIRECT ACCESS TO SOURCE DATA/NOTES

The Investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, IRB review, and regulatory inspection.

# 13. QUALITY CONTROL AND QUALITY ASSURANCE

## 13.1 Conduct of the Study

The study team shall implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with US Food and Drug Administration (FDA) regulations (Code of Federal Regulations, Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95).

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate competent authority and IRB, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the patient having to be withdrawn from the study and render that patient non-evaluable.

## 13.2 Study Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative or designee will review the protocol and eCRF with the Investigators and the investigative staff. During the study, the clinical monitor (the CRA) will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The investigator must ensure that eCRFs are completed within a timely period of patient visits, as per individual site agreements, and must allow the CRA and the Sponsor representative or designee periodic access to patient records and all study-related materials, including relevant hospital or clinical records, to confirm their consistency with the eCRF entries. No information in these records about the identity of the patients will leave the study center. The Sponsor monitoring standards require full verification for the presence of the signed ICF, adherence to the inclusion/exclusion criteria,

documentation of SAEs, and recording of primary efficacy and safety variables. The CRA will review source data compared with the eCRFs and will verify source data according to the study-specific monitoring plan. The design of the study, the frequency of patient visits, and the site enrollment rate will determine the frequency of monitoring visits. Upon study completion, the CRA will visit the site to conduct a study termination visit, which will include collection of any outstanding documentation.

It is recommended that the Investigator/investigative staff log into the eCRF system every working day or at minimum twice weekly in order to provide a prompt response to queries. The Investigator/investigative staff should respond to queries and make any relevant changes to the study data within 3 working days.

# 14. ETHICS

## 14.1 Institutional Review Board

Prior to the start of the study, the Investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IRB. The IRB shall be appropriately constituted and perform its functions in accordance with FDA, ICH, GCP, and local requirements as applicable.

The IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, patient recruitment procedures (e.g., advertisements), written information to be provided to the patients and caregivers, the Investigator's Brochure, available safety information, information about payment and compensation available to patients, the Investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IRB and regulatory authority (competent authority) as applicable.

## 14.2 Written Informed Consents

The Investigator (physician) or investigative staff, in accordance with local regulations, will explain to each patient (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, alternative treatment, the potential risks and benefits involved, and any discomfort that may occur. Each patient will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

If written consent is not possible, oral consent can be obtained if witnessed and followed by a signed statement from one or more persons not involved in the study, indicating why the patient was unable to sign the form. No patient can enter the study before his/her informed consent has been obtained, as required by country regulations.

The ICF is part of the protocol and must be submitted by the Investigator/investigative staff with the protocol for IRB approval. The Sponsor will supply an ICF which complies with regulatory requirements and country laws and is considered appropriate for the study. Any changes to the ICF suggested by the Investigator must be agreed to by the Sponsor before submission to the IRB and a copy of the approved version must be provided to the clinical monitor after IRB approval.

# 15. DATA HANDLING AND RECORDKEEPING

## 15.1 Electronic Case Report Forms/Source Data Handling

The investigator shall be provided with standardized eCRFs and shall ensure that all data from patient visits are promptly entered into the eCRFs in accordance with the specific instructions given. The Investigator must sign each eCRF to verify the integrity of the data recorded.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to the start of the study. As a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analyzed at that laboratory.

The Investigator must maintain source documents such as laboratory reports, consultation reports, and complete medical history and physical examination reports.

## 15.2 Retention of Essential Documents

Essential documents, as defined by ICH GCP, include the signed protocol and any amendment(s); copies of the completed eCRFs (for site archiving of eCRF data for specific patients will be provided); signed ICFs; hospital records and other source documents; IRB approvals and all related correspondence including approved documents; drug accountability records; study correspondence; and a list of patients' names and addresses.

The Investigator/investigative staff must retain copies of these essential documents for the period specified by ICH GCP and by applicable regulatory requirements. The Investigator/investigative staff will inform the Sponsor of the location where the essential documents are stored and must contact the Sponsor for approval before disposing of any essential documents. The Investigator/investigative staff should take measures to prevent accidental or premature destruction of these documents.

## 16. FINANCING AND INSURANCE

Financing and insurance are addressed in a separate agreement.

## 17. PUBLICATION POLICY

The Sponsor will retain ownership of all data. When the study is complete, the Sponsor will arrange the analysis, tabulation of data, and preparation of a clinical study report. The Sponsor may also use the data for publication, presentation at scientific meetings, and submission to regulatory authorities. All proposed publications based on this study must be subject to the Sponsor's approval requirements.

## 18. REFERENCES LIST

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# CLINICAL STUDY PROTOCOL A3309-012

# A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH)

| | |
|---|---|
| IND number: | 141078 |
| Test product: | Elobixibat |
| Indication: | Nonalcoholic Fatty Liver Disease or Nonalcoholic Steatohepatitis |
| Sponsor: | Elobix AB |
| Development phase: | Phase 2 |
| Sponsor medical monitor: | [redacted] |
| Principal investigator: | [redacted] |
| Date of the protocol: | 25 February 2019 |
| Version of the protocol: | Version 1.0 (Original) |

| Version No. | Previous Version Number | Effective Date |
|---|---|---|
| 1.0 | N/A | 25 February 2019 |

## SPONSOR SIGNATURE PAGE

**PROTOCOL TITLE: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH)**

PROTOCOL NUMBER: A3309-012

**Elobix AB**

[redacted]

## INVESTIGATOR SIGNATURE PAGE

**PROTOCOL TITLE: A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH)**

PROTOCOL NUMBER: A3309-012

I have read this protocol and agree that it contains all necessary details for performing this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practice (GCP), local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

I will use only the informed consent approved by the Institutional Review Board (IRB) and will fulfill all responsibilities for submitting pertinent information to the IRB responsible for this study.

I agree that the Sponsor (Elobix AB) shall have access to any source documents from which case report form (CRF) information may have been generated.

I further agree not to originate or use the name of Elobix AB or elobixibat (A3309) in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to this protocol, to any amendment to the protocol, or to the performance of this protocol without the prior written consent of Elobix AB.

Name of Investigator

Signature

Date (day/month/year)

## 1. ADMINISTRATIVE INFORMATION

| | |
|---|---|
| **Protocol no.:** | A3309-012 |
| **Date of initial protocol:** | 25 February 2019 |
| **Date and no. of amendments:** | N/A |
| **Sponsor:** | Elobix AB<br>Arvid Wallgrens backe 20<br>413 46 Göteborg<br>Sweden |
| **Clinical research organization:** | [redacted] |
| **Sponsor Medical Monitor:** | [redacted] |
| **Principal Investigator:** | [redacted] |

## 2. STUDY SYNOPSIS

| **Name of Sponsor/Company:** Elobix AB | **Name of Product:** Elobixibat | **Name of Active Ingredient:** Elobixibat |
|---|---|---|

**Title of Study:**
A Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Explore the Efficacy and Safety of Elobixibat in Adults with Nonalcoholic Fatty Liver Disease (NAFLD) or Nonalcoholic Steatohepatitis (NASH)

**Principal Investigator:** [redacted]

**Study Centers:** Up to 15 sites will be initiated for this study in the United States (US)

**Publication(s):** Not applicable

**Planned Study Period:** Q2 2019 to Q2 2020 | **Development Phase:** Phase 2

**Objectives:**

*Primary Objective*

The primary objective is to evaluate the efficacy of repeated once-daily doses of 5 mg elobixibat on serum levels of low-density lipoprotein cholesterol (LDL-C) in patients with NAFLD or NASH.

*Secondary Objectives*

- To assess the safety and tolerability of elobixibat in patients with NAFLD or NASH
- To evaluate the effect of elobixibat on liver steatosis as measured by magnetic resonance imaging (MRI) for (i) liver fat fraction (using proton density fat fraction [PDFF]) and (ii) total liver fat (using whole liver fat volume)
- To evaluate the effect of elobixibat on liver function using alanine aminotransferase (ALT)
- To evaluate the effect of elobixibat on lipids and serum bile acids (s-BA) in patients with NAFLD or NASH

**Methodology:**

This is a double-blind, randomized, placebo-controlled, Phase 2 study to explore the efficacy and safety of elobixibat (oral dose of 5 mg) once daily for 16 weeks in patients with NAFLD or NASH. The study includes a 6-week Screening period, followed by a 16-week Treatment period, and a Follow-Up visit 2 weeks after the last dose of study drug. Continued collection of efficacy data for patients who discontinue treatment will be made for as long as possible per the schedule of assessments.

After completing the Screening period, eligible patients will be randomized on Day 1 (Visit 2) in a 1:1 fashion to either 5 mg/day elobixibat or matching placebo. There will be a total of 7 scheduled visits during the study. Additional unscheduled visits may be required for patients who need direct site assistance (e.g., due to adverse event [AE] monitoring, in order to fulfill screening requirements, and/or for safety maintenance).

**Number of Patients:** Approximately 46 patients diagnosed with NAFLD/NASH and in accordance with the inclusion/exclusion criteria will be randomized.

**Inclusion Criteria:**

Patients must meet all of the following criteria to be included in the study:

1. Be willing to participate in the study and provide written informed consent
2. Be a man or woman ≥18 years of age
3. Have a current biopsy-confirmed NASH within 6 months of screening or a suspected diagnosis of NAFLD/NASH based on the criteria outlined below:

| **Name of Sponsor/Company:** Elobix AB | **Name of Product:** Elobixibat | **Name of Active Ingredient:** Elobixibat |
|---|---|---|

a. Biopsy-confirmed NASH is defined as histological NASH diagnosis with fibrosis stage F1 through F3 and a NAFLD activity score (NAS) of ≥4 with a score of ≥1 in each of the NAS components below as assessed by a pathologist using the NASH Clinical Research Network criteria (Kleiner 2005):

   i. Steatosis (scored 0 to 3)

   ii. Ballooning degeneration (scored 0 to 2)

   iii. Lobular inflammation (scored 0 to 3)

**OR**

b. The suspected diagnosis of NAFLD/NASH is based on each of the following criteria being met:

   i. Serum AST ≥20 U/L and ALT ≥40 U/L

   ii. Diagnosis of metabolic syndrome as having any 3 of the following 5 risk factors at Screening:

   - Fasting plasma glucose ≥100 mg/dL or undergoing drug treatment for elevated glucose
   - High-density lipoprotein-cholesterol (HDL-C) <40 mg/dL in males or <50 mg/dL in females or undergoing drug treatment for reduced HDL-C
   - Triglycerides ≥150 mg/dL or undergoing drug treatment for elevated triglycerides
   - Waist circumference >102 cm in males or >88 cm in females
   - Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or undergoing drug treatment for hypertension, or antihypertensive drug treatment in a patient with a history of hypertension

4. Screening MRI-PDFF with ≥10% liver steatosis
5. Fasting serum LDL-C >130 mg/dL at screening, >110 mg/dL on lipid-lowering medications
6. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (beta human chorionic gonadotropin) at Screening and must agree to use highly effective birth control throughout the study and up to 30 days after the last dose of study drug. Highly effective contraception measures include combined estrogen- and progestogen-containing hormonal contraception (oral, intravaginal, and transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, and implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner (only in the event that the vasectomized partner is the sole sexual partner of the WOCBP), and sexual abstinence (defined as refraining from heterosexual intercourse) only in the event that this is the preferred lifestyle of the patient.

   Childbearing potential is defined as being fertile following menarche and until becoming postmenopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)

   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

   Men with partners who are WOCBP must either be surgically sterile or agree to use a barrier contraceptive for the duration of the study and up to 30 days after the last dose of study drug

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|---|---|---|

7. Be willing to maintain a stable diet and physical activity throughout the course of the study

**Exclusion Criteria:**

1. Women who are pregnant, breastfeeding, or plan to become pregnant during the study
2. Body mass index (BMI) <25 kg/m$^2$
3. Fibrosis-4 Index (Fib-4) >2.6
4. Any of the following laboratory abnormalities:
    a. ALT >5 × upper limit normal (ULN) or AST >5 × ULN
    b. International normalized ratio (INR) ≥1.3, unless on anticoagulant therapy
    c. Total bilirubin > ULN, except with an established diagnosis of Gilbert's syndrome
    d. Platelet count less than the lower limit of normal (LLN)
    e. Creatinine clearance as calculated by the modification of diet in renal disease (MDRD) estimated glomerular filtration rate (eGFR) equation <60 mL/min

    NOTE: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor.
5. Acute or chronic liver disease other than NAFLD/NASH including but not limited to the following:
    a. Hepatitis B (as defined by the presence of hepatitis B surface antigen at Screening) or hepatitis C (as defined by the presence of hepatitis C virus [HCV] antibody [anti-HCV]. Patients with positive anti-HCV who test negative for HCV ribonucleic acid at Screening will be allowed to participate in the study as long as there is evidence of viral negativity for a minimum of 12 months prior to Screening)
    b. Evidence of ongoing autoimmune hepatitis
    c. History of primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, homozygous alpha-1-anti-trypsin deficiency, hemochromatosis or iron overload, drug-induced or alcoholic liver disease, or known bile duct obstruction
    d. Suspected or proven hepatocellular carcinoma
6. Known history of human immunodeficiency virus
7. Medical history of liver cirrhosis
8. Clinical evidence of portal hypertension to include any history of ascites, hepatic encephalopathy, or presence of esophageal varices
9. Use of drugs historically associated with NAFLD (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 for >2 weeks in the year prior to Screening
10. Use of the following medications:
    a. Glucagon-like peptide-1 (GLP-1) agonists unless on a stable dose 3 months prior to liver biopsy or Screening
    b. Ursodeoxycholic acid, thiazolidinediones, or obeticholic acid within 3 months prior to Screening
    c. Statins and other lipid-modifying therapies must have been stable for ≥3 months prior to Screening

| Name of Sponsor/Company: | Name of Product: | Name of Active Ingredient: |
|---|---|---|
| Elobix AB | Elobixibat | Elobixibat |

d. Oral antidiabetic drugs (other than those specifically excluded) must have been stable for ≥3 months prior to Screening

e. Agents (including herbal over-the-counter weight loss preparations) or medications known to significantly impact body weight within 3 months prior to screening (e.g., sibutramine, phenetamine, and orlistat)

11. History of significant alcohol consumption, defined as an average of >20 g/day in female patients and >30 g/day in male patients, for a period of >3 consecutive months within 1 year prior to Screening, hazardous alcohol use (Alcohol Use Disorders Identification Test score ≥8), or an inability to reliably quantify alcohol consumption based upon judgment of the Investigator
12. Weight change ≥10% within the 6 months prior to Screening or ≥5% within the 3 months prior to Screening
13. Prior or planned (during the study period) bariatric surgery (e.g., gastroplasty and roux-en-Y gastric bypass)
14. Type 1 diabetes by medical history
15. Uncontrolled Type 2 diabetes defined as hemoglobin A1c (HbA1c) >9.5% at Screening (patients with HbA1c >9.5% may be rescreened) or requiring insulin dose adjustment >10% within 2 months prior to Screening
16. Clinical hyperthyroidism or hypothyroidism or Screening hormone results pointing to thyroid dysfunction. Patients receiving dose-stable thyroid replacement therapy for ≥3 months prior to Screening will be allowed to participate as long as thyroid tests (thyroid-stimulating hormone/triiodothyronine/thyroxine) show that the patient is euthyroid
17. History of any condition causing malabsorption such as chronic pancreatitis, extensive bowel/small intestine surgery, celiac disease, or bile flow obstruction
18. History of any condition associated with acute or chronic diarrhea such as inflammatory bowel disease (IBD), functional diarrhea, irritable bowel syndrome (IBS) with predominant diarrhea, IBS with mixed bowel habits, or unclassified IBS
19. Uncontrolled hypertension (either treated or untreated) defined as systolic blood pressure >160 mmHg or a diastolic blood pressure >100 mmHg at Screening. A retest of blood pressure, (after establishing good blood pressure control within a reasonable period of time and up to the Baseline visit) is permissible at the discretion of the Investigator
20. History of New York Heart Association Class III or IV heart failure, or known left ventricular ejection fraction <30%
21. History of myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke or major surgery within 6 months prior to Screening
22. Active substance abuse, within 1 year prior to Screening
23. Participation in an investigational new drug trial in the 30 days prior to Screening or within 5 half-lives of an investigational agent, whichever is longer
24. Malignancy within 5 years, except for basal- or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated. Patients with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor's Medical Monitor. Patients under evaluation for malignancy are not eligible
25. Patients with known intolerance to MRI or with conditions contraindicated for MRI procedures
26. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, compromise the well-being of the patient, or interfere with the study outcomes

| **Name of Sponsor/Company:** Elobix AB | **Name of Product:** Elobixibat | **Name of Active Ingredient:** Elobixibat |
|---|---|---|
| **Test Product, Dose, and Mode of Administration:** Elobixibat, 5 mg once a day, orally administered | | |
| **Reference Therapy, Dose and Duration of Administration:** Matching placebo, orally administered | | |
| **Duration of Treatment:** Up to 16 weeks | | |

**Variables**

**Efficacy:**

*Primary Efficacy Endpoint*

The primary efficacy endpoint is the change from baseline in serum LDL-C at Week 16.

*Secondary Efficacy Endpoints*

Secondary efficacy endpoints include the following:

- Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
- Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI
- Change from Baseline to Week 16, and Follow-Up in the following:
    - Serum ALT, AST, and gamma-glutamyl transferase
    - HDL-C, non-HDL-C, LDL-C/HDL-C ratio and triglycerides
    - Serum total bile acids

*Exploratory Efficacy Endpoints*

The following exploratory efficacy endpoints will be assessed:

- Change from Baseline (unless otherwise specified) to Week 4, Week 8, Week 12, Week 16, and Follow-Up in the following:
    - Fasting glucose, insulin, homeostatic model assessment-insulin resistance, HbA1c, free fatty acids
    - GLP-1, fibroblast growth factor-19 (FGF-19), and C4 levels
    - High-sensitivity C-reactive protein (CRP)
    - Lanosterol and beta-sitosterol
    - Body weight, BMI, waist circumference, and waist-to-hip ratio
    - MRI-based measurement of pulse wave velocity to measure aortic stiffness
    - Apolipoprotein A1 and Apolipoprotein B

**Safety:**

Safety criteria are as follows:

- Occurrence of treatment-emergent adverse events categorized by causality, severity, and seriousness assessments made by Investigator by comparing study-drug exposure to placebo
- Trends in safety evaluated for the following assessments:
    - Physical examinations
    - Concomitant medications
    - Vital signs
    - 12-lead ECG
    - Laboratory test results (including clinical chemistry, hematology/coagulation, and urinalysis)

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|---|---|---|
| Elobix AB | Elobixibat | Elobixibat |

**Statistical Methods**
**Analysis Populations:**

- The intent-to-treat (ITT) population will include all patients who are randomized in the study and receive at least 1 dose of study drug. The ITT population will be used for all efficacy analyses based on the treatment randomized unless otherwise specified
- The per protocol (PP) population will include all ITT patients who finish Visit 7/End of Treatment (EOT) with valid LDL-C measurements and do not have any major protocol deviations. Allocation of patients to the PP analysis set will be performed before unblinding of the study
- The safety population will include all patients who are randomized and receive at least 1 dose of study drug and will be used for all safety analyses based on the treatment received
- Summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) at all visits and change or percent change from Baseline will be provided for efficacy and safety continuous variables. Count and frequency will be used to tabulate categorical variables
- Demographics, disposition, and study populations will be summarized descriptively

**Efficacy:**

- The primary efficacy endpoint is the change from Baseline in serum LDL-C at Week 16. Baseline is defined as the last non-missing LDL-C value prior to the first dose of study drug
- To address the potential missing data from patients who are lost to follow-up after treatment discontinuation, multiple imputation method will be used. Data from patients who discontinue the study drug but stay in the study with scheduled assessments collected will be used to impute missing values for patients lost to follow-up. This imputation will be done within each treatment group. Interim missing data will be handled as missing at random (predictable from observed data from subjects in the same treatment group)
- After the imputation is performed, an analysis of covariance (ANCOVA) will be used to analyze the primary efficacy endpoint. The model will include treatment arm and Baseline LDL-C scores
- Least square (LS) mean (SE), LS mean difference (SE), 95% confidence intervals, and *P*-values between elobixibat 5 mg and placebo will be provided. The model assumptions will be checked before the analysis. If there are concerns on model assumptions, i.e., normality and homogeneity of variances, a non-parametric ANCOVA based on the rank scores can be used as a sensitivity analysis
- Exploratory comparisons between elobixibat 5 mg and placebo will be performed for the following secondary efficacy endpoints:
    - Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
    - Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI
- The analysis methods for the other secondary endpoints and exploratory endpoints will be detailed in the Statistical Analysis Plan for the study.

**Safety:**

- The safety endpoints for this study include clinical laboratory assessments, vital signs, AEs, ECGs, physical examinations, and concomitant medications
- AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedRA). TEAEs will be defined as AEs that are new or worsening after the first dose of study drug. A general summary of patients with TEAEs and serious adverse events (SAEs) will be

| **Name of Sponsor/Company:** Elobix AB | **Name of Product:** Elobixibat | **Name of Active Ingredient:** Elobixibat |
|---|---|---|

tabulated with numbers and percentages of patients and repeated for severity and relationship to study drug per treatment group. The number of AEs leading to withdrawal and SAEs leading to death will also be summarized. The incidence of TEAEs will be summarized by body system and treatment group

- The safety laboratory data will be summarized by visit and by treatment group, along with changes from Baseline. Values outside of the reference range will be flagged and laboratory abnormalities of special interest will be summarized

**Sample Size Determination:**

Due to the exploratory nature of this study, no formal power calculations were used to determine the sample size. The number of subjects (46 patients in total, 23 patients per treatment group) was chosen based on clinical experience with other similar proof-of-concept studies.

**Date of the Protocol:** 25 February 2019

## 3. TABLE OF CONTENTS

## 3.1 List of Tables

## 4. LIST OF ABBREVIATIONS, ACRONYMS, AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| A3309 | elobixibat |
| AE(s) | adverse event(s) |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| Anti-HCV | hepatitis C antibody |
| APRI | AST to platelet ratio index |
| ASBT | apical sodium-dependent bile acid transporter (also known as IBAT) |
| AST | aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| BMI | body mass index |
| C4 | 7α-hydroxy-4-cholesten-3-one |
| CRA | clinical research associate |
| CRF | case report form |
| CRP | C-reactive protein |
| ECG(s) | electrocardiogram(s) |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| EOT | End of Treatment |
| FDA | US Food and Drug Administration |
| FGF-19 | fibroblast growth factor-19 |
| Fib-4 | fibrosis-4 |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| GLP-1 | glucagon-like peptide-1 |
| H&E | hematoxylin and eosin |
| HbA1c | hemoglobin A1c |
| HCV | hepatitis C virus |

| Abbreviation | Definition |
|---|---|
| HDL-C | high-density lipoprotein-cholesterol |
| IBAT | ileal bile acid transporter (also known as ASBT) |
| IBD | inflammatory bowel disease |
| IBS | irritable bowel syndrome |
| ICF(s) | informed consent form(s) |
| ICH | International Council on Harmonisation |
| INR | international normalized ratio |
| IRB | institutional review board |
| ITT | intent to treat |
| IWRS | Interactive Web Response System |
| LDL | low-density lipoprotein |
| LDL-C | low density lipoprotein-cholesterol |
| LLN | lower limit of normal |
| LPLV | last patient last visit |
| LS | least square |
| MDRD | modification of diet in renal disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| MRI-PDFF | magnetic resonance imaging—proton density fat fraction |
| N/A | not applicable |
| NAFLD | nonalcoholic fatty liver disease |
| NAS | NAFLD activity score |
| NASH | nonalcoholic steatohepatitis |
| ob/ob (mice) | leptin-deficient mice |
| PCS | potentially clinically significant |
| PDFF | proton density fat fraction |
| PP | per protocol |
| PVM | pharmacovigilance manager |
| RNA | ribonucleic acid |
| s-BA | serum bile acid(s) |

| Abbreviation | Definition |
|---|---|
| SAE(s) | serious adverse event(s) |
| SAP | statistical analysis plan |
| SE | standard error |
| SOC | system organ class |
| SOP(s) | standard operating procedure(s) |
| Sponsor | Elobix AB |
| SUSAR | suspected unexpected serious adverse reaction(s) |
| TEAE(s) | treatment-emergent adverse event(s) |
| ULN | upper limit of normal |
| US | United States |
| VLDL | very low-density lipoprotein |
| WHO | World Health Organization |
| WOCBP | Women (woman) of childbearing potential |
| α-SMA | alpha-smooth muscle actin |

# 5. INTRODUCTION

## 5.1 Investigational Medicinal Product

Elobixibat is a potent inhibitor of the ileal bile acid transporter (IBAT; also known as the apical sodium bile acid transporter [ASBT]). The IBAT, expressed mainly in the distal ileum, is a key element in the enterohepatic circulation of bile acids because it facilitates the very efficient process of bile acid reabsorption. Elobixibat is orally administered and acts locally in the gut where it binds reversibly to the IBAT to decrease the reuptake of bile acids to the liver. Elobixibat has minimal systemic exposure at expected therapeutic dose ranges.

## 5.2 Background

### 5.2.1 Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

Recent data suggest that bile acids may play an important role in NASH pathogenesis (Ferslew 2015; Aranha 2008; Puri 2018). Bile acids are signaling molecules involved in lipid, glucose, and energy homeostasis, which are metabolic pathways linked to NAFLD/NASH and comorbidities such as metabolic syndrome, obesity, and diabetes. Bile acids as well as free cholesterol, which is the precursor from which bile acids are synthesized, can act as lipotoxic agents that drive inflammation and fibrosis. Studies have shown that both serum and liver bile acids are increased in patients with NASH, and recent data have suggested that the presence and severity of NASH is associated with specific changes in circulating bile acids (Puri 2018). Thus, targeting of bile acid pathways has therapeutic potential in patients with NASH.

The enterohepatic circulation of bile acids plays a crucial role in whole body sterol balance. Bile acids are secreted to the intestine via the bile duct and then reabsorbed, mainly by a specific bile acid transporter located in the ileum (IBAT or ASBT) and delivered back to the liver, completing the enterohepatic circulation (Prawitt 2011).

Bile acid reabsorption from the intestine is a very efficient process where 95% of the secreted bile acids are reabsorbed and IBAT appears to be the major regulator of the bile acid pool in animals and humans. IBAT inhibitors reduce the reabsorption of bile acids from the ileum and prevent their return to the liver. The liver compensates for the

decrease in bile acid levels by upregulating cholesterol 7α-hydroxylase, the rate-limiting enzyme for bile acid synthesis. This results in lower hepatic cholesterol levels and an increased number of low-density lipoprotein (LDL) receptors in the liver leading to reduced plasma low-density lipoprotein cholesterol (LDL-C; [Bertolotti 2003; Naoumova 1999]). Bile acids also positively regulate glucagon-like peptide-1 (GLP-1) levels via activation of TGR5 (Prawitt 2011; Schaap 2014). GLP-1 is an insulinotropic hormone but has many other roles, e.g., slowing gastric emptying and increasing satiety signals leading to weight loss (Andersen 2018).

Inhibition of bile acid absorption locally in the intestine has the potential to positively influence NASH, cardiovascular disease, and metabolic disease by targeting multiple mechanisms, as follows: lowering of LDL-C by increased bile acid synthesis; improving metabolic status and weight loss by increasing GLP-1 levels; and reducing hepatic cell damage by lowering toxic bile acid and free cholesterol in the liver.

### 5.2.2 Summary of Nonclinical Studies in NASH

One nonclinical study with elobixibat in a NASH model has been completed. The study evaluated the effects of elobixibat in leptin-deficient ob/ob mice treated with a diet high in trans fats, fructose, and cholesterol. Although elobixibat did not reduce liver NAFLD activity score or fibrosis stage, there were indicators of relevant effects, including reduction in liver alpha-smooth muscle actin (α-SMA), which is a marker of stellate cell activation and thereby an indirect marker for fibrosis formation. Administration of 10 and 30 mg/kg/day elobixibat decreased liver steatosis as quantified by lipid fractional area in hematoxylin and eosin (H&E)-stained liver sections in a dose-dependent fashion. This was further evident in animals treated with 30 mg/kg elobixibat that showed reduced liver triglycerides and liver total cholesterol as determined by biochemical analyses. Analysis of liver gene expression by next generation RNA sequencing revealed pronounced and dose-dependent effects of elobixibat. It affected the expression of genes in key pathways associated with NASH pathology.

Additional nonclinical studies with elobixibat are summarized in the Investigator's Brochure (M1.14.4.1).

## 5.3 Rationale

Bile acids act as signaling molecules in lipid, glucose, and energy homeostasis. Studies have shown that both serum and liver bile acids are increased in patients with NASH (Ferslew 2015), and recent data have suggested that the presence and severity of NASH is associated with specific changes in circulating bile acids (Puri 2018; Sanyal 2018). Inhibition of bile acid absorption from the intestine has the potential to improve the pathophysiology in NASH, including the related cardiovascular and metabolic disease due to impingement on multiple key metabolic feedback mechanisms, as follows: lowering of LDL-C by increased bile acid synthesis, and improving insulin sensitivity by increasing GLP-1 levels. A reduction of cardiovascular risk is particularly desirable for any pharmacological NASH treatment, because cardiovascular complications contribute to a significant amount of mortality in patients with NAFLD/NASH, with their annual risk being 2-fold increased (Mahfood Haddad 2017; Younossi 2018). IBAT inhibition reduces the levels of bile acid that circulate to the liver, and triggers increased hepatic bile acid synthesis from cholesterol. Thus, besides having a positive impact on cardiovascular health, IBAT inhibition might also reduce hepatic cell damage by lowering free cholesterol and changing the composition of toxic bile acids in the liver.

## 5.4 Risk/Benefit

Elobixibat is orally administered and acts locally in the gut where it binds reversibly to the IBAT to decrease the reuptake of bile acids into the liver, thereby increasing the concentration of bile acids in the colon. Due to its mechanism of action, most adverse events (AEs) are gastrointestinal (GI) tract disorders, such as abdominal pain, diarrhea, abdominal distention, flatulence, and nausea; the incidence of these has increased with increasing dose levels. Diarrhea has been the most prominent dose-limiting side effect. No clinically significant findings in laboratory measures or electrocardiograms (ECGs) have been reported.

There is no established benefit for subjects participating in this Phase 2 study. Based upon these data, the risk/benefit for subjects participating in this trial is acceptable.

This study will be conducted in compliance with the protocol and with the International Council on Harmonisation (ICH) guidelines on GCP.

# 6. STUDY OBJECTIVES

## 6.1 Primary Objective

The primary objective is to evaluate the efficacy of repeated once-daily doses of 5 mg elobixibat on serum levels of LDL-C in patients with NAFLD or NASH.

## 6.2 Secondary Objectives

- To assess the safety and tolerability of elobixibat in patients with NAFLD or NASH
- To evaluate the effect of elobixibat on liver steatosis as measured by magnetic resonance imaging (MRI) for (i) liver fat fraction (using proton density fat fraction [PDFF]) and (ii) total liver fat (using whole liver fat volume)
- To evaluate the effect of elobixibat on liver function using alanine aminotransferase (ALT)
- To evaluate the effect of elobixibat on lipids and serum bile acids (s-BA) in patients with NAFLD or NASH

# 7. INVESTIGATIONAL PLAN

## 7.1 Overall Study Design and Plan

### 7.1.1 Description

This is a double-blind, randomized, placebo-controlled, Phase 2 study to explore the efficacy and safety of elobixibat (oral dose of 5 mg) once daily for 16 weeks in patients with NAFLD or NASH. The study includes a 6-week Screening Period, followed by a 16-week Treatment Period, and a Follow-Up Visit 2 weeks after the last dose of study drug. Continued collection of efficacy data for patients who discontinue treatment will be made for as long as possible as per the schedule of assessments (Table 1).

After completing the Screening Period, eligible patients will be randomized on Day 1 (Visit 2) in a 1:1 fashion to either 5 mg/day elobixibat or matching placebo. Visit windows applicable to each visit are presented in the schedule of assessments (Table 1). There will be up to 7 clinic visits during the study, as follows:

- Visit 1: Screening period (Week -6 through Day -1)
- Visit 2: Day 1/Randomization visit
- Visit 3: Week 4
- Visit 4: Week 8
- Visit 5: Week 12
- Visit 6: Week 16/End of Treatment (EOT). Any patient that discontinues treatment prematurely should complete this visit at the time of discontinuation
- Visit 7: Follow-Up period. The Follow-Up visit will occur 2 weeks after the last dose of study drug whether the patient completes the study or discontinues prematurely

Additional unscheduled visits may be required for patients who need direct site assistance (due to AE monitoring, in order to fulfill screening requirements, and/or for safety maintenance).

#### 7.1.1.1 Screening Period

Informed consent must be obtained at Visit 1 prior to performing any study procedures. After signing the informed consent form (ICF), patients will be considered enrolled and evaluated for study eligibility.

#### 7.1.1.2 Treatment Period

Eligibility for randomization will be determined at Visit 2 using the assessment of eligibility in accordance to the inclusion/exclusion criteria.

The patient will return to the clinic at Visits 3-6 for assessments. Patients will be requested to return study drug bottles as part of drug accountability during the Treatment period.

#### 7.1.1.3 Follow-Up Period

The patient will return to the clinic for Visit 7 approximately 2 weeks after the last dose of study drug. This visit will be completed for patients that may discontinue the study prematurely.

#### 7.1.1.4 End of Study

The end of the study is defined as last patient last visit (LPLV) and all sites are closed.

### 7.1.2 Schedule of Assessments

The schedule of assessments is presented in Table 1.

**Table 1 Schedule of Assessments**

| VISIT | SCREENING PERIOD | TREATMENT PERIOD | | | | | FOLLOW-UP PERIOD |
|---|---|---|---|---|---|---|---|
| | VISIT 1 | VISIT 2/ RANDOMIZA-TION | VISIT 3 | VISIT 4 | VISIT 5 | VISIT 6/ END OF TREATMENT | VISIT 7 |
| STUDY WEEK | WEEK -6 TO DAY -1 | DAY 1 | WEEK 4 | WEEK 8 | WEEK 12 | WEEK 16 | WEEK 18 |
| VISIT WINDOW | | | ±3 DAYS | ±3 DAYS | ±3 DAYS | ±3 DAYS | ±3 DAYS |
| Informed consent | X | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | |
| Medical/surgical history | X | | | | | | |
| Demographics | X | | | | | | |
| Serology[a] | X | | | | | | |
| 12-lead ECG | X | | | | | X | |
| Physical examination[b] | X | X | | | | X | |
| Vital signs[c] | X | X | X | X | X | X | X |
| Pregnancy test[d] | X | X | X | X | X | X | X |
| MRI[e] | X | | | | | X | |
| Liver biopsy[f] | X | | | | | | |
| Randomization[g] | | X | | | | | |
| Clinical safety laboratory tests[h] | X | X | X | X | X | X | X |

*(Continued on next page)*

| VISIT | SCREENING PERIOD | TREATMENT PERIOD | | | | | FOLLOW-UP PERIOD |
|---|---|---|---|---|---|---|---|
| | VISIT 1 | VISIT 2/ RANDOMIZA-TION | VISIT 3 | VISIT 4 | VISIT 5 | VISIT 6/ END OF TREATMENT | VISIT 7 |
| STUDY WEEK | WEEK -6 TO DAY -1 | DAY 1 | WEEK 4 | WEEK 8 | WEEK 12 | WEEK 16 | WEEK 18 |
| VISIT WINDOW | | | ±3 DAYS | ±3 DAYS | ±3 DAYS | ±3 DAYS | ±3 DAYS |
| Endocrinology[8] | X | X | X | | | X | |
| GLP-1, FGF-19, C4[h] | X | X | X | X | X | X | X |
| Total serum bile acids[h] | X | X | X | X | X | X | X |
| Lipid profile[h] | X | X | X | X | X | X | X |
| Fibrosis and inflammation markers[h] | | X | X | | | X | |
| High-sensitivity CRP | X | | X | | | X | |
| Stored blood sample for future testing[i] | X | X | X | X | X | X | X |
| Dispense study drug | | X | X | X | X | | |
| Review alcohol consumption[j] | X | | | | | | |
| Review concomitant medications | X | X | X | X | X | X | X |
| Review adverse events | X | X | X | X | X | X | X |

[a] Includes hepatitis B virus surface antigen and hepatitis C virus antibody and RNA

[b] Includes height (at Screening only), weight, waist circumference, and waist-to-hip ratio. Body mass index will be calculated based on height and weight. A full physical examination will be performed at Screening and at Visits 6 and 7.

[c] Vital signs include blood pressure, heart rate, respiratory rate, and oral body temperature.

*(Continued on next page)*

[d] For women of childbearing potential, a serum pregnancy test will be performed at Screening, and a urine pregnancy test will be performed at each visit at which study drug is dispensed.

[e] Patients will have MRI to measure liver fat (PDFF), total liver volume, and pulse wave velocity. Patients who discontinue before Visit 6 (Week 16) should have an MRI performed at End of Treatment if they completed at least 4 weeks of treatment.

[f] Liver biopsy results for confirmed NASH within 6 months of Screening to confirm patient eligibility will be collected in the eCRF, if available.

[g] Randomization will occur at Visit 2 to assign patients to either 5 mg/day elobixibat or placebo in 1:1 ratio.

[h] See Table 2, Laboratory Parameters. Clinical safety laboratory tests include clinical chemistry, hematology/coagulation, and urinalysis

[i] See Section 9.2.4.

[j] History of alcohol consumption will be obtained at Screening.

Abbreviations: C4: 7α-hydroxy-4-cholesten-3-one; CRF: case report form; CRP: C-reactive protein; ECG: electrocardiogram; EOT: End of Treatment; FGF-19: fibroblast growth factor-19; GLP-1: glucagon-like peptide-1; INR: international normalized ratio; MRI: magnetic resonance imaging; NASH: nonalcoholic steatohepatitis; PDFF: proton density fat fraction

### 7.1.3 Study Procedures and Assessments

#### 7.1.3.1 Screening Period (-6 Weeks to Day -1)

##### 7.1.3.1.1 Visit 1

Patients will undergo a Screening visit up to 6 weeks prior to the planned first day of study treatment. Screening procedures and assessments are as follows:

- Obtain written informed consent
- Assess inclusion/exclusion criteria (Sections 7.2.1 and 7.2.2, respectively)
- Medical and surgical history (date of diagnosis of NAFLD/NASH; any surgery performed; any other diagnosis)
- Record demographics (age, full date of birth, gender, race, and ethnicity)
- Serology
- 12-lead ECG (Section 10.2.6)
- Physical examination (Section 10.2.4)
- Vital signs (Section 10.2.5)
- Pregnancy test
- MRI (Section 9.2.2)
- Liver biopsy (applicable for patients' biopsy-confirmed NASH within 6 months of Screening)
- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total s-BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)

- Fibrosis and inflammation markers (Section 10.2.1)
- High-sensitivity CRP
- Stored sample for future testing (Section 10.2.1)
- Review of alcohol consumption
- Document concomitant medications
- AE monitoring

#### 7.1.3.2 Treatment Period (Day 1 to Week 16)

##### 7.1.3.2.1 Study Day 1/Visit 2 (Randomization)

At the randomization visit, the following assessments will be conducted:

- Review inclusion/exclusion criteria (Sections 7.2.1 and 7.2.2, respectively)
- Physical examination (Section 10.2.4)
- Vital signs (Section 10.2.5)
- Pregnancy test
- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total s-BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)
- Fibrosis and inflammation markers (Section 10.2.1)
- Stored sample for future testing (Section 10.2.1)
- Study drug is dispensed and patients are instructed to administer daily from Day 1
- Review of concomitant medications
- AE monitoring

#### 7.1.3.2.2 Study Weeks 4-12/Visits 3-5

The following procedures and assessments will be conducted:

- Vital signs (Section 10.2.5)
- Pregnancy test
- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Visit 3 only; Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total s-BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)
- Fibrosis and inflammation markers (Visit 3 only; Section 10.2.1)
- High-sensitivity CRP (Visit 3 only; Section 10.2.1)
- Stored sample for future testing (Section 10.2.1)
- Study drug is dispensed; review of compliance
- Review of concomitant medications
- AE monitoring

#### 7.1.3.2.3 Study Week 16/Visit 6/EOT

The last dose of study drug will be taken in the morning the day before Visit 6 and the following procedures and assessments will be conducted (also conducted at the time a patient prematurely withdraws):

- 12-lead ECG (Section 10.2.6)
- Physical examination (Section 10.2.4)
- Vital signs (Section 10.2.5)
- Pregnancy test
- MRI (Section 9.2.2)

- Clinical safety laboratory tests (Section 10.2.1)
- Endocrinology (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total s-BA (Section 9.2.3)
- Lipid profile (Section 9.2.1)
- Fibrosis and inflammation markers (Section 10.2.1)
- High-sensitivity CRP
- Stored sample for future testing (Section 10.2.1)
- Review of concomitant medications
- AE monitoring

#### 7.1.3.3 Follow-Up Period

##### 7.1.3.3.1 Study Week 18/ Visit 7

All patients will complete a Follow-Up visit approximately 2 weeks after the last dose of study drug for the following assessments:

- Vital signs (Section 10.2.5)
- Pregnancy test
- Clinical safety laboratory tests (Section 10.2.1)
- GLP-1, FGF-19, C4 (Section 10.2.1)
- Total s-BA (Section 9.2.3)
- Lipid profile (Section 10.2.1)
- Stored sample for future testing (Section 10.2.1)
- Review of concomitant medications
- AE monitoring

## 7.2 Study Population

A total of approximately 46 patients with a clinical diagnosis of NAFLD/NASH (in accordance with the protocol definition) will be randomized.

### 7.2.1 Inclusion Criteria

Patients must meet all the following criteria to be included in the study:

1. Be willing to participate in the study and provide written informed consent
2. Be a man or woman ≥18 years of age
3. Have a current biopsy-confirmed NASH within 6 months of screening **or** a suspected diagnosis of NAFLD/NASH based on the criteria outlined below:
    a. Biopsy-confirmed NASH is defined as histological NASH diagnosis with fibrosis stage F1 through F3 and a NAFLD activity score (NAS) of ≥4 with a score of ≥1 in each of the NAS components below as assessed by the central pathologist using the NASH Clinical Research Network criteria (Kleiner 2005)
        i. Steatosis (scored 0 to 3)
        ii. Ballooning degeneration (scored 0 to 2)
        iii. Lobular inflammation (scored 0 to 3)

    **OR**

    b. The suspected diagnosis of NAFLD/NASH is based on each of the following criteria being met:
        i. Serum aspartate aminotransferase (AST) ≥20 U/L and ALT ≥40 U/L
        ii. Diagnosis of metabolic syndrome as having any 3 of the following 5 risk factors at Screening:
            - Fasting plasma glucose ≥100 mg/dL or undergoing drug treatment for elevated glucose

- High-density lipoprotein-cholesterol (HDL-C) <40 mg/dL in males or <50 mg/dL in females or undergoing drug treatment for reduced HDL-C
- Triglycerides ≥150 mg/dL or undergoing drug treatment for elevated triglycerides
- Waist circumference >102 cm in males or >88 cm in females
- Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or undergoing drug treatment for hypertension, or antihypertensive drug treatment in a patient with a history of hypertension

4. Screening MRI-PDFF with ≥10% liver steatosis
5. Fasting serum LDL-C >130 mg/dL at Screening, >110 mg/dL on lipid-lowering medications
6. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test (beta human chorionic gonadotropin) at Screening and must agree to use highly effective birth control throughout the study and up to 30 days after the last dose of study drug. Highly effective contraception measures include combined estrogen- and progestogen-containing hormonal contraception (oral, intravaginal, and transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, and implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner (only in the event that the vasectomized partner is the sole sexual partner of the WOCBP), and sexual abstinence (defined as refraining from heterosexual intercourse) only in the event that this is the preferred lifestyle of the patient.

   Childbearing potential is defined as being fertile following menarche and until becoming postmenopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

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.

Men with partners who are WOCBP must either be surgically sterile or agree to use a barrier contraceptive for the duration of the study and up to 30 days after the last dose of study drug.

7. Be willing to maintain a stable diet and physical activity throughout the course of the study

### 7.2.2 Exclusion Criteria

Patients who meet any of the following criteria will not be included in the study:

1. Women who are pregnant, breastfeeding, or plan to become pregnant during the study
2. Body mass index (BMI) <25 kg/$m^2$
3. Fibrosis-4 index (Fib-4) >2.6
4. Any of the following laboratory abnormalities:
    a. ALT >5 × upper limit of normal (ULN) or AST >5 × ULN
    b. International normalized ratio (INR) ≥1.3, unless on anticoagulant therapy
    c. Total bilirubin >ULN, except with an established diagnosis of Gilbert's syndrome
    d. Platelet count less than the lower limit of normal (LLN)
    e. Creatinine clearance as calculated by the modification of diet in renal disease (MDRD) estimated glomerular filtration rate (eGFR) equation <60 mL/min

NOTE: Unless otherwise specified, repeat testing may be performed in consultation with the Medical Monitor.

5. Acute or chronic liver disease other than NAFLD/NASH including but not limited to the following:

    a. Hepatitis B (as defined by the presence of hepatitis B surface antigen at screening) or hepatitis C (as defined by the presence of hepatitis C virus [HCV] antibody [anti-HCV]). Patients with positive anti-HCV who test negative for HCV ribonucleic acid at screening will be allowed to participate in the study as long as there is evidence of viral negativity for a minimum of 12 months prior to screening)

    b. Evidence of ongoing autoimmune hepatitis

    c. History of primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, homozygous alpha-1-anti-trypsin deficiency, hemochromatosis or iron overload, drug-induced or alcoholic liver disease, or known bile duct obstruction

    d. Suspected or proven hepatocellular carcinoma

6. Known history of human immunodeficiency virus

7. Medical history of liver cirrhosis

8. Clinical evidence of portal hypertension to include any history of ascites, hepatic encephalopathy, or presence of esophageal varices

9. Use of drugs historically associated with NAFLD (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 for >2 weeks in the year prior to screening

10. Use of the following medications:

    a. GLP-1 agonists unless on a stable dose 3 months prior to liver biopsy or Screening

    b. Ursodeoxycholic acid, thiazolidinediones, or obeticholic acid within 3 months prior to Screening

c. Statins and other lipid-modifying therapies must have been stable for ≥3 months prior to Screening

d. Oral antidiabetic drugs (other than those specifically excluded) must have been stable for ≥3 months prior to Screening

e. Agents (including herbal over-the-counter weight-loss preparations) or medications known to significantly impact body weight within 3 months prior to Screening (e.g., sibutramine, phenetamine, and orlistat)

11. History of significant alcohol consumption, defined as an average of >20 g/day in female patients and >30 g/day in male patients, for a period of >3 consecutive months within 1 year prior to Screening, hazardous alcohol use (Alcohol Use Disorders Identification Test score ≥8), or an inability to reliably quantify alcohol consumption based upon judgment of the Investigator

12. Weight change ≥10% within the 6 months prior to Screening or ≥5% within the 3 months prior to Screening

13. Prior or planned (during the study period) bariatric surgery (e.g., gastroplasty and roux-en-Y gastric bypass)

14. Type 1 diabetes by medical history

15. Uncontrolled Type 2 diabetes defined as hemoglobin A1c (HbA1c) >9.5% at Screening (patients with HbA1c >9.5% may be rescreened) or requiring insulin dose adjustment >10% within 2 months prior to Screening

16. Clinical hyperthyroidism or hypothyroidism or screening hormone results pointing to thyroid dysfunction. Patients receiving dose-stable thyroid replacement therapy for ≥3 months prior to Screening will be allowed to participate as long as thyroid tests (thyroid-stimulating hormone/triiodothyronine/thyroxine) show that the patient is euthyroid

17. History of any condition causing malabsorption such as chronic pancreatitis, extensive bowel/small intestine surgery, celiac disease, or bile flow obstruction

18. History of any condition associated with acute or chronic diarrhea such as inflammatory bowel disease (IBD), functional diarrhea, irritable bowel syndrome

(IBS) with predominant diarrhea, IBS with mixed bowel habits, or unclassified IBS

19. Uncontrolled hypertension (either treated or untreated) defined as systolic blood pressure >160 mmHg or a diastolic blood pressure >100 mmHg at Screening. A retest of blood pressure, (after establishing good blood pressure control within a reasonable period of time and up to the Baseline visit) is permissible at the discretion of the Investigator

20. History of New York Heart Association Class III or IV heart failure, or known left ventricular ejection fraction <30%

21. History of myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft, or stroke or major surgery within 6 months prior to Screening

22. Active substance abuse within 1 year prior to Screening

23. Participation in an investigational new drug trial in the 30 days prior to Screening or within 5 half-lives of an investigational agent, whichever is longer

24. Malignancy within 5 years, except for basal- or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated. Patients with a history of other malignancies that have been treated with curative intent and which have no recurrence within 5 years may also be eligible if approved by the Sponsor's Medical Monitor. Patients under evaluation for malignancy are not eligible

25. Patients with known intolerance to MRI or with conditions contraindicated for MRI procedures

26. Any other condition which, in the opinion of the Investigator, would impede compliance, hinder completion of the study, compromise the well-being of the patient, or interfere with the study outcomes

### 7.2.3 Withdrawal of Patients

Patients will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and that they are not obliged to state their reasons.

Any withdrawal, and reasons for withdrawal, must be fully documented in the electronic case report form (eCRF) and source documents and the patient followed by the investigator/investigative staff. Even after the study is completed at the Follow-Up visit, the investigator/investigative staff will, regardless of reason for withdrawal, record any patient data they receive concerning serious adverse events (SAEs), and all drug-related non-serious AEs, and report these in the eCRF. Withdrawn patients will not be replaced.

Patients will be withdrawn in the following circumstances:

- A patient’s desire for withdrawal for any reason
- Lost to follow-up (every effort must be made to contact the patient; a certified letter must be sent)
- An AE that, in the opinion of the Investigator, necessitates withdrawal
- Death
- A patient’s substantial noncompliance (study drug compliance) or protocol violation
- An Investigator’s opinion that continuing the patient in the study is not appropriate. The Investigator may withdraw a patient at any time if it is considered to be in the patient’s best interest

A patient who withdraws from treatment prematurely will have EOT (Visit 6) assessments at the time of withdrawal and a Follow-Up assessment (Visit 7) approximately 2 weeks following the last dose of study drug, and the patient will be recorded as withdrawn.

### 7.2.4 Study Termination by Sponsor

This study may be terminated at any time by the Sponsor if serious side effects should occur, if the Investigator does not adhere to the protocol, or if, in the Sponsor's judgment,

there are no further benefits to be achieved from the study. In this event, the Sponsor or its designee will inform the study investigators, institutions, and all regulatory authorities.

The Sponsor may temporarily or permanently discontinue the study at an investigative site at any time for safety, ethical, compliance, or other reasons. If this is necessary, the Sponsor will endeavor to provide advance notification to the site. If a site or the study is suspended or discontinued, the Investigator/investigative staff will be responsible for promptly informing the IRB. If required by local regulations, the Sponsor or its designee will be responsible for informing the IRB and the regulatory authority of study or site discontinuation. In such an event, all study data and unused study drug must be returned to the Sponsor or its designee.

# 8. TREATMENT OF PATIENTS

## 8.1 Identity of Study Drug

Elobixibat and placebo will be supplied as tablets for oral administration during the Treatment phase of the study. White tablets containing elobixibat or placebo will be provided.

The elobixibat and placebo tablets will be identical in appearance. Tablet filling weight will also be identical for elobixibat and placebo. Bottles containing 34 tablets will be given to the patient at each visit. Refer to the study reference manual.

## 8.2 Administration of Study Drug

Patients will be dosed with elobixibat at a dose of 5 mg or placebo once daily for 16 weeks. Study drug will be dispensed to the patient at Visits 2-5 together with instructions on how to store and take the drug. Study drug compliance will be evaluated at each study visit.

Elobixibat should be taken in the morning, prior to the first meal. On clinic visit days when laboratory assessments are conducted, study drug should be taken after the visit and after laboratory samples are taken.

## 8.3 Study Treatment Packaging and Labeling

### 8.3.1 Packaging and Labeling

The tablets will be packed in high-density polyethylene bottles, with child-proof polypropylene caps. Packaging and labeling will be prepared to comply with applicable regulatory requirements.

### 8.3.2 Storage

Treatment bottles containing elobixibat tablets should be stored and dispensed in accordance with regulations in their original containers. The storage facility at the investigative site should be locked and the storage temperature should be between 15°C and 25°C.

Caregivers should be informed of appropriate storage conditions (i.e., room temperature, between 15°C and 25°C).

Any deviations from the recommended storage conditions should be immediately reported to the Sponsor and the study drug should not be used until authorization has been given by the Sponsor.

### 8.3.3 Blinding and Randomization of Study Drug

A double-blind design is employed so that both the investigators and the patients will be unaware of the treatment assignment during the study.

After written informed consent is obtained from an eligible patient, a 6-digit patient number will be assigned. The first 3 digits will be the site number followed by a 3-digit patient sequence number. This number will be created and allocated by the Interactive Web Response System (IWRS), when the patient first enters the system at Screening. The randomization codes will be computer-generated by a statistician independent from the project team. The randomization will be done in blocks to ensure approximate balance between dose schemes (1:1). Randomization codes will be assigned sequentially as patients become eligible for randomization.

Patients who are eligible for randomization will be assigned a unique 4-digit randomization number by IWRS. This randomization number identifies which treatment will be allocated to the patient. Patients who withdraw from the study after randomization visit are not to be replaced and their randomization number will not be reused.

To ensure blinding, the study drug and the matching placebo have the same shape and size. Labels on the treatment bottles will not identify the treatment to which a patient has been randomized. Traceability of the treatment is ensured by the bottle number.

The 5-digit bottle number will identify the study-drug bottle and will be detailed on the study-drug label. Dispensing of the study drug will be coordinated by IWRS.

The system will assign a study-drug number corresponding to the randomization arm. The randomization number will be used in the background only to ensure that there is no unblinding and will not be displayed to end-users in the IWRS.

## 8.4 Procedure for Breaking the Randomization Code

Should a situation arise where unblinding is urgently required, i.e., only where knowledge of the study drug is required to adequately manage a life-threatening situation,

the Investigator at that study site may perform immediate unblinding through IWRS. The responsibility to break the treatment code in emergency situations resides solely with the Investigator. The Investigator should make every effort to discuss the rationale (status and outcome) for emergency unblinding with the Sponsor's Medical Monitor as soon as possible to review the individual patient details.

The study-site Investigator and appropriate project team members will be authorized to access the emergency unblinding functionality within the IWRS. Once the randomization code is broken for a patient, he/she must be withdrawn from the study and all assessments and procedures for Visit 6/EOT should be performed. Once a randomization code has been broken, the Investigator must inform the project team and Sponsor's Medical Monitor in writing within 24 hours. In case of technical issues accessing the system online, please see the IWRS site user manual for contact telephone numbers for the help desk 24/7 system support.

## 8.5 Patient Compliance

Patients will return all unused study drug at Visits 3 through 6. The study-site staff will count all returned drug, assess compliance, and record details in the eCRF.

Any noncompliance will be documented and explained in the source documents.

Treatment compliance = 100 × ([number of study drug dispensed—number of study drug returned]/number of study drug that should be taken)

Treatment compliance between 80% and 120% is acceptable.

## 8.6 Study Drug Accountability

Records shall be maintained of the delivery of study treatment(s) to the study site(s), of the inventory at the study site(s), of each use of the study treatment(s) for each patient and the return or destruction of used and unused study treatment(s). Local destruction of used/unused study treatment(s) will follow institution standard operating procedures (SOPs) and will require Sponsor pre-approval.

These records shall include dates, quantities, batch numbers, expiry dates, and the unique code numbers assigned to the study drug and to the study patients.

The Investigator will be responsible for ensuring that the records adequately document that the patients were provided the quantities specified in the protocol and that all study drug received from the Sponsor or its designee is reconciled.

## 8.7 Concomitant Therapy and Prohibited Medications

The Investigator will note all ongoing medication and any medication recently stopped (within 3 months prior to Visit 2) in the eCRF. At Visits 2 through 6, all changes in medication (stopping or starting new medication or changes in dose) will be recorded in the eCRF.

All medications taken by a patient within 3 months prior to the first intake of study drug are regarded as prior medication.

All medications taken by a patient on or after the first intake of study drug, and which continue to be taken during the study, are regarded as concomitant medication.

# 9. ASSESSMENT OF EFFICACY

## 9.1 Efficacy Endpoints

### 9.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline in serum LDL-C at Week 16.

### 9.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
- Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI
- Change from Baseline to Week 16, and Follow-Up in the following:
    - Serum ALT, AST, and gamma-glutamyl transferase
    - HDL-C, non-HDL-C, LDL-C/HDL-C ratio, and triglycerides
    - Serum total bile acids

### 9.1.3 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be assessed:

- Change from Baseline (unless otherwise specified) to Week 4, Week 8, Week 12, Week 16, and Follow-Up in the following:
    - Fasting glucose, insulin, homeostatic model assessment-insulin resistance, HbA1c, free fatty acids
    - GLP-1, FGF-19, and C4 levels
    - High-sensitivity CRP
    - Lanosterol and beta-sitosterol
    - Body weight, BMI, waist circumference, and waist-to-hip ratio

- MRI-based measurement of pulse wave velocity to measure aortic stiffness
- Apolipoprotein A1 and Apolipoprotein B

## 9.2 Efficacy Assessments

### 9.2.1 Lipid Profile

Fasting blood samples for analysis of LDL-C will be drawn at all visits, according to the schedule of assessments (Table 1). Fasting should be for at least 8 hours prior to the collection of the blood sample. Samples will be processed and transported to a central laboratory per instructions in the study reference manual.

### 9.2.2 Magnetic Resonance Imaging

Patients will have an MRI at Screening and EOT to assess liver fat by MRI-PDFF, total liver volume, and aortic pulse wave velocity. Details of the image acquisition and analysis can be found in the study reference manual.

### 9.2.3 Serum Bile Acids

Fasting blood samples for analysis of total s-BA will be drawn at all visits, according to the schedule of assessments (Table 1). Fasting should be for at least 8 hours prior to the collection of the blood sample. All s-BA results during the treatment period will be blinded. Samples will be processed and transported to a central laboratory per instructions in the study reference manual.

### 9.2.4 Biomarkers and Blood Samples for Future Testing

Blood samples for analysis of additional markers of disease, fibrosis, inflammation, and cardiovascular risk factors, and other pharmacodynamic markers will be drawn at the appropriate visits, according to the schedule of assessments (Table 1). These include a bile acid profile, including primary and secondary bile acids, interleukin-6, Pro-C3, tumor necrosis factor alpha, and cytokeratine-18. Samples will be processed and transported to a central laboratory per instructions in the study reference manual.

# 10. ASSESSMENT OF SAFETY

The timing and frequency of safety assessments are described in Section 7.1.3 and in Table 1.

The primary safety analysis will include the occurrence of treatment-emergent adverse events (TEAE) and TEAEs categorized by causality, severity, and seriousness assessments made by the Investigator by comparing study drug exposure to placebo.

Trends in safety will also be evaluated for the following assessments:

- AEs, including discontinuations due to AEs
- Physical examinations
- Concomitant medications
- Vital signs
- 12-lead ECG
- Laboratory test results (including clinical chemistry, hematology/coagulation, and urinalysis)

## 10.1 Adverse Events

### 10.1.1 Definitions and Investigator Assessments

An AE is defined as any untoward medical occurrence in an enrolled patient regardless of causal relationship with study drug. An AE can therefore be any clinically significant unfavorable and unintended sign, symptom, or disease that occurs once a patient is enrolled (ICF is signed) in the study until the patient is discharged from the study, whether or not related to the study drug.

#### 10.1.1.1 Clinical Significance

Clinical significance is defined as any abnormal finding that results in further clinical investigation(s), treatment(s), or the diagnosis of a new condition. Patient-reported events and protocol-mandated laboratory values, vital signs, and physical examination findings can be considered clinically significant (i.e., an AE) if there is a deterioration as compared to Baseline. Examples of clinically significant worsening from Baseline could

include, but is not limited to, events causing withdrawal from the study and events requiring medical intervention outside of the study causing apparent clinical manifestations or judged to be relevant by the Investigator.

#### 10.1.1.2 Serious Adverse Events

Serious criteria are applied by the investigator to each AE as specifically defined below. These criteria are used to determine whether an AE is serious or non-serious. The assessment is made independently of severity assessment (Section 10.1.1.3). For example, the development of a severe rash that occurs after signing of the ICF may not meet serious criteria as defined below and therefore would be considered a severe, non-serious AE.

Any AE that meets any 1 of the following 6 criteria is considered to be an SAE:

- The outcome of the AE is **death**
- The AE is immediately **life-threatening**. Life-threatening means that the patient is, in the opinion of the Investigator, at immediate risk of death from the reaction as it occurred. This does not include an AE that, if more severe, might have caused death
- The AE results in persistent or significant **disability/incapacity**. Disability means a substantial disruption of a person's ability to conduct normal life functions
- The AE requires or prolongs **hospitalization**
- The AE results in a **congenital anomaly/birth defect**
- **The AE is an important medical event**. Important medical events may meet serious criteria should the Investigator assess that they may significantly jeopardize the patient, represent a significant hazard, or require medical/surgical intervention to prevent one of the outcomes listed above. Examples of potential SAEs based on these criteria include, but are not limited to, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions even if they do not result in inpatient hospitalization, or the development of drug dependency and drug abuse.

#### 10.1.1.3 Severity Assessment

Severity assessments are based on the intensity of the event in relation to expectation. The Investigator will assess the intensity of AEs based on the following definitions:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

Severity is a measure of intensity where seriousness is defined by the criteria outlined in Section 10.1.1.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not meet serious criteria, and therefore would be assessed as a severe AE but not an SAE.

#### 10.1.1.4 Causality Assessment

The Investigator determines the causality of all AEs to the study drug using medical judgment and considering all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study drug, and de-challenge or re-challenge. The causality assessment of the AE/SAE is to be made as follows:

**Related to Study Drug (Possibly, Probably, or Definitely Related)**

Based on medical judgment, there is at least a reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
- The event follows a known pattern of response to study drug
- The event disappears or decreases on cessation or reduction in dose of the study drug. (It should be noted that in some situations an AE will not disappear or

decrease in intensity upon discontinuation of study drug despite other clear indications of relatedness)

- The event reappears or worsens when the study drug is re-administered

**Unrelated to Study Drug (Unlikely or Unrelated)**

Based on medical judgment there is no reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of study drug
- The event could be reasonably attributed to the known characteristics of the patient's clinical state, concurrent illness, environment or toxic factors, or other modes of therapy administered to the patient
- The event does not follow a known pattern of response to study drug
- The event does not disappear or decrease on cessation or reduction in dose of the study drug, and it does not reappear or worsen when the study drug is re-administered

### 10.1.2 Recording of Adverse Events

It is the Investigator's responsibility to assess whether each untoward event is a clinically significant worsening from Baseline, thereby considered an AE. For all AEs, the severity, seriousness, and causality to study drug for each AE as outlined in Section 10.1.1 will be assessed and recorded in the eCRF.

All serious and non-serious AEs are collected once the caregiver/patient has signed the ICF and until the post-treatment follow-up (Visit 7) or 14 days after the last dose of study drug.

Any AEs or SAEs that are unresolved at the patient's last AE assessment are followed up by the Investigator until resolution or stabilization up to the database lock and recorded in the eCRF. The Sponsor retains the right to request additional information for any patient with ongoing AE(s) or SAE(s) at the end of the study.

TEAEs are defined as any AE that occurs after randomization (Day 1). All AEs that occur in the Screening period, i.e., after enrollment and prior to randomization, will be collected on the eCRF as non-TEAEs.

If there is a clinically significant deterioration of a laboratory value/vital sign or other routine study assessment that is associated with a diagnosis, the clinical diagnosis will be reported as an AE and the associated signs and symptoms will be considered additional information unless the sign or symptom is more severe than expected given the diagnosis. For example, if an Investigator diagnoses a study patient with hepatitis during the study period, hepatitis would be considered the AE and the concomitant signs and symptoms of abdominal pain, vomiting, and elevated ALT and AST would not be reported separately unless, in the opinion of the Investigator, one of these signs or symptoms is more severe than expected and therefore a separate AE assessment is indicated.

### 10.1.3 Recording and Reporting of Serious Adverse Events

Every SAE (regardless of severity and causality) that occurs once the patient has signed the ICF and through 14 days after the final dose of study drug, should immediately and not later than within 24 hours of knowledge of the event, be reported by the Investigator or delegate in the SAE report form.

Report of a SAE must include at least the following information:

- Patient identification information (study number, site number, and date of birth [as per local country requirements for data protection])
- The last study drug administration date
- The diagnosis of the event with the description (or a brief description of signs/symptoms/clinical course if the diagnosis is not available) and the date of onset
- The action used to treat the event (i.e., treatment medications, temporary discontinuation)
- The reason(s) for considering the event serious
- The relationship of the event to the study drug or to the study procedure (i.e., the Investigator’s assessment of causality)

- A brief narrative of the SAE

Follow-up reports including all new information obtained of the subsequent course of the SAE must be prepared and the information collected in the SAE report form submitted to the CRA, [redacted] by e-mail within 24 hours of knowledge of the event.

The pharmacovigilance manager (PVM) of the CRA may contact the Investigator to obtain further information on a reported SAE. The investigator/investigative staff must respond to any request for follow-up information or answers to questions regarding the SAE within the same timelines as for initial reports.

The PVM reports the occurrence of the SAE and follow-up to the Sponsor's Medical Monitor for medical assessment of the case.

Should an outcome of death occur within the study period or within 14 days after the last administration of study drug, an SAE form should be completed including the main and contributory causes of death.

All SAE reports must be e-mailed to the following e-mail address within **24 hours**: [redacted]

If email is unavailable, SAEs may be transmitted via fax to the following number: [redacted]

### 10.1.4 Reporting of Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reaction (SUSAR) is an SAE that occurs in a patient, the nature or severity of which is not expected per the applicable product information (e.g., the Investigator's Brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

Reporting and tracking of SUSARs will be in accordance with all applicable competent authority regulations. The IRBs and all Investigators involved in this study will be informed according to local requirements.

## 10.2 Laboratory Values, Vital Signs, Physical Examinations, and Other Safety Assessments

### 10.2.1 Laboratory Assessments

Samples will be collected for clinical chemistry, hematology, urinalysis, and other lab assessments at the time points specified in Table 1. The parameters assessed are presented in Table 2. All samples will be processed and transported to a central laboratory per instructions in the study reference manual.

The observed values will be recorded and assessed as “normal” or “abnormal not clinically significant” or “abnormal clinically significant.”

Additional blood samples may be needed due to follow-up of an abnormal value or analysis failure. The blood samples collected for safety laboratory analysis will be destroyed after the analyses have been completed.

Stored blood sample for future testing are detailed in Section 9.2.4.

**Table 2: Laboratory Parameters**

| CLINICAL CHEMISTRY (FASTING) | HEMATOLOGY/COAGULATION | URINALYSIS |
|---|---|---|
| • Albumin<br>• ALT<br>• Alkaline phosphatase<br>• Amylase<br>• AST<br>• Bicarbonate<br>• Blood urea nitrogen<br>• Calcium<br>• Chloride<br>• Creatine kinase<br>• eGFR by MMRD (screening only)<br>• Gamma-glutamyl transferase<br>• Glucose<br>• Hemoglobin HbA1C<br>• Inorganic phosphorus<br>• Lactate dehydrogenase<br>• Lipase<br>• Potassium<br>• Sodium<br>• Total bilirubin<br>• Total protein<br>• Uric acid | • Hematocrit<br>• Hemoglobin<br>• Platelet count<br>• Red blood cell count<br>• White blood cell count and differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)<br>Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.<br>• International normalized ratio (INR)<br>• Prothrombin time (PT) | • Bilirubin<br>• Blood<br>• Glucose<br>• Ketones<br>• Leukocytes esterase<br>• Microscopy including leukocytes (performed only as needed based on positive dipstick test results)<br>• Nitrites<br>• pH<br>• Protein<br>• Specific gravity<br>• Urobilinogen |

*(Continued on next page)*

| LIPID PROFILE (FASTING) | OTHER TESTS | ENDOCRINOLOGY |
|---|---|---|
| • Apolipoprotein A1<br>• Apolipoprotein B<br>• Chylomicron cholesterol<br>• Chylomicron triglycerides<br>• High-density lipoprotein (HDL) cholesterol<br>• Lipoprotein(a) cholesterol<br>• Low-density lipoprotein (LDL) cholesterol by calculation<br>• LDL triglyceride<br>• Non-high-density lipoprotein cholesterol<br>• Total cholesterol<br>• Triglycerides<br>• Very low-density lipoprotein (VLDL) cholesterol<br>• VLDL triglyceride<br>• Lanosterol<br>• Beta-sitosterol | • High-sensitivity C-reactive protein (CRP)<br>• C4<br>• Fibroblast growth factor-19 (FGF-19)<br>• Fibrosis and inflammation markers: FIB-4, APRI, and NAS<br>• Glucagon-like peptide-1 (GLP-1) | • Follicle-stimulating hormone[1]<br>• Homeostatic model assessment-insulin resistance<br>• Insulin<br>• Thyroxine[2]<br>• Triiodothyronine[2]<br>• Thyroid-stimulating hormone[2]<br>• Free fatty acids<br>• Adipose tissue insulin resistance<br>• Adiponectin |
| **BILE ACIDS (FASTING)** | **PREGNANCY** | **SEROLOGY** |
| • Total serum bile acids | • Serum<br>• Urine | • Hepatitis B virus surface antigen<br>• Hepatitis C virus antibody and ribonucleic acid |

[1] A postmenopausal state is defined as no menses for ≥12 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, performed at Screening visit only.

[2] Thyroid function test will be performed during Screening visit only.

### 10.2.2 Individual Patient Safety Monitoring

#### 10.2.2.1 Liver Monitoring

Strategies to monitor markers of liver disease throughout the study are outlined below where the ULN will be based on central laboratory reference values for age and gender. Patients will be monitored as described below for drug-induced liver injury from randomization to 2 weeks following the last administration of study drug.

**Elevated ALT**

- ALT >5 × ULN or >3 × Baseline (if ALT elevated at Baseline): repeat AST, ALT, total bilirubin, alkaline phosphatase (ALP), and INR within 72 hours and closely monitor the patient. If liver enzyme elevation is confirmed, interrupt the study drug. The study drug can be restarted only if a competing etiology is identified or liver tests return to Baseline.

**Elevated AST**

- AST >5 × ULN or 3 × baseline (if AST elevated at baseline): repeat AST, ALT, total bilirubin, ALP, and INR within 72 hours and closely monitor the patient. If liver enzyme elevation confirmed, interrupt the study drug. The study drug can be restarted only if a competing etiology is identified or liver tests return to Baseline.

**Elevated Total Bilirubin**

- Total bilirubin >2 × ULN or >1.5 × Baseline (if total bilirubin elevated at Baseline), regardless of ALT or AST levels: repeat AST, ALT, total bilirubin, ALP, and INR within 72 hours and closely monitor the patient. If liver enzyme elevation confirmed, interrupt the study drug. The study drug can be restarted only if a competing etiology is identified or liver tests return to Baseline.

**Other Clinical Symptoms**

- Clinical signs of hepatitis or indicators of immunological reaction (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, jaundice, rash, eosinophilia >5% or symptoms/signs of hepatic decompensation): discontinue the

study drug and repeat AST, ALT, total bilirubin, ALP, and INR within 72 hours and closely monitor. Other causes of hepatitis should be excluded.

When close monitoring of a patient is not possible while the patient is on study drug, interrupt the study drug and closely monitor the patient.

### 10.2.3 Demographics/Medical and Surgical History

Demographic information per country regulations (age, full date of birth, gender, race, and ethnicity), along with medical and surgical history, will be obtained and recorded in the eCRF at Visit 1.

Medical and surgical history will be entered in the eCRF at Visit 1. This includes date of diagnosis of NASH/NAFLD, ongoing medication, any surgery performed, and any other diagnoses.

### 10.2.4 Physical Examination

A physician or suitably trained qualified assistant will perform a complete physical examination at Screening, at Visit 2, and at Visit 6. Height (Screening only), weight, waist circumference, and waist-to-hip ratio will also be collected. BMI will be calculated based on height and weight.

A complete physical examination will include assessment of general appearance, eyes, ears, nose, throat, head/neck/thyroid, lymph nodes, cardiovascular, lungs/chest, abdomen, genitourinary, extremities, skin, musculoskeletal, neurologic, and other.

### 10.2.5 Vital Signs

Evaluation of vital signs will be performed at all visits. This includes blood pressure (systolic and diastolic), pulse, respiratory rate, and oral temperature.

### 10.2.6 12-Lead ECG

A 12-lead ECG will be performed at the Screening visit and the EOT visits.

### 10.2.7 Overdose

Elobixibat is minimally absorbed and has a very low systemic availability. It is not known whether elobixibat can be removed from the systemic circulation by dialysis.

There are no known antidotes for elobixibat overdoses. If an overdose occurs, the patient should be carefully monitored and treated with supportive therapy.

# 11. STATISTICAL EVALUATION

All personnel involved with the analysis of the study will remain blinded until database lock for the double-blind treatment period and until major protocol violations have been identified.

All statistical analyses will be performed using SAS version 9.3 or higher.

## 11.1 Sample Size and Power

Due to the exploratory nature of this study, no formal power calculations were used to determine the sample size. The number of subjects (46 patients in total, 23 patients per treatment group) was chosen based on clinical experience with other similar proof-of-concept studies.

## 11.2 Statistical Methods

### 11.2.1 Statistical Analysis Populations

**ITT Population**

The intent-to-treat (ITT) population will include all patients who are randomized in the study and receive at least 1 dose of study drug. The ITT population will be used for all efficacy analyses based on the treatment randomized unless otherwise specified.

**Per Protocol Population**

The per protocol (PP) population will include all ITT patients who finish Visit 7/EOT with valid LDL-C measurements and do not have any major protocol deviations. Allocation of patients to the PP analysis set will be performed before unblinding of the study.

**Safety Population**

The safety population will include all patients who are randomized and receive at least 1 dose of study drug and will be used for all safety analyses based on the treatment received.

### 11.2.2 Methods of Statistical Analyses

#### 11.2.2.1 General Principles

Summary statistics (number of patients, mean, standard deviation, median, minimum, and maximum) at all visits and change or percent change from Baseline will be provided for efficacy and safety continuous variables. Count and frequency will be used to tabulate categorical variables.

##### 11.2.2.1.1 Efficacy

The primary efficacy endpoint is the change from Baseline in serum LDL-C at Week 16. Baseline is defined as the last non-missing LDL-C value prior to the first dose of study drug.

Exploratory comparisons between elobixibat 5 mg and placebo will be performed for the following secondary efficacy endpoints:

- Absolute change from Baseline to Week 16 in liver fat fraction (%) as measured by MRI-PDFF
- Absolute change from Baseline to Week 16 in total liver fat (mL) as measured by MRI

The analysis methods for the other secondary and exploratory endpoints will be detailed in the statistical analysis plan (SAP).

##### 11.2.2.1.2 Safety

The safety endpoints for this study include clinical laboratory assessments, vital signs, AEs, ECGs, physical examinations, and concomitant medications.

AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedRA). TEAEs will be defined as AEs that are new or worsening after the first dose of study drug. A general summary of patients with TEAEs and serious adverse events (SAEs) will be tabulated with numbers and percentages of patients and repeated for severity and relationship to study drug per treatment group. The number of AEs leading to withdrawal and SAEs leading to death will also be summarized. The incidence of TEAEs will be summarized by body system and treatment group.

The safety laboratory data will be summarized by visit and by treatment group, along with changes from Baseline. Values outside of the reference range will be flagged and laboratory abnormalities of special interest will be summarized.

#### 11.2.2.2 Missing Data

Continued collection of efficacy data for patients who discontinue treatment will be made for as long as possible as per the schedule of assessments (Table 1). Missing data handling for the primary efficacy endpoint is specified under Section 11.2.2.6. Details on missing data handling for secondary and exploratory endpoints will be specified in the SAP.

#### 11.2.2.3 Demographic and Baseline Characteristics

Descriptive summaries of demographics and other baseline characteristics (including medical and surgical history) will be presented by treatment group and overall using the ITT population.

Prior medication will be summarized by treatment group and overall using the ITT population.

#### 11.2.2.4 Subject Disposition

The following will be summarized descriptively (by treatment group and overall where applicable):

- Patients enrolled (who signed the informed consent)
- Patients randomized
- Patients treated
- Patients completing the study
- Patients withdrawing early (including withdrawal reason)

#### 11.2.2.5 Evaluation of Primary Efficacy Endpoints

To address the potential missing data from patients who are lost to follow-up after treatment discontinuation, multiple imputation method will be used. Data from patients who discontinue the study drug but stay in the study with scheduled assessments

collected will be used to impute missing values for patients lost to follow-up. This imputation will be done within each treatment group. Interim missing data will be handled as missing at random (predictable from observed data from subjects in the same treatment group).

After the imputation is performed, an analysis of covariance (ANCOVA) will be used to analyze the primary efficacy endpoint. The model will include treatment arm and Baseline LDL-C scores.

Least square (LS) mean (SE), LS mean difference (SE), 95% confidence intervals, and *P*-values between elobixibat 5 mg and placebo will be provided. The model assumptions will be checked before the analysis. If there are concerns on model assumptions, i.e., normality and homogeneity of variances, a non-parametric ANCOVA based on the rank scores can be used as a sensitivity analysis.

Sensitivity analyses may be performed and will be detailed in the SAP.

#### 11.2.2.6 Evaluation of Secondary and Exploratory Efficacy Endpoints

Descriptive statistics will be provided for secondary and exploratory endpoints listed in Sections 9.1.2 and 9.1.3, respectively, unless otherwise specified.

#### 11.2.2.7 Evaluation of Safety Endpoints

Safety data will be analyzed using descriptive statistics and summaries by treatment group of SAEs, AEs, vital signs, clinical safety laboratory tests (hematology, coagulation, clinical chemistry, and urinalysis), and concomitant medication. Analyses will be performed using the safety analysis set.

Summaries of AEs (coded according to the MedDRA system organ class [SOC] and MedDRA preferred term) will include the following:

- Overview of the incidence of TEAEs (TEAEs, drug-related TEAEs, TEAEs leading to study discontinuation, and treatment-emergent SAEs)
- TEAEs by SOC and preferred term
- Intensity of TEAEs by SOC and preferred term
- Drug-related TEAEs by SOC and preferred term
- TEAEs leading to study discontinuation by SOC and preferred term
- Treatment-emergent SAEs by SOC and preferred term

Concomitant medication use during the treatment period will be summarized by Anatomical Therapeutic Chemical (ATC) class and World Health Organization (WHO) preferred name.

Summaries of vital signs will be presented. For each visit, the actual results and the change from Baseline, and the number and percentage of patients with potentially clinically significant (PCS) values as defined in the SAP, observed post-baseline will be presented.

Summaries of clinical safety laboratory data will be presented. For each visit, the actual result and the change from Baseline, and the number and percentage of patients with PCS values as defined in the SAP, observed post-baseline will be presented.

Data listings will be provided for each patient for all safety parameters.

#### 11.2.2.8 Compliance and Exposure

Exposure will be analyzed by calculating the number of days with exposure to study drug. Results will be presented by treatment group using the safety analysis set.

The percentage compliance will be described by treatment group and the number of patients with a compliance <80%, between 80% and 120%, and >120% will be presented based on the safety analysis set.

## 12. DIRECT ACCESS TO SOURCE DATA/NOTES

The Investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, IRB review, and regulatory inspection.

# 13. QUALITY CONTROL AND QUALITY ASSURANCE

## 13.1 Conduct of the Study

The study team shall implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted, and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with US Food and Drug Administration (FDA) regulations (Code of Federal Regulations, Sections 312.50 and 312.56) and with ICH GCP (CPMP 135/95).

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate competent authority and IRB, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the patient having to be withdrawn from the study and render that patient non-evaluable.

## 13.2 Study Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Sponsor representative or designee will review the protocol and eCRF with the Investigators and the investigative staff. During the study, the clinical monitor (the CRA) will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications.

The investigator must ensure that eCRFs are completed within a timely period of patient visits, as per individual site agreements, and must allow the CRA and the Sponsor representative or designee periodic access to patient records and all study-related materials, including relevant hospital or clinical records, to confirm their consistency with the eCRF entries. No information in these records about the identity of the patients will leave the study center. The Sponsor monitoring standards require full verification for

the presence of the signed ICF, adherence to the inclusion/exclusion criteria, documentation of SAEs, and recording of primary efficacy and safety variables. The CRA will review source data compared with the eCRFs and will verify source data according to the study-specific monitoring plan. The design of the study, the frequency of patient visits, and the site enrollment rate will determine the frequency of monitoring visits. Upon study completion, the CRA will visit the site to conduct a study termination visit, which will include collection of any outstanding documentation.

It is recommended that the Investigator/investigative staff log into the eCRF system every working day or at minimum twice weekly in order to provide a prompt response to queries. The Investigator/investigative staff should respond to queries and make any relevant changes to the study data within 3 working days.

# 14. ETHICS

## 14.1 Institutional Review Board

Prior to the start of the study, the Investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IRB. The IRB shall be appropriately constituted and perform its functions in accordance with FDA, ICH, GCP, and local requirements as applicable.

The IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, patient recruitment procedures (e.g., advertisements), written information to be provided to the patients and caregivers, the Investigator's Brochure, available safety information, information about payment and compensation available to patients, the Investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IRB and regulatory authority (competent authority) as applicable.

## 14.2 Written Informed Consents

The Investigator (physician) or investigative staff, in accordance with local regulations, will explain to each patient (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, alternative treatment, the potential risks and benefits involved, and any discomfort that may occur. Each patient will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

If written consent is not possible, oral consent can be obtained if witnessed and followed by a signed statement from one or more persons not involved in the study, indicating why the patient was unable to sign the form. No patient can enter the study before his/her informed consent has been obtained, as required by country regulations.

The ICF is part of the protocol and must be submitted by the Investigator/investigative staff with the protocol for IRB approval. The Sponsor will supply an ICF which complies with regulatory requirements and country laws and is considered appropriate for the study. Any changes to the ICF suggested by the Investigator must be agreed to by the

Sponsor before submission to the IRB and a copy of the approved version must be provided to the clinical monitor after IRB approval.

# 15. DATA HANDLING AND RECORDKEEPING

## 15.1 Electronic Case Report Forms/Source Data Handling

The investigator shall be provided with standardized eCRFs and shall ensure that all data from patient visits are promptly entered into the eCRFs in accordance with the specific instructions given. The Investigator must sign each eCRF to verify the integrity of the data recorded.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to the start of the study. As a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analyzed at that laboratory.

The Investigator must maintain source documents such as laboratory reports, consultation reports, and complete medical history and physical examination reports.

## 15.2 Retention of Essential Documents

Essential documents, as defined by ICH GCP, include the signed protocol and any amendment(s); copies of the completed eCRFs (for site archiving of eCRF data for specific patients will be provided); signed ICFs; hospital records and other source documents; IRB approvals and all related correspondence including approved documents; drug accountability records; study correspondence; and a list of patients' names and addresses.

The Investigator/investigative staff must retain copies of these essential documents for the period specified by ICH GCP and by applicable regulatory requirements. The Investigator/investigative staff will inform the Sponsor of the location where the essential documents are stored and must contact the Sponsor for approval before disposing of any essential documents. The Investigator/investigative staff should take measures to prevent accidental or premature destruction of these documents.

## 16. FINANCING AND INSURANCE

Financing and insurance are addressed in a separate agreement.

## 17. PUBLICATION POLICY

The Sponsor will retain ownership of all data. When the study is complete, the Sponsor will arrange the analysis, tabulation of data, and preparation of a clinical study report. The Sponsor may also use the data for publication, presentation at scientific meetings, and submission to regulatory authorities. All proposed publications based on this study must be subject to the Sponsor's approval requirements.

## 18. REFERENCES LIST

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