Study Population:

Subjects with PBC, with inadequate response to UDCA

Number of Patients (planned): 45 patients (15 per treatment group)

Number of Sites (planned):~20 clinical units

Country (planned): US, UK, Spain, Germany

Study duration per patient:

A screening period (1 to 4 weeks before randomization) will precede a 12-week double-blind treatment period, after which there will be a follow-up period of up to 30 days.

Schedule:

- Screening visit: Week-4 to Week-1 prior to randomization
- Week 0 to Week 12: period of treatment with elafibranor (GFT505) 80mg or 120 mg or placebo for 12 weeks. Patients will attend study visits at randomization, Week 2, 4, 8, and 12.
- Week 12 to Week 16: patients who complete the 12 week double blind treatment period will have a follow up period and attend an End of Study visit at least 16 days but no more than 30 days after Visit 5 (V5)

Inclusion Criteria:

1. Must have provided written informed consent (IC)
2. Males or females 18 to 75 years of age
3. Definite or probable PBC diagnosis as demonstrated by the presence of at least 2 of the following 3 diagnostic factors:
    - History of elevated ALP levels for at least 6 months Positive Anti-Mitochondrial Antibodies (AMA) titers (> 1/40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay [ELISA]) or positive PBC-specific antinuclear antibodies
    - Liver biopsy consistent with PBC
4. ALP ≥ 1.67x upper limit of normal (ULN) ('inadequate response to UDCA')
5. Taking UDCA for at least 12 months (stable dose for ≥ 6 months) prior to screening visit
6. Contraception: Females participating in this study must be of non-childbearing potential or must be using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:
    a) Cessation of menses for at least 12 months due to ovarian failure
    b) Surgical sterilization such as bilateral oopherectomy, hysterectomy, or medically documented ovarian failure
    c) Using a highly effective non-hormonal method of contraception (bilateral tubal occlusion, vasectomised partner or intra-uterine device)
    d) Double contraception with barrier **and** highly effective hormonal method of contraception (oral, intravaginal or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation, oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation or intrauterine hormone-releasing system). The hormonal contraception must be started at least one month prior to randomization.
7. Must agree to comply with the trial protocol.

Exclusion criteria:

1. History or presence of other concomitant liver diseases including:
    - Positive hepatitis B surface antigen (HBsAg) at Screening
    - Positive HCV RNA (tested for in case of known cured HCV infection, or positive HCV Ab at screening)
    - Alcoholic liver disease
    - Primary sclerosing cholangitis (PSC)
    - Definite autoimmune hepatitis (AIH), or 'AIH-PBC overlap syndrome'; the existence of AIH is defined as continuing use of budesonide or other systemic corticosteroid therapy, and/or azathioprine, and/or other immunosuppressive therapy following an historical AIH diagnosis (EASL 2015). 'AIH-PBC overlap syndrome' is based upon fulfilment of the 'Paris criteria' (Chazouillères 1998) for both AIH (ALT ≥5x ULN; IgG ≥2x ULN or smooth muscle antibody; interface hepatitis), and PBC(ALP ≥2x ULN; AMA, and non-suppurative bile duct injury/destruction), requiring corticosteroid therapy for

Table 2: Study Biological Assessment Schedule

	Screening period	**Treatment period**						**Follow-up period**
Visit	**SV SBx**	**V1 Bx1**	**V2 Bx2**	**V3 Bx3**	**V4 Bx4**	**V5 Bx5**	**EOT[c] BEOT**	**EOS**
Week	*[-4,-1]*	*0*	*2*	*4*	*8*	*12*	***16 to 30*** *days after last drug intake*	*16 to 30 days after V 5*
Labs - Haematology haemoglobin, haematocrit, RBC, WBC, differential count, platelet count, prothrombin time, reticulocytes count	X	X	X	X	X	X	X	X
Labs- Urinary Pregnancy test[a]	X	X		X	X	X	X	X
Labs – Serology HIV Ab I/II, HBsAg and HCV Ab (HCV RNA in case HCV Ab>0,	X							
Labs – Biochemistry								
Special B1: alkaline phosphatase, ALT, AST, GGT, CPK, 5' nucleotidase, total and conjugated bilirubin, albumin, creatinine, eGFR, sodium, MELD-score	X							
Total: alkaline phosphatase, ALT, AST, GGT, CPK, 5 nucleotidase, total and conjugated bilirubin, creatinine, eGFR, total proteins, albumin, electrolytes (sodium, potassium, chloride, calcium), hsCRP, fibrinogen, haptoglobin, lipase, amylase		X	X	X	X	X	X	X
Labs – Lipids								
Total Cholesterol, HDL-C, TG, LDL-C		X	X	X	X	X	X	X
Inflammatory markers TNF-α, TGF-β, IL-6, PAI-1		X				X	X	X
Other IgM, urinary myoglobin [b]		X				X	X	X
Liver markers: CK18 (M65 & M30), lysiphosphatidic acid, C4, FGF19, bile acids[d]		X				X	X	X
Labs – Urinalysis (dipstick done by central lab) Specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocytes	X	X	X	X	X	X	X	X
Safety markers Serum Cystatin C Urinary albumin, urinary creatinine, urinary ACR		X	X	X	X	X	X	X

Abbreviations: ACR = albumin/creatinine ratio; B = biological assessment visit; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MELD = model end stage liver disease; RBC = red blood cell; TG = triglyceride; V = visit; WBC = white blood cell.

[a] for Women of Childbearing potential only (WOCBP)

[b] assessment of presence of myoglobin in urine may be done locally at the discretion of the PI, **only** in case of clinically significant CPK elevation

[c] in case of premature discontinuation, end of treatment visit should be performed between 16 and 30 days after last drug intake

[d] Bile acid panel includes the following: **(**cholic acid (CA), glycocholic acid (GCA), taurocholic acid (TCA), chenodeoxycholic acid (CDCA), glycochenodeoxycholic acid (GCDCA), taurochenodeoxycholic acid (TCDCA), deoxycholic acid (DCA), glycodeoxycholic acid (GDCA), taurodeoxycholic acid (TDCA), lithocholic acid (LCA), glycolithocholic acid (GLCA), taurolithocholic acid (TLCA), ursodeoxycholic acid (UDCA), glycoursodeoxycholic acid (GUDCA), tauroursodeoxycholic acid (TUDCA), hyocholic acid (HCA), glycohyocholic acid (GHCA), taurohyocholic acid (THCA), hyodeoxycholic acid (HDCA), glycohyodeoxycholic acid (GHDCA) and taurohyodeoxycholic acid (THDCA).

4. PATIENT SELECTION

4.1. INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the trial:

1. Must have provided written informed consent (IC)
2. Males or females 18 to 75 years of age
3. Definite or probable PBC diagnosis as demonstrated by the presence of at least 2 of the following 3 diagnostic factors:
    - History of elevated ALP levels for at least 6 months
    - Positive Anti-Mitochondrial Antibodies (AMA) titers (> 1/40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay [ELISA]) or positive PBC-specific antinuclear antibodies
    - Liver biopsy consistent with PBC
4. ALP ≥ 1.67x upper limit of normal (ULN) ('inadequate response to UDCA')
5. Taking UDCA for at least 12 months (stable dose for ≥ 6 months) prior to screening visit
6. Contraception: Females participating in this study must be of non-childbearing potential or must be using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:
    a) Cessation of menses for at least 12 months due to ovarian failure
    b) Surgical sterilization such as bilateral oopherectomy, hysterectomy, or medically documented ovarian failure
    c) Using a highly effective non-hormonal method of contraception (bilateral tubal occlusion, vasectomised partner or intra-uterine device)
    d) Double contraception with barrier and highly effective hormonal method of contraception (oral, intravaginal or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation, oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation or intrauterine hormone-releasing system). The hormonal contraception must be started at least one month prior to randomization.
7. Must agree to comply with the trial protocol.

4.2. EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from entering the study:

1. History or presence of other concomitant liver diseases including:
    - Positive hepatitis B surface antigen (HBsAg) at Screening
    - Positive HCV RNA (tested for in case of known cured HCV infection, or positive HCV Ab at Screening)
    - Alcoholic liver disease
    - Primary sclerosing cholangitis (PSC)

3.5. STUDY PERIODS AND SCHEDULE OF ASSESSMENTS

The study will be comprised of 3 periods. The Screening Period (-4 weeks to -1 week) will precede a 12-week double-blind Treatment Period (Figure 1). A pre-randomization visit (to confirm eligibility), will take place 1 week prior to randomization at Visit 1. The study follow-up period will last up to 30 days after Visit 5.

A schedule of assessment by visit is presented in Table 1, and a schedule of biological assessment by visit is presented in Table 2.

3.5.1. Screening Period

3.5.1.1. Screening Visit [SV] (Week -4 to Week -1)

The following screening procedures will be performed for all potential patients at the SV conducted between Week -4 and Week -1 prior to Randomization:

- Signature of informed consent witnessed by the Investigator or designated person.
- Patient number allocation via IVRS/IWRS.
- Check medical history/demographics.
- Check inclusion/exclusion criteria (as described in Section 4).
- Physical examination (described in Section 6.2.1).
- Review dietary, fluids and recommendations (described in Section 5.1.1) including alcohol restrictions.
- Record vital signs (described in Section 6.2.2).
- Record height and weight.
- Check concomitant/prior medication (described in Section 7.12 and Appendix III)
- Check AEs from time of Informed Consent Form (ICF) signature (described in Section 6 and Section 8).

The Screening biological assessment (SBx) will be performed at the SV.

The following biological assessments (detailed in Table 2 will be performed at SB:

- Blood samples (described in Table 2).
- Urinalysis collection (dipstick will be done at central lab).
- Urinary pregnancy test (for women of childbearing potential only [WOCBP]).

If needed, a retesting of abnormal creatine phosphokinase (CPK) results or testing of hepatitis C virus (HCV) RNA, may be performed during the screening window to determine the eligibility for the study as described in exclusion criteria 1 and 2 (see Section 3.5.5.1 and Section 4.2). Any other retest deemed necessary by the Investigator should be discussed with the Study Medical Monitor.

At the SVpotentially eligible patients will be asked if they agree to participate in the study and sign the ICF. Preliminary entrance criteria will be reviewed. Each patient who has signed the ICF will be allocated a patient number composed of 7 digits which is generated by the IVRS/IWRS.

- First 3 digits corresponding to the ISO numeric country code (this number will be predefined),
- Next 2 digits corresponding to the site number (this number will be predefined),
- Last 2 digits corresponding to the numerical order of the patient entry at the study site.

A specific IVRS/IWRS procedure manual will be provided to the Investigator.

HCV	hepatitis C Virus
HDL-C	High-density lipoprotein cholesterol
HIV	human immunodeficiency virus
hPPAR	human peroxisome proliferator-activated receptor
HRT	Hormonal replacement therapy
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL-6	interleukin-6
IgM	immunoglobulin M
INR	international normalized ratio
IP	investigational product
IR	insulin resistance
IRB	Institutional Review Board
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
LDL-C	Low-density lipoprotein cholesterol
LPLV	last patient last visit
LSS	Life Science Services
M2	anti-inflammatory macrophages
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for end-stage liver disease
MDRD	Modification of diet in renal disease
NASH	nonalcoholic steatohepatitis
NCEP ATP III	National Cholesterol Education Program's Adult Treatment Panel III
NF-κB	Nuclear factor kappa B
NICE	National Institute for Health and Care Excellence
PBC	Primary Biliary Cholangitis
PD	pharmacodynamics
PK	pharmacokinetics
PKS	Pharmacokinetic set
PPAR	peroxisome proliferator-activated receptor
PPS	per protocol set
PRV	Pre-randomization visit
PT	prothrombin time
QD	once daily
QoL	quality of life
QTc	corrected QT
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBx	screening biological assessment visit
SOP	Standard Operating Procedure
SS	safety set
SUSAR	suspected unexpected serious adverse reactions

3. TRIAL DESIGN

This is a Phase II, double-blind, randomized, parallel group,, placebo-controlled study, evaluating the efficacy and safety of elafibranor at doses of 80 mg and 120 mg QD versus placebo in an adult PBC population.

It is planned to randomize patients to either active or placebo treatment in a 1:1:1 ratio.

The overall study design is presented in Figure 1.

Patient participation will be 20 weeks maximum (including authorized margins). At the Screening Visit (Week -4 to Week -1), eligibility criteria will be checked. The Screening Visit will be followed by a pre-randomization visit, which should take place 1 week prior to randomization at V1 (Day 0/Week 1). Patients will then be randomized on a 1:1:1 basis at Visit 1 (Day 0/Week 0). The patients will then attend the following visits:

- Visit 2 (Week 2) – Intermediate visit – 2 weeks after Day 0
- Visit 3 (Week 4) – Intermediate visit – 4 weeks after Day 0
- Visit 4 (Week 8) – Intermediate visit – 8 weeks after Day 0
- Visit 5 (Week 12) – Final treatment period visit – 12 weeks after Day 0
- End of Study (EOS) visit, for all patients who complete the double-blind treatment period (at least 16 days but not more than 30 days after Visit 5).
- End of treatment (EOT) visit in case of premature discontinuation (at least 16 days and at the latest 30 days after the final administration of study drug)

3.1. NUMBER OF PATIENTS

It is planned to randomize 45 patients to either elafibranor 80 mg (15 patients) or elafibranor 120 mg (15 patients) or placebo (15 patients) treatment in a 1:1:1 ratio.

3.2. METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

Patients who satisfy all eligibility criteria will be randomly allocated to one of the following groups in a 1:1:1 ratio:

- Elafibranor 80 mg
- Elafibranor 120 mg
- Placebo

Treatment assignments will be made using an interactive voice/web response system (IVRS/IWRS).

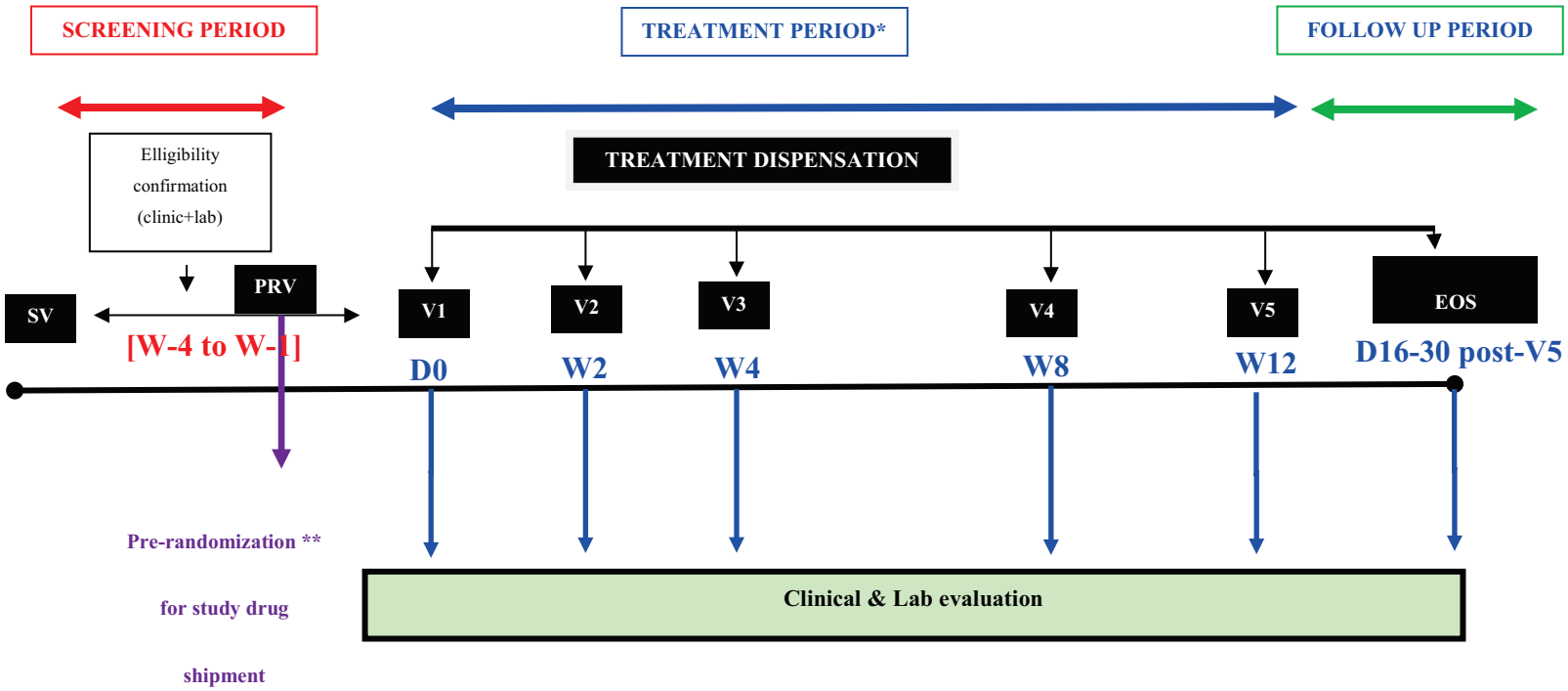
3.3. DOSE ADJUSTMENT CRITERIA

Not applicable. Patients will be randomized to a fixed dose with no allowance for dose adjustment.

3.4. DURATION OF STUDY PARTICIPATION

The estimated duration of the study will be a maximum of 20 weeks (screening period of up to 4 weeks, + treatment period of up to 12 weeks, + follow-up period of 16 to 30 days) for each complete patient.

Figure 1: Overview of Study Design



*Note: An EOT visit will occur during the treatment period if it is decided that a subject will discontinue prematurely.

**Note: Pre-randomization will be done at least 1 week before Visit 1

3.5.1.2. Pre-Randomization Visit [PRV] (Week -1)

Upon receipt of the SB results or any retesting/additional testing results from the central laboratory, the Investigator should check the eligibility with inclusion/exclusion criteria.

If the patient meets all inclusion criteria and none of the exclusion criteria (clinical, histological, and biological), the Investigator or authorized, designated Study Coordinator/Research Nurse will inform the patient of his/her inclusion by a phone call at least 1 week prior to the Randomization Visit V1. As soon as this randomization date is validated, the Investigator or authorized, designated Study Coordinator/Research Nurse will register immediately the patient eligibility and provisional randomization date in the IVRS/IWRS in order to pre-randomize the patient. When the IVRS/IWRS confirms the pre-randomization, it will provide the Investigator with a treatment number for the patient and will immediately forward the information to the drug distribution centre which will be responsible to send to the site the treatment allocated to the patient within 1 week at most.

In case of ineligibility, the patient should be contacted as soon as possible.

3.5.2. Treatment Period (Week 0 to Week 12)

Efficacy of elafibranor versus placebo on PBC will be evaluated in the double-blind treatment period of 12 weeks.

During these 12 weeks of treatment, visits will be scheduled at Weeks 0, 2, 4, 8 and 12. Clinical and biological evaluation will be performed during this Treatment Period.

3.5.2.1. Randomization Visit V1 (Week 0)

Eligible patients will return to the site at the Randomization Visit (V1) and at Weeks 2, 4, 8 and 12 during the Treatment Period of the study. The patient will be contacted at least 1 week before each visit to be reminded of procedures and investigational product (IP) return.

The following will be performed only at V1:

- Check inclusion/exclusion criteria (detailed in Section 4).
- IVRS/IWRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.2)
- Confirmation of dietary, fluids and lifestyle recommendations (described in Section 5.1.1) including alcohol restrictionsCheck concomitant/prior medication (described in Section 7.12 and Appendix III)
- Quality of life assessment (described in Section 6.2.4) and pruritus score
- Check AEs
- Study placebo or drug dispensation (described in Section 7.6)
- Blood samples (described in Table 2)
- Urinalysis collection (dipstick done by central lab) (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- 12-lead ECG (described in Section 6.2.3)
- PK blood sampling (predose, 15 min, 30 min, 1h, 1h30, 2h, 4h, 6h and 24h postdose, see Section 6.1.2).

3.5.4. End of Study Visit [EOS]

All patients who complete the double-blind treatment period will undergo an EOS Visit at least 16 days but not more than 30 days after Visit 5.

The patient will be contacted at least 1 week before this visit to be reminded of procedures and any outstanding investigational product (IP) return (if required). The following procedures will be performed at the EOS Visit:

- IVRS/IWRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.2)
- Confirmation of alcohol restrictions (described in Section 5.1.1)
- Check concomitant/prior medication (described in Section 7.12 and Appendix III)
- Pruritus scale (5D-itch scale & VAS)
- Quality of life assessment
- Review concomitant medications/prohibited medications
- Check AEs (described in Section 6 and Section 8)
- Blood samples (described in Table 2)
- Urinalysis collection (dipstick performed by central lab)(described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Drug accountability (if required, i.e. if not completed already at Visit 5)
- 12-lead ECG (described in Section 6.2.3)

3.5.5. Optional Visits

3.5.5.1. Retesting Screening Visits

Upon receipt of results from biological assessment done at SV, and in case a retesting or additional testing is needed according to the selection criteria, an additional visit will be scheduled according to the recommended timeframe for retesting.

Permitted retesting or additional testing in case of abnormal value at SV are:

- CPK: can be repeated prior to Pre-Randomization Visit (PRV)..

- HCV RNA testing, in case positive HCV Ab test: required latest 2 weeks prior to Randomization (V1) (meaning at least one week prior to pre-Randomization). In case of known cured HCV infection, HCV RNA testing can be done at SV without waiting for HCV Ab results.

Any other screening period retest deemed necessary by the Investigator should be discussed with the Study Medical Monitor.

3.5.5.2. Unscheduled Visits

An unscheduled visit is defined as any visit to the study unit outside of the protocol-evaluation timepoints where the patient is seen by study unit personnel, e.g. when follow-up assessments are required for safety reasons (such as abdominal imaging in case of elevation of lipase or amylase) or when repeat measurements are required out of the Screening Period (either to confirm a measurement or in case of errors, measuring device failure, etc.).

Unscheduled visits will be needed for patients who may require further follow-up due to safety.

- HCV Ab (positive HCV RNA in case HCV Ab > 0 to be performed at Retesting Screening Visit or at screening visit if known cured hepatitis C virus infection)

6.1.1.4. Other Parameters

Other markers will be measured as described in Table 2.

6.1.2. Pharmacokinetics Evaluation

6.1.2.1. Description of Pharmacokinetic Evaluation Parameters

The aim of the PK section of the study is to assess the pharmacokinetic profile of elafibranor in patients with PBC.

Elafibranor and its main active metabolite GFT1007 plasma concentrations will be evaluated at 9 timepoints at V1 and after 2 weeks of repeated once daily exposure (V2).

6.1.2.2. Pharmacokinetic Analysis

The PK analysis will be conducted at ADME BIOANALYSES (75, Chemin de Sommières - 30310 Vergèze - France) in compliance with the Standard Operating Procedures in use at ADME BIOANALYSES.

Elafibranor and GFT1007 will be assayed by measuring concentrations according to an analytical method previously developed and validated by ADME BIOANALYSES (References: PKH/MOA/528).

6.1.2.3. Pharmacokinetic Blood Sampling Timepoints

Blood sampling will be performed for elafibranor and its main active metabolite GFT1007 plasma concentration ,, at the following timepoints (predose and 15min, 30 min, 1h, 1h30, 2h, 4h, 6h, and 24 post dosing) at V1 and at steady-state after 2 weeks of treatment (V2). Allowable windows for PK sample collection follow. Samples outside of the allowable windows will be a protocol deviation, but should still be collected and sent to central lab for analysis.

Timepoint	Allowable Window
Predose	0 min
15 min	0 min
30 min	0 min
1 hour	0 min
1 hour 30 min	10 min
2 hours	10 min
4 hours	10 min
6 hours	10 min
24 hours	10 min

6.1.2.4. Pharmacokinetic Blood Handling Procedures

Blood samples will be collected into one 6 mL lithium heparin Vacutainer® tube . The samples must be protected from light, e.g.: wrapped in aluminum foil, and plasma will be separated in a refrigerated centrifuge (ca. +4°C) at ca. 2500 rpm for 15 minutes and a volume of exactly 1 mL of

plasma will be dispensed in a polypropylene opaque tube for aliquot 1, and 1.5 mL of plasma for aliquot 2. The plasma samples will be stored at –70°C/-112°F at the site facilities.

Thereafter, the plasma samples will be transported, in dry ice, first to the central laboratory (as for all the other blood samples) where they will be stored at –80 ± 10°C (-112 ± 50°F) until shipped to ADME BIOANALYSE for analysis.

6.2. OTHER SAFETY ASSESSMENTS AND ONGOING SAFETY MONITORING

6.2.1. Physical Examination

A physical examination will be performed by a qualified medical professional, and weight measured at each visit. Height will be measured at the Screening Visit only.

6.2.2. Vital Signs

Blood pressure (mmHg) and pulse rate (beats per minute) will be measured at each visit according to the "Recommendations for Blood Pressure Measurement in Humans and Experimental Animals" published in an American Heart Association scientific statement.

Systolic BP and diastolic BP will be measured after 5 minutes rest in the seating position with a standard mercury sphygmomanometer or a validated sphygmomanometer. Where possible, the validated manometer should be the same for a given patient throughout the visits.

6.2.3. Electrocardiogram

A standard 12-lead ECG will be obtained at V1, 3, 4, 5 and EOT or EOS Visits.

Electrocardiograms will be recorded using 12-lead ECG recorders. A minimum of 3 cycles will be recorded per lead.

The ECGs will be analyzed by the Investigator. Any potential clinical significance of ECG changes will be determined by the Investigator with relation to the patient's medical history, physical examination, and concomitant medications and recorded in the eCRF.

6.2.4. Patient Reported Outcomes Questionnaires

A standardized and validated questionnaire for quality of life (PBC 40QOL) will be completed by patients at V1, V3, V4, V5 and EOS or EOT Visits respectively. In addition, patients will complete the 5D Itch scale and the Visual Analog Scale (VAS) at these visits.

6.3. IMPORTANT SPECIFIC BIOLOGICAL CONSIDERATIONS AND PATIENT DISCONTINUATION RULES

6.3.1. Creatine Phosphokinase

If at any visit during the treatment period, a patient experiences diffuse myalgia, muscle tenderness, and/or marked increase in muscle CPK values between 3 x and 5 x ULN (≥ 3 x ULN and ≤ 5 ULN), an unscheduled site visit and test must be performed within 48 to 72 hours, and an assessment of myoglobinuria may be done locally. If, during that visit, the patient still experiences diffuse myalgia, muscle tenderness and/or marked increase in muscle CPK values between 3 x and 5 x ULN (≥ 3 x ULN and ≤ 5 ULN), myopathy must be considered and the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.2.

If at any visit during the treatment period, a patient experiences marked increase in muscle CPK values >5 x ULN, the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.2.

6.3.2. Liver Function Monitoring

Rules for liver monitoring and for discontinuation in case of liver biochemical test elevations are described below.

6.3.2.1. Monitoring of Patients With Normal Baseline Aminotransferase Values

Liver function monitoring requirements for patients with normal baseline ALT and AST at V1:

- Increase in ALT or AST to >3 x ULN but ⩽5 x ULN: retest after 48 to 72 hours
  If during the following retest:
  - ALT or AST remains >3 x ULN but ⩽5 x ULN: continue the drug with close serial monitoring (once a week)
  - ALT or AST increases to >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit

- Increase in ALT or AST >5 x ULN: retest after 48 to 72 hours
  If during the following retest:
  - ALT or AST remains >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit
  - ALT and AST reduces to ⩽5 x ULN: continue the drug with close serial monitoring (once a week).

- Increase in ALT or AST >3 x ULN AND increase in total bilirubin > 2 ULN : permanently discontinue patient from study drug and schedule EOT Visit

- Increase in ALT or AST >3 x ULN AND increase in INR>1.5: permanently discontinue patient from study drug and schedule EOT Visit

- Increase in ALT or AST >3 x ULN AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%): permanently discontinue patient from study drug and schedule EOT Visit

6.3.2.2. Monitoring of Patients With Increased Baseline AT Values

Liver function monitoring requirements for patients with increased AT baseline values at V1:

- Increase in ALT or AST to >3 x baseline value but ⩽10 x ULN: retest after 48 to 72 hours
  - ALT or AST remains >3 x baseline value but ⩽ 10 x ULN: continue the drug with close serial monitoring (once a week)
  - ALT or AST increases > 5 x baseline value or >10 x ULN: permanently discontinue patient from study drug and schedule EOT Visit

- Increase in ALT or AST >3 x baseline value AND increase in total bilirubin > 2 ULN: permanently discontinue patient from study drug and schedule EOT Visit

- Increase in ALT or AST >3 x baseline value AND increase in INR>1.5: permanently discontinue patient from study drug and schedule EOT Visit

an event is a treatment-emergent AE. An AE is considered to be treatment emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or (2) it is present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the last study visit.

8.1.2. Serious Adverse Events

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

- Results in death
- Is life-threatening (see Section 8.1.2.1)
- Requires inpatient hospitalization or prolongation of existing hospitalization (see Section 8.1.2.2)
- Results in persistent or significant disability/incapacity (see Section 8.1.2.3)
- Is a congenital anomaly/birth defect (including fetal malformations associated with spontaneous abortions or elective abortions)
- Is another medically important condition (see Section 8.1.2.4).

In addition, any illnesses reported before starting active treatment or AE meeting the criteria of seriousness (as defined above) and considered to be possibly related (according to the Investigator) to any study-specific procedure (e.g., laboratory testing procedure) must be reported as an SAE.

8.1.2.1. Life-Threatening Adverse Events

A life-threatening AE in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.1.2.2. Inpatient or Prolonged Hospitalization

An inpatient hospitalization or prolongation of a hospitalization means that the patient stays overnight in the hospital. Visits to the ER will not be considered hospital admission. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization, for example:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol..Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals fall in the same category.
- Hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

8.1.2.3. Significant or Incapacitating Disability

Only a persistent or significant or incapacitating disability is intended. This item refers to a substantial disruption of a person's ability to conduct normal life functions. Thus, disability is not

intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma.

8.1.2.4. Medically Important Conditions

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias or convulsions that do not result in hospitalization.
- Development of drug dependency or drug abuse.

8.1.3. Clarification on Serious Adverse Events

- Death is an outcome of an AE, not an AE in itself.
- An SAE may occur even if the patient was not being treated with the investigational medicinal product at the occurrence of the event.
- Life-threatening means that patient is at immediate risk of death. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.
- Patient hospitalization means that the patient stays overnight in the hospital. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization.
- A procedure for protocol/disease-related investigations (e.g., biopsy) should not be reported as SAE. Hospitalization or prolonged hospitalization for a complication of such procedures should be reported as SAE.

8.1.4. Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended and that is considered causally related to an investigational medicinal product. A serious ADR (SADR) is an ADR which meets the seriousness criteria.

8.1.5. Unexpected Adverse Event

Expectedness is assessed by the Sponsor. An unexpected AE is defined as an event that has a nature of severity or specificity that is not consistent with the applicable Investigator Brochure or that is symptomatically and pathophysiologically related to a known toxicity but differs because of a greater severity or specificity.

“Unexpected” refers to an ADR that has not been previously observed and reported rather than an event that has not been anticipated based on the properties of the drug.

8.2. ASSESSMENTS

The Investigator will establish whether or not any AEs have occurred at each visit from the date of consent through the EOS/EOT visit (or 30 days after the last drug intake whichever is later). The patient will be questioned in a general manner to determine specific symptoms without offering the patient any suggestion.

8.2.1. Intensity Assessment

The intensity of the AE will be graded as follows:

- **Mild**: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate**: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe**: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

8.2.2. Relation to the Study Treatment

The Investigator will make a clinical and scientific judgment regarding whether or not the AE was related to study treatment. The Investigator will evaluate any changes in laboratory values, make a determination as to whether or not the change is clinically important, and whether or not the changes were related to study drug. However, even if the Investigator feels there is no relationship to the study drug, the AE or clinically significant laboratory abnormality must be recorded in the eCRF.

The Investigator will record the relation to the study treatment according to the following causality terms:

- **Related:** the AE follows a reasonable temporal sequence from the time of drug administration and it cannot be explained by the patient's clinical state or the study procedures/conditions. The AE abates upon discontinuation of the study drug and reappears when the study drug is introduced.
- **Possibly related:** the AE follows a reasonable temporal sequence from the time of drug administration, but could have been produced by the patient's clinical state or the study procedures/conditions.
- **Unlikely related:** the temporal association between the AE and the study drug is such that the study drug is not likely to have any reasonable association with the AE. The relationship is not likely because of other plausible explanations.
- **Not related:** the AE must definitely be caused by the patient's clinical state or the study procedure/conditions. A reasonable explanation must be given, e.g., no IP taken, preplanned elective medical intervention, or incompatible temporal relationship.
- **Not assessable**: the report suggesting an adverse reaction cannot be judged because information is insufficient or contradictory and data cannot be supplemented or verified.

8.2.3. Action Taken and Outcome

The Investigator will record the action taken with drug and outcome of the event for each AE according to the following:

Action taken with investigational drug

- Drug permanently withdrawn – in case a patient is permanently withdrawn from the study drug
- Drug temporarily withdrawn – in case the study drug is temporarily withdrawn
- Dose not changed – in case no action is taken regarding the study drug
- Unknown
- Not applicable – an AE started before initiation of treatment with study drug, the treatment had been completed prior to reaction/event, or the patient has died.

Outcome

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown

Note: In case of irreversible congenital anomalies the choice not recovered/not resolved should be used. “Fatal” should be used when death is possibly related to the reaction/event.

8.3. REPORTING

8.3.1. Reporting an Adverse Event

All AEs regardless of seriousness or relationship to study drug, including those occurring during the Screening Period, are to be recorded on the corresponding page(s) of the eCRF and in the patient’s medical record from the ICF signature until the EOS/EOT visit (or 30 days after last drug intake, whichever is later). Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, maximal intensity, action taken with respect to study drug, corrective therapy given, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug.

Adverse event reporting begins from signature of the patient ICF at the first Screening Visit and ends at the EOS/EOT visit (or 30 days after last drug intake, whichever is later).

8.3.2. Reporting a Serious Adverse Event

Serious AE reporting begins from signature of the patient ICF and ends at the EOS/EOT visit (or 30 days after last drug intake, whichever is later).

Any SAE that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported.

Investigators must notify, by fax or e-mail, the Sponsor designated representative SGS Life Science Services (LSS) Medical Affairs of all SAEs **IMMEDIATELY (within 24 hours of the Investigator becoming aware of the event).**

ANY SERIOUS ADVERSE EVENTS, WHETHER OR NOT RELATED TO THE STUDY DRUG, MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) TO SGS LSS MEDICAL AFFAIRS AT THE FOLLOWING FAX NUMBERS:

FAX numbers: +32 (0)15 29 93 94 or 1-800-746-6618

Contact Person: SGS LSS Medical Affairs Department

E-mail: be.life.saefax-ma@sgs.com

All SAEs independent of the circumstances or suspected cause must be reported in ENGLISH on a SAE Form. The SAE Form should include a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

The Investigator is also required to submit follow-up SAE reports to SGS LSS Medical Affairs within 24 hours of becoming aware of additional information such as diagnosis, outcome, causality assessment, results of specific investigations, and any new significant information that has not been previously reported.

It is critical that the information provided on the initial or follow-up SAE Form matches the information recorded in the source documents and the eCRF for the same event.

Copies of additional laboratory tests, consultation reports, postmortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. All provided reports must be anonymized.

Follow-up reports relative to the patient's subsequent course must be submitted to SGS LSS Medical Affairs until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

The Sponsor or its designated representative will report all the relevant safety information to the concerned Competent Authorities and to the Independent Ethics Committee(s) (IRB/IEC) concerned according to the country-specific requirements.

Investigator must fulfill his/her regulatory obligations to the Regulatory Authorities and/or to the Ethics Committee in accordance with local regulations.

Depending on local regulations in different regions and countries, the Sponsor or designated clinical research organization (CRO) may be required to expedite report to the Regulatory Authorities for:

- SAEs (including events related to study procedures)
- SADRs
- Suspected unexpected serious adverse reactions (SUSARs)

Each SAE report received from the Investigators will be evaluated by the designated CRO for pharmacovigilance who will assess the seriousness of the event. Each SAE report will be evaluated by the Sponsor and/or his designees who will assess the relationship to study procedure or study treatment and the expectedness of the event. Expectedness will be assessed using the reference safety information included in the Investigator Brochure.

The Investigator will contact the patient at the expected time of delivery for follow-up. If the outcome of pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect), the Investigator should follow the procedure for reporting SAEs as detailed in Section 8.3.2.

The pregnancy itself is not considered an AE.

8.6.2. Medication Error

Medication error is defined as an unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer. All medication errors will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.3. Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information and will be reported in the eCRF. All misuse will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.4. Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information (see Section 8.1.1 and Section 8.3.1). Clinical judgment should always be applied.

8.6.5. Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

- Change from baseline in Quality of Life (using PBC 40 questionnaire)
- Adverse Events (AEs)
- Cardiovascular parameters (12-lead ECG, heart rate, blood pressure)
- Hematology and safety parameters

9.2.3. Exploratory Endpoint

The exploratory endpoint is to determine PK parameters of elafibranor (GFT505) and its metabolite GFT1007 at two daily doses 80 mg and 120 mg in patients with PBC and explore an exposure-response relationship.

Details on all endpoints will be given in the SAP.

9.3. ANALYSIS SETS

The following analysis sets will be used in this study:

- Enrolled: all patients who sign informed consent. This set will be used to summarize disposition.
- ITT: all randomized patients. This set will be used to summarize efficacy. The main analysis of the primary and key secondary endpoints will be based on the ITT. All ITT-based analyses will group patients according to the treatment they were randomized to regardless of the treatment received during the course of the study.
- Safety set (SS): all randomized patients who receive at least 1 dose of study drug. This set will be used to summarize safety.
- Per protocol set (PPS): all patients who receive at least 1 dose of study drug and do not have any important protocol deviations leading to exclusion from the PPS. Important protocol deviations will be defined in the SAP and agreed prior to database lock. Supportive analysis of the primary and key secondary endpoints will be based on the PPS. All analyses using the PPS will group patients according to the treatment actually received.
- PK set (PKS): All patients who have taken at least 1 dose of elafibranor and have sufficient plasma concentrations to be able to derive the various PK parameters.

Patients in the ITT will be analyzed based on randomized treatment. Patients in the SS or PKS will be analyzed based on actual treatment received.

9.4. ANALYSIS OF PRIMARY ENDPOINT

9.4.1. Reduction in Serum Alkaline Phosphatase

Percent change in ALP levels between baseline and end-point will be computed as follows:

[(End-point value – Baseline Value) / Baseline value)] x 100.

Baseline value will be computed as value at randomization visit (V1).

End-point will be computed as:

- Value at visit V5 or
- Value at EOT (must be post baseline value) if patient prematurely dropped out

The laboratory value used for calculation will be the first value (and not the retest value) in order to reduce the delay between last study drug intake and specimen date collection.

The primary analysis elafibranor's effect on ALP changes will be performed using a randomization-based analysis of covariance method with an adjustment for the baseline ALP level (LaVange, Durham and Koch, 2005). A supportive analysis of elafibranor's effect on ALP changes will be conducted based on an Analysis of Covariance (ANCOVA) model, with percentage change in ALP as the response variable and with the treatment group and baseline ALP level as explanatory variables. If there are baseline imbalances that are deemed to be important in influencing the relative change of ALP due to random chance, the corresponding variables may be added as further explanatory variables in the primary and supportive models. The analyses will be carried out based on the ITT population and, in addition, analyses based on the PPS population will be performed.

9.5. OTHER STATISTICAL ANALYSIS

9.5.1. Secondary Endpoints

The differences in proportions or rates among the three treatment arms with respect to responses to composite endpoints, risk scores, normalization of bilirubin and albumin will be tested using the Fisher Exact Test. If there are important baseline imbalances that occurred by chance, these confounding factors may be added into a binomial regression model (Spiegelman and Hertzmark, 2005) to compare the differences in proportions among the three arms in the study.

Continuous endpoints, including changes from baseline in laboratory parameters (including lipid parameters), inflammatory and liver fibrosis markers, will be examined using an ANCOVA model similar to that used in the analysis of the primary endpoint, i.e., the change in the variable of interest will be included as the response variable whereas the treatment group and baseline level of the variable will be included as explanatory variables. If there are important baseline imbalances that occurred by chance, these confounding factors may be added into the model.

For other items such as change in baseline in pruritus or QOL, only the descriptive statistics will be presented.

The analyses defined above will be performed based on the ITT population with additional analyses based on the PPS population.

Further details will be in the SAP.

9.6. STRATEGIES TO CONTROL TYPE I ERROR

The overall type I error for the primary endpoints in this study is two-sided α=0.05.

Statistical testing for all other secondary endpoints will be of exploratory nature.

9.7. SAMPLE SIZE CALCULATION

All sample size calculations were done in PASS 13 software.

9.7.1. Reduction in ALP

It is planned to randomized 15 patients per treatment group.

Fifteen patients each in elafibranor arms and placebo arm or 45 patients in total would achieve more than 80% power to detect a percentage difference of -20% for each dose-placebo comparison. This calculation assumes that the standard deviation (on the % of relative change from baseline) in each elafibranor arm is 18 and for placebo arm is 15 and were based on the results from the phase 2B elafibranor trial. The significance level (alpha) is 0.05 and test is based on two-sided two-sample unequal-variance t-test.

9.8. PHARMACOKINETIC ANALYSIS

Pharmacokinetic measurements: AUC0→24 and Cmax will be analysed for elafibranor and GFT1007 (main metabolite).

Pharmacokinetic parameters of elafibranor and GFT1007 will be summarized by mean, standard deviation, coefficient of variation, minimum and maximum, and median.

An exposure-response relationship will be explored.

9.9. SAFETY ANALYSIS

Safety data (exposure, AEs, clinical laboratory tests, vital signs, and ECGs) will summarized by treatment group using descriptive statistics. The main summaries of safety will be based on the Safety Set.

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). An overall summary of AEs will be provided. The number and percentage of patients reporting AEs will also be presented by MedDRA System Organ Class and preferred term. The AEs will be summarized by worst severity and relationship to study drug. Serious AEs, and AEs leading to discontinuation will also be summarized. Narratives will be written for all SAEs.

Clinical laboratory tests (hematology, chemistry, and urinalysis) recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics. Clinical laboratory values for each parameter will be assigned a classification according to whether the value is lower than, within, or higher than the reference range for that parameter. The values will then be summarized using shift tables to evaluate categorical changes from baseline to end of the 12 week treatment period with respect to reference ranges. The number and percentage of patients reporting markedly abnormal clinical laboratory values will also be summarized by treatment group.

Vital signs recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics.

disease management, either currently or in the past.

- Biopsy confirmed Nonalcoholic Steatohepatitis (NASH)
- Known history of alpha-1 antitrypsin deficiency, or other metabolic forms of chronic liver disease
- Gilbert's Syndrome (due to interpretability of bilirubin levels)

2. Screening CPK > ULN
3. Screening ALT or AST > 5 ULN
4. Screening total bilirubin > 2 ULN
5. Screening serum creatinine > 1.5 mg/dl and eGFR < 60 mL/min/1.73 m2, at screening
6. Significant renal disease, including nephritic syndrome, chronic kidney disease
7. Patients with moderate or severe hepatic impairment (defined as Child-Pugh class B, C)
8. Platelet count <150 X 10^3/microliter
9. Albumin <3.5 g/dL
10. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
    - Current Model for End Stage Liver Disease (MELD) score ≥ 15; current placement on a liver transplant list, or history of undergoing liver transplantation
    - Any record of complications of cirrhosis and/or portal hypertension such as:
        - Gastroesophageal variceal bleeding and endoscopic therapy and/or transjugular intrahepatic portosystemic shunt [TIPS] insertion
        - Ascites formation requiring intervention, e.g. diuretic therapy
        - Spontaneous bacterial peritonitis
        - Hepatic encephalopathy
        - Confirmed or suspected hepatocellular carcinoma
11. Hepatorenal syndrome (type I or II) Administration of the following medications is prohibited as specified below:
    - From pre-randomization to EOT or V5 visit : indomethacin
    - 2 months preceding screening and throughout the trial (up to the last study visit): fibrates or obeticholic acid, thiazoledinediones, glitazones
    - 3 months prior to screening and throughout the trial (up to the last study visit): azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline; budesonide and other chronic systemic corticosteroids; and potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)
    - 12 months prior to inclusion visit and throughout the trial (up to the last study visit): antibodies or immunotherapy directed against interleukins or other cytokines or chemokines
    - NOTE : Anti-pruritus treatment, including rifamycin, is allowed if prescribed for at least 6 months prior to screening, and on stable dose at least 3 months prior to screening. and continues at the same dose throughout the study
12. If female: known pregnancy, or has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating
13. Known history of human immunodeficiency virus (HIV) infection
14. Medical conditions that may cause non-hepatic increases in ALP (e.g., Paget's disease)
15. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the trial
16. Anticipated changes to current medications (that will be continued) during the course of the trial
17. History of alcohol abuse, defined as consumption of more than 30 g pure alcohol per day for men, and more than 20 g pure alcohol per day for women, or other substance abuse within 1 year prior to Day 0 (randomization visit)
18. Participation in another trial with an investigational drug, biologic, or medical device using active substance within 30 days prior to screening, or within 5 half lives of the active substance, whichever is longer.
19. History of noncompliance with medical regimens, or patients who are considered to be potentially unreliable
20. Mental instability or incompetence, such that the validity of informed consent or compliance with the trial is uncertain

- Definite autoimmune hepatitis (AIH), or 'AIH-PBC overlap syndrome'; (the existence of) AIH is defined as continuing use of budesonide or other systemic corticosteroid theray, and/or azathioprine, and/or other immunosuppressive therapy following an historical AIH diagnosis (EASL 2015). 'AIH-PBC overlap syndrome' is based upon fulfilment of the Paris criteria (Chazouilléres 1998)for both AIH (ALT ≥5x ULN; IgG ≥2x ULN or smooth muscle antibody; interface hepatitis), and PBC (ALP ≥2x ULN; AMA, and non-suppurative bile duct injury/destruction),, and requiring corticosteroid therapy for disease management, either currently or in the past.
- Biopsy confirmed Nonalcoholic Steatohepatitis NASH)
- Known history of alpha-1 antitrypsin deficiency, or other metabolic forms of chronic liver disease.
- Gilbert's Syndrome (due to interpretability of bilirubin levels)

2. Screening CPK > ULN
3. Screening ALT or AST > 5 ULN
4. Screening total bilirubin > 2 ULN
5. Screening serum creatinine > 1.5 mg/dl and eGFR < 60 mL/min/1.73 m^2,
6. Significant renal disease, including nephritic syndrome, chronic kidney disease
7. Patients with moderate or severe hepatic impairment (defined as Child-Pugh class B, C).
8. Platelet count <150 X 10^3/microliter
9. Albumin <3.5 g/dL
10. Presence of clinical complications of PBC or clinically significant hepatic decompensation, including:
    - Current Model for End-Stage Liver Disease score ≥15; current placement on a liver transplant waiting list, or history of undergoing liver transplantation.
    - Any record of complications of cirrhosis and/or portal hypertension such as:
        - Gastroesophageal variceal bleeding and endoscopic therapy and/or transjugular intrahepatic portosystemic shunt [TIPS] insertion
        - Ascites formation requiring intervention, e.g. diuretic therapy
        - Spontaneous bacterial peritonitis
        - Hepatic encephalopathy
        - Confirmed or suspected hepatocellular carcinoma
11. Hepatorenal syndrome (type I or II) Administration of the following medications is prohibited as specified below:
    - From pre-randomization to EOT or V5 visit : indomethacin
    - 2 months preceding screening throughout the trial (up to last study visit) : fibrates or obeticholic acid, thiazoledinediones (glitazones)
    - 3 months prior to screening and throughout the trial (up to last study visit) : azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline; budesonide and other chronic systemic corticosteroids; and potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)

SV	Screening Visit
TGF-β	transforming growth factor beta
TNFα	Tumor Necrosis Factor-alpha
UDCA	Ursodeoxycholic Acid
UK	United Kingdom
ULN	upper limit of normal
UV-LLNA	UV- Local Lymph Node Assay
VAS	Visual Analogue Score
Vx	Visit x
WOCBP	women of childbearing potential

3.5.2.2. Treatment Period Visits V2 to V5 (Week 2 to Week 12)

The following procedures will be performed at each of the 12-week visits from V2 to V5:

- IVRS/IWRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.2)
- Confirmation of dietary, fluids and lifestyle recommendations (described in Section 5.1.1) including alcohol restrictionsCheck concomitant/prior medication (described in Section 7.12 and Appendix III)
- Quality of life assessment (except at V2) (described in Section 6.2.4)
- Check AEs (described in Section 6 and Section 8)
- Study placebo or drug dispensation (except at V2 and V5) (described in Section 7.6)
- Blood samples (described in Table 2)
- Urinalysis collection (dipstick done by central lab)(described in Table 2)
- Urinary pregnancy test (for WOCBP only, except at V2)
- 12-lead ECG **(**except at V2; described in Section 6.2.3)
- Pruritus scale (5D-itch scale & VAS)
- Drug accountability and compliance assessment
- PK blood sampling only at V2 (predose, 15min, 30min, 1h, 1h30, 2h, 4h, 6h and 24h postdose, see Section 6.1.2).

3.5.3. End of Treatment Visit [EOT]

All patients who permanently discontinue their study medication prior to study completion will undergo an EOT Visit at least 16 days and at the latest 30 days after the final administration of study drug.

If a patient discontinues from the study, every attempt should be made to have the patient return to the site and complete the EOT Visit.

The patient will be contacted at least 1 week before the visit to be reminded of procedures and IP return (if required). The following procedures will be performed at the EOT Visit:

- IVRS/IWRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.2)
- Confirmation of dietary, fluids and lifestyle recommendations (described in Section 5.1.1) including alcohol restrictionsCheck concomitant/prior medication (described in Section 7.12 and Appendix III)
- Pruritus scale (5D-itch scale & VAS)
- Quality of life assessment (described in Section 6.2.4)
- Check AEs (described in Section 6 and Section 8)
- Blood samples (described in Table 2)
- Urinalysis collection (dipstick done by central lab)(described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- 12-lead ECG (described in Section 6.2.3)
- Drug accountability

Patients discontinuing study drug or discontinuing the study will be asked to return all used and unused study treatments at the EOT Visit.

Table 1: Study General Assessment Schedule

	Screening period	**Treatment period**								**Follow-up period**
Visit	**SV**	**V1**	**V1 (PK)**	**V2**	**V2 (PK)**	**V3**	**V4**	**V5**	**EOT [g]**	**EOS**
Week	***[-4,-1]***	***0***		***2***		***4***	***8***	***12***	***16 to 30 days after last drug intake***	***16 to 30 days after V5***
Day	***[-28, -7]***	***0***		***14***		***28***	***56***	***84***		***100-114***
Permitted Margin		0		14 +/- 1 day		28 +/- 2 days	28 +/- 2 days	28 +/- 2 days		*16 + 14 days*
Obtain informed consent	X									
Medical history / demographics	X									
Check inclusion / exclusion criteria	X	X[a]								
Physical examination	X	X		X		X	X	X	X	X
Vital signs & height[b] & weight measurement	X	X		X		X	X	X	X	X
12-Lead ECG		X				X	X	X	X	X
Lab evaluation (see table "study biological assessment schedule")	X	X		X		X	X	X	X	X
PK blood sampling[c]		X	X[d]	X	X[d]					
Pre-randomization	X[e]									
Phone call to the patient		X[f]		X		X	X	X	X	X
Randomization		X								
IVRS/IWRS registration	X	X	X	X	X	X	X	X	X	X
Review prior/concomitant/ medication	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Pruritus scoring (5D itch scale & VAS)		X		X		X	X	X	X	X
Quality of life questionnaire (PBC40)		X				X	X	X	X	X
Study placebo or drug dispensation		X				X	X			
Drug accountability and compliance assessment				X		X	X	X	X	X

Abbreviations: ECG = electrocardiogram; IVRS/IWRS = integrated voice/web response system; PK = pharmacokinetic; SV = screening visit*; V = visit.*

[a] All inclusion/exclusion criteria, including biological and histological criteria, assessed at V1
[b] Height is measured only at SV
[c] There are a total of 9 PK sampling time point: 8 each at V1 and V2; the 9th sample is taken at 24h on the following day (V1(PK) and V2(PK), respectively).
[d] 24 h sampling timepoint to be done at ambulatory visit (pre-dose, fasting)
[e] At least 1 week before visit V1 and after eligibility confirmation
[f] A pre-randomization confirmation
[g] only in case of premature discontinuation, EOT needs to be performed

- Increase in ALT or AST >3x baseline value AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%): permanently discontinue patient from study drug and schedule EOT Visit

6.3.3. Specific Biological Monitoring

At any visit, if a patient experiences clinically significant lipase and/or amylase elevations, imaging CT Scan may be performed for the diagnosis of pancreatitis.

6.3.4. Safety and Efficacy Data Review

Data Safety Monitoring Board (DSMB): Not applicable.

A DMSB was not specifically set-up for this study for the following reasons:
- The study is conducted in a small number of participants, for a short duration
- GFT505 showed in previous clinical studies a very good safety profile

The medical monitors will assist the investigators for all medical matters, whenever required, and will make sure that they respect the Protocol and the study procedures, including reporting of adverse events.

6.3.5. Guidance for Investigators

Summary of safety data (for completed studies only)

The safety and tolerability of elafibranor were confirmed in Phase I and Phase II studies.

A Phase I program to assess the safety and tolerability, as well as the PK profile, of elafibranor has been conducted through 12 clinical trials. A total of 621 volunteers were randomized in these studies performed in Phase I centers, including 549 healthy lean subjects, 60 overweight or obese subjects, and 12 patients with type 2 diabetes.

A Phase II program was initiated to assess the safety and efficacy profile of elafibranor in patients suffering from cardiometabolic disorders. To date, 5 Phase IIa pilot trials have been completed in which 297 patients were randomized. A Phase IIb trial has been completed, and evaluated the efficacy and safety of elafibranor 80 mg and 120 mg on steatohepatitis in 274 patients with NASH.

Of the 69 SAEs that have been reported cumulatively in the completed clinical development program, 48 occurred with elafibranor, 13 with placebo, and 8 prior to administration of study medication. For all SAEs, the treatment code has been broken (end of study unblinding).

Of the 48 SAEs that occurred with elafibranor, only 9 were considered as having a reasonable possibility of relationship to elafibranor by the investigators (serious adverse reaction). They consisted of:

- Atrial fibrillation in a patient with history of arterial hypertension and suspected chronic coronary disease treated with elafibranor 80 mg
- Acute cholecystitis and pancreatitis that occurred in a patient on the second day of drug administration of elafibranor 80 mg
- Spontaneous abortion in a pregnant patient treated for 6 months with elafibranor 80 mg
- Ataxia, tremor and fasciculations in a patient treated for 51 weeks with elafibranor 80 mg

Any unexpected safety issue that changes the risk benefit analysis and is likely to have an impact on the patients who have participated in the trial will be reported by the Sponsor as soon as possible to the Competent Authority(ies) concerned together with proposed actions.

8.3.3. Follow-Up

The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AE until the return to normal or until stabilization of the patient's condition, even if this goes beyond the EOS orEOT visit.

The patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study and that additional investigations may be requested by the Sponsor. This information should be documented in the patient's medical records.

8.4. POST STUDY REPORTING REQUIREMENTS

Any SAEs and deaths that occur within 30 days of the last dose of the study drug, regardless of causality, should be reported.

Any SAE that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported.

8.5. CLINICAL LABORATORY ABNORMALITIES AND OTHER ABNORMAL ASSESSMENTS AS ADVERSE EVENTS OR SERIOUS ADVERSE EVENTS

Laboratory abnormalities are not necessarily recorded as AEs or SAEs. However, laboratory abnormalities that are considered clinically relevant by the Investigator must be recorded as an AE or SAE as applicable.

8.6. SPECIAL SITUATION REPORTS

Special situations reports include pregnancy reports, reports of medication error, abuse, misuse or overdose, and reports associated with product complaints.

8.6.1. Pregnancy

In case of pregnancy a communication will be sent by the Investigator to SGS LSS Medical Affairs by faxing a completed pregnancy form within 24 hours of his/her knowledge of the pregnancy.

Pregnancies of females partners of male patients exposed to study medication should also be reported to SGS LSS Medical Affairs using the corresponding pregnancy form.

Female patients must be instructed to discontinue the study drug immediately and inform the Investigator as soon as possible once they are aware of being pregnant or suspect that they are pregnant during the study or within 30 days of the last dose of the study drug.

Female patients will be requested, as part of the general ICF, to provide informed consent to allow reasonable attempts to be made to obtain information on any possible medicinal product exposure to an embryo or fetus and to follow up on the outcome of the pregnancy.

9. STATISTICAL METHODS AND DATA ANALYSIS

This section is an overview of the key elements of the statistical analysis for this study. Unless stated otherwise, statistical tests will be 2-sided and use a 5% significance level, leading to 95% (2-sided) confidence intervals (CIs). No adjustment for multiplicity will be made for the primary and secondary efficacy variables. Further details on statistical reporting and analyses will be contained in a separate statistical analysis plan (SAP). This SAP may be revised during the study only to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data collection that could affect planned analyses. In all circumstances, a final SAP should be issued prior to database lock and treatment unblinding.

Descriptive summary statistics for continuous variables will include the number of patients, mean, standard deviation (SD), median, and range. Descriptive summary statistics for categorical variables will include frequency counts and percentages. Unless stated otherwise, the denominator for percentage calculations will be the number of patients with non-missing data. Descriptive statistics will be reported for the primary and all secondary endpoints.

9.1. RANDOMIZATION AND TREATMENT ASSIGNMENT

Random allocation will be made to the 3 treatment groups (elafibranor 80 mg, 120 mg and placebo) in a 1:1:1 ratio.

Details regarding the randomization process are in Section 3.2.

9.2. ENDPOINTS

9.2.1. Primary Endpoint

The primary endpoint of the study is to evaluate the efficacy of elafibranor 80 mg or 120 mg with respect to relative change from baseline in serum ALP levels compared to placebo.

9.2.2. Secondary Endpoints

The secondary endpoints are to assess at Week 12:

- Response to treatment based on composite endpoints:
  - ALP < 1.67 × ULN and total bilirubin within normal limit and > 15% decrease in ALP
  - ALP < 2 × ULN and total bilirubin within normal limit and > 40% decrease in ALP
- Response according to Paris I, Paris II, Toronto I, Toronto II, UK-PBC risk score
- Response to treatment on normalization of ALP
- Response to treatment on normalization of bilirubin
- Response to treatment on normalization of albumin
- Response on 10%, 20%, 40% decrease in ALP
- Change from baseline in ALT, AST, GGT, 5'nucleotidase, total bilirubin, conjugated bilirubin, albumin
- Change from baseline in lipid parameters
- Change from baseline in bile acids
- Change from baseline in C4, FGF19
- Change from baseline in IgM
- Change from baseline in inflammatory and liver fibrosis markers
- Change from baseline in pruritus (through 5D-itch scale & visual analogue score VAS)

10. DATA HANDLING AND RECORD KEEPING

10.1. CASE REPORT FORM AND SOURCE DOCUMENTS

A case report form (CRF) is required and should be completed for each screened patient. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized Sponsor's representatives or appropriate regulatory authorities, without written permission from the Sponsor.

The Investigator will ensure that all data are entered promptly, legibly, completely, accurately and conform to source documents, in accordance with specific instructions accompanying the eCRFs designed specifically for this study. The CRF being used for this study is an electronic CRF that has been fully certified as being compliant with the FDA regulations at 21 Code of Federal Regulations (CFR) Part 11.

All study required patient data generated during the study will be recorded in the eCRF, with the exception of SAE forms and PBC-40 or pruritus score which will be collected in paper. Patients will not be identified by name in the eCRF or on any study documents to be collected by the Sponsor (or designee), but will be identified by a patient number.

The Investigator will review and approve each completed eCRF; the Investigator's validation serving as attestation of the Investigator's responsibility for ensuring that all clinical and laboratory data entered in the eCRF are complete, accurate, and authentic.

Should a correction be made, the corrected information will be recorded in the eCRF by the authorized person and explained (if necessary). All corrected data will be tracked through an audit trail.

It is the Investigator's obligation to ensure documentation of all relevant data in the patient's medical file (medical history, concomitant diseases, patient identification number, date of informed consent, visit dates, administration of study medication, AEs [start and stop dates] and all concomitant medications [start and stop dates]). All data recorded in the eCRF will be documented by source data.

10.2. RETENTION OF RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

The Investigator will be provided with a study file, which should be used to file the Investigator Brochure, protocol/amendments, drug accountability records, sample informed consent, staff curriculum vitae, correspondence with the IRB/IEC, Sponsor, and other study-related documents.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients, all original signed ICFs, copies of all eCRFs, source documents, and detailed records of treatment disposition.

The Investigator must retain the study documentation until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. However these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. All hospital records will be archived according to local regulation.