

**CLINICAL PROTOCOL – PHASE 2****Protocol N° GFT505B-216-1****EudraCT N°2016-003817-80****IND number: 132202****Final 3.0 – Release date 04 December 2017**

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Elafibranor at doses of 80 mg and 120mg After 12 Weeks of Treatment in Patients With Primary Biliary Cholangitis and Inadequate Response to Ursodeoxycholic Acid

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CLINICAL STUDY PROTOCOL SIGNATURE PAGE

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In signing below, I give agreement to the protocol.

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PROTOCOL TITLE: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Elafibranor at Doses of 80mg and 120mg After 12 Weeks of Treatment in Patients With Primary Biliary Cholangitis and Inadequate Response to Ursodeoxycholic Acid.

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885 Avenue Eugène Avinée,
59120 LOOS - France

In signing below, I confirm having read the protocol, and give agreement to the protocol.

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INSTITUTION NAME: _____

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DATE: _____ / _____ / _____

Day Month Year

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Protocol N°: **GFT505B-216-1/ EudraCT N° 2016-003817-80/ IND n° 132202**

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| | [REDACTED] | [REDACTED] |

CLINICAL TRIAL SYNOPSIS

| <u>Sponsor:</u> | <u>Study Drug:</u> | <u>Protocol Number:</u> |
|-----------------|--------------------|-------------------------|
| GENFIT | Elafibranor | GFT505B-216-1 |

Title of the study:

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Elafibranor at Doses of 80 mg and 120mg after 12 Weeks of Treatment in Patients With Primary Biliary Cholangitis (PBC) and Inadequate Response to Ursodeoxycholic Acid.

Phase:

Phase 2 proof of concept study

Indication:

Primary biliary cholangitis

Study Design and dose levels :

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

The study will include a screening visit, followed by a 12 week double-blind treatment period, and a follow-up period of at least 16 days but not more than 30 days after Visit 5. Patients will attend study visits at randomization, Week 2, 4, 8, and 12 during the treatment period.

Elafibranor and/or placebo is administered per os, once daily at 80 mg or 120mg, for 12 weeks.

Route of Administration:

Oral

Primary Objectives:

To evaluate the efficacy of elafibranor 80 and 120 mg with respect to relative change from baseline in serum ALP levels compared to placebo.

Secondary Objectives:

To assess the following end-points at week 12

- the response to treatment based on composite endpoints:
 - ALP < $1.67 \times$ upper limit of normal (ULN) and total bilirubin within normal limit and > 15% decrease in ALP
 - ALP < $2 \times$ 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
- ALP response rates of 10%, 20% and 40% decrease
- response based on the percent of patients who normalized ALP
- response based on the percent of patients who normalized bilirubin
- response based on the percent of patients who normalized albumin
- the change from baseline in ALT, AST, GGT, 5' nucleotidase, total bilirubin, conjugated bilirubin and albumin
- the change from baseline in lipid parameters
- the change from baseline in bile acids :
- the change from baseline in C4, FGF19
- the change from baseline in IgM
- The change from baseline in inflammatory and liver fibrosis markers
- the change from baseline in:
 - 5D-itch scale
 - PBC 40 QOL
 - VAS
- the tolerability and safety of elafibranor 80 and 120 mg in patients with PBC

Exploratory Objective:

- Determine the pharmacokinetics (PK) parameters of elafibranor (GFT505) 80 and 120 mg and its main active circulating metabolite, GFT1007, in patients with PBC and to explore an exposure-response relationship

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 $\geq 1.67 \times$ 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 oophorectomy, 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 $\geq 5 \times$ ULN; IgG $\geq 2 \times$ ULN or smooth muscle antibody; interface hepatitis), and PBC(ALP $\geq 2 \times$ ULN; AMA, and non-suppurative bile duct injury/destruction), 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 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 10³/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
-

-
21. Known hypersensitivity to the investigational product or any of its formulation excipients
 22. Evidence of any other unstable or untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease.
-

Randomization:

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

- Elafibranor 80 mg
- Elafibranor 120 mg
- Placebo

A central randomization system will be used (interactive voice/web response system [IVRS/IWRS]).

Criteria for Evaluation:

Primary Endpoint:

Relative change in serum ALP from baseline to end of treatment in each elafibranor arm, compared to placebo

Secondary Endpoints:

The secondary endpoints are to assess at Week 12:

- Response rate in elafibranor 80mg and 120 mg and placebo groups with response defined as ALP less than 1.67 times ULN and total bilirubin within normal limits and ALP reduction > 15%.
- Response rate in elafibranor 80mg and 120 mg and placebo groups with response defined as ALP less than 2 times ULN and total bilirubin within normal limits and ALP reduction > 40%
- Response rate according to Paris I, Paris II, Toronto I, Toronto II, UK PBC risk score
- Alkaline phosphatase response rates of 10%, 20% and 40% decrease
- Response rate in elafibranor 80mg and 120 mg and placebo groups with response defined as percent of patients with normalized ALP at the end of treatment
- Response rate in elafibranor 80mg and 120 mg and placebo groups with response defined as percent of patients with normalized bilirubin at the end of treatment
- Response rate in elafibranor 80mg and 120 mg and placebo groups with response defined as percent of patients with normalized albumin at the end of treatment
- Changes from baseline in:
 - Gamma-glutamyl transferase (GGT)
 - Alanine aminotransferase (ALT)
 - Aspartate aminotransferase (AST)
 - 5' nucleotidase
 - Bilirubin (total and conjugated)
 - Albumin
 - total cholesterol, LDL-chol, HDL-Chol, Triglycerides
 - Bile acids :
 - C4, FG19
 - IgM
 - Quality of Life: PBC 40 QOL
 - Pruritus: 5-D Pruritus Questionnaire and Visual Analogue Score (VAS)
 - Biomarkers of inflammation and liver fibrosis: TNF- α , TGF- β , IL-6, CK-18 and lysophosphatidic acid
- Adverse Events (AEs)
- Cardiovascular parameters (12-lead ECG, heart rate, blood pressure)
- Hematology and safety parameters
- Liver Markers
- Other biochemical safety markers

Exploratory Endpoint:

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.

Study Duration (planned): estimated 14 months (First Patient First Visit [FPFV]-Last patient last visit [LPLV])

- Regulatory/ethics committee submission: September 2016- December 2016
 - Initiation visits: January 2017 – March 2017
 - Recruitment period: March 2017 – December 2017
 - FPFV: March 2017
 - LPLV: April 2018
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LIST OF ABBREVIATIONS

| | |
|--------|--|
| AASLD | American Association for the Study of Liver Diseases |
| ACR | Albumin/creatinine ratio |
| ADR | adverse drug reaction |
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANCOVA | Analysis of Covariance |
| AST | aspartate aminotransferase |
| AT | aminotransferase |
| ATP | Adult Treatment Panel |
| BCL6 | B-cell lymphoma 6 |
| BMI | body mass index |
| BP | blood pressure |
| BUN | blood urea nitrogen |
| Bx | biological assessment visit |
| CA | competent authorities |
| CEC | Clinical Events Committee |
| CFR | Code of Federal Regulations |
| CK-18 | cytokeratin-18 |
| CPK | creatine phosphokinase |
| CRN | Clinical Research Network |
| CRO | Clinical Research Organization |
| CRP | C-reactive protein |
| CSR | Clinical Study Report |
| CYP | cytochrome P450 |
| C4 | Serum 7α-hydroxy-4-cholesten-3-one |
| DCA | deoxycholic acid |
| DDI | drug-drug interaction |
| DILI | Drug-induced liver injury |
| DSMB | Data Safety Monitoring Board |
| EASL | European Association for the Study of the Liver |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| EOS | end of study |
| EOT | end of study treatment |
| FDA | Food and Drug Administration |
| FGF19 | Fibroblast Growth Factor 19 |
| FITT | full intent-to-treat set |
| FPFV | first patient first visit |
| FSS | full safety set |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| HBsAg | hepatitis B surface antigen |
| HCC | hepatocellular carcinoma |

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

| | |
|--------------|---------------------------------|
| SV | Screening Visit |
| TGF- β | transforming growth factor beta |
| TNF α | 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 |

1. INTRODUCTION AND RATIONALE

1.1. BACKGROUND AND RATIONALE FOR ELAFIBRANOR IN PRIMARY BILIARY CHOLANGITIS

Characterization of the Disease

Primary Biliary Cholangitis (PBC) is a rare, chronic, progressive liver disease of autoimmune etiology, characterized by injury of the intrahepatic bile ducts that, in untreated patients or non-responders to existing therapies, may progress to hepatic fibrosis, cirrhosis, hepatic decompensation, and death unless they receive a liver transplant (Kuiper 2010; Kumagi 2008). PBC disproportionately affects women versus men (approximately 10:1) and is typically diagnosed in patients between 40 years to 60 years of age. The incidence and prevalence rates for PBC in Europe, North America, Asia, and Australia are reported as ranging from 0.33 to 5.8 per 100,000 inhabitants and 1.91 to 40.2 per 100,000 inhabitants, respectively (Boonstra 2012). Kim et al estimated that there were 47,000 prevalent cases of PBC in the United States white population and that approximately 3500 new cases are diagnosed each year (Kim 2000). Over 60% of the newly diagnosed cases are asymptomatic. The majority of asymptomatic patients become symptomatic within 10 years and the estimates for developing symptoms at 5 and 20 years are 50% and 95%, respectively (Kumagi 2008). Patients with PBC progress at varying rates, some having liver decompensation over a period of several years while for others progression occurs over more than a decade (Al-Harthy 2012; Selmi 2011). PBC is one of the leading indications for liver transplantation. Despite its rarity, PBC remains therefore an important cause of morbidity in the Western world. PBC has also been identified as an important risk factor for hepatocellular carcinoma (Ali 2015).

PBC is characterized by cholestasis caused by autoimmune destruction of biliary ductules with progressive impairment of bile flow in the liver. This results in increased hepatocellular bile acid concentrations which are toxic to the liver. Such hepatocellular injury is associated with a local inflammatory response resulting early on in an abnormal elevation of serum alkaline phosphatase (ALP) levels, a hallmark of the disease. Antimitochondrial antibody and immunoglobulin M are specific immunological hallmarks of PBC, and antimitochondrial antibody is a diagnostic marker of the disease in approximately 90% of patients (Hirschfield 2013). Liver biopsy, while confirmatory, is no longer the standard of care.

ALP is also routinely used to clinically monitor the disease and serves as a leading indicator of disease progression. ALP increases with disease progression as bilirubin starts to decline in more advanced disease (as the excretory function starts to decline), and both have been shown to be highly predictive of long-term clinical outcomes, e.g., transplant-free survival (Beuers 2011; Lammers 2014; Carbone 2013). Two large clinical PBC databases, the PBC Study Group (>6100 patients) and the UK-PBC Research Cohort (>5900 patients) have confirmed a near log-linear correlation of both elevated ALP and bilirubin after 1 year of follow up with long-term liver transplant-free survival (Lammers 2014).

As PBC advances, the transaminases alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may also be elevated due to hepatocellular damage secondary to cholestasis. While gamma-glutamyl transferase (GGT) lacks specificity, elevation of this enzyme in the presence of elevated ALP is confirmatory of a cholestatic condition such as PBC (Giannini 2005).

The most common symptoms of PBC are fatigue and pruritus (Crosignani 2008). The mechanisms underlying these symptoms are not well elucidated and neither correlates with disease stage or clinical outcomes.

Current Treatment Options

Ursodeoxycholic acid (UDCA), an epimer of the primary human bile acid chenodeoxycholic acid, was the only medicine currently approved to treat PBC until May 2016. UDCA has been shown to improve ALP and bilirubin, and to delay histological progression, thereby increasing liver transplant-free survival ([Corpechot 2008](#)). Accordingly, UDCA treatment has been recommended as first line therapy for patients with PBC in the treatment guidelines of the American Association for the Study of Liver Diseases (AASLD: [Lindor 2009](#)) and the European Association for the Study of the Liver ([EASL 2009](#)). While UDCA has had a marked impact on clinical outcomes in PBC, a large proportion of patients have an inadequate response. It is estimated ([Ali 2015](#)) that up to 40% of UDCA-treated patients have a suboptimal response to UDCA. Lammers and colleagues found that ALP remains elevated in up to 70% of patients who are currently being treated or are intolerant to UDCA ([Lammers 2014](#)). Such patients remain at risk of disease progression and longer term adverse clinical outcomes.

Ocaliva (obeticholic acid, OCA), at doses from 5 to 10 mg, was approved as a second line therapy by the Food and Drug Administration (FDA) in May 2016 under the accelerated approval regulations based on a reduction in ALP, either as a monotherapy in adults unable to tolerate UDCA or in combination with UDCA in adults with an inadequate response.

On 12 December 2016, the European Commission granted a conditional Marketing Authorization (MA) valid throughout the European Union for Ocaliva for the same indication. In the UK, the National Institute for Health and Care Excellence (NICE) recently approved Ocaliva for use as treatment in the UK making it available to patients. Ocaliva is also approved in Germany, and Spain.

Data from the Phase 2a study suggest the potential for exacerbation of pruritis. In a Phase 1 dose ranging study, more severe pruritus (although with no higher incidence) was observed in the 10 mg OCA group than in the placebo arm. This Adverse Event (AE) was shown to be clearly OCA-dose related ([Hirschfield 2015](#)). The incidence of pruritus in the open-label extension study phase was 87% (68/78), and 13% (10/78) discontinued OCA due to severe pruritus ([Ali 2015](#)).

At present, despite near universal use of UDCA, 10%, 22% and 44% of UDCA-treated patients are progressing to liver transplant or death over 5, 10, and 15 years, respectively ([Lammers 2014](#)). While research has been conducted on a number of other drugs (eg, malotilate, thalidomide, silymarin, atorvastatin, azathioprine, methotrexate, colchicine, D-penicillamine, cyclosporin A, chlorambucil and glucocorticosteroids), little to no evidence supports the benefit of these compounds ([Lindor 2009](#), [Rudic 2012](#), [EASL 2009](#)). The European Association for the Study of the Liver ([EASL 2009](#)) mentioned, however, that the PPAR α agonist, bezafibrate, deserved further studies as well as sulindac and the antiretroviral strategy consisting of a combination of lamivudine and zidovudine (Combivir).

Rationale for Evaluation of Elafibranor in PBC

Elafibranor is being developed by Genfit for the treatment of PBC, based on its pharmacological properties as a PPAR α/δ agonist. Activation of PPAR α receptors leads to a decrease in bile acid synthesis, increase in bile acid uptake, and increased detoxification of bile acids through the increased uptake in micelles. PPAR α and PPAR δ receptor activation also has anti-inflammatory effects by acting on different pathways of inflammation (NF- κ B and BCL6 pathways).

Ligand-activated PPAR α contributes to a range of actions, including cholesterol and bile acid homeostasis. PPAR α primarily downregulates bile acid synthesis. PPAR α also interferes with pro-inflammatory transcription factor pathways leading to the hypothesis that fibrates may exert their beneficial effect on cholestatic liver function by also regulating anti-inflammatory pathways.

Fenofibrate may also ameliorate cholestatic liver disease through its transcriptional activation of MDR3 ([Ghoneim 2015](#)).

While large-scale multicenter clinical studies are awaited, several pilot studies have consistently shown that fibrates might be of therapeutic benefit in patients with cholestatic liver diseases, particularly PBC. Use of fibrates results in a significant reduction in cholestatic parameters (serum ALP and GGT), transaminases, and immunoglobulin M (IgM) levels in PBC. Effects of fibrates on biochemical parameters can be observed as early as one month after the beginning of therapy, and most patients sustained the biochemical response as long as they were on fibrates. Discontinuation of fibrates results in rebound elevation of biochemical indices in patients with PBC, and an improvement in the biochemical indices is almost always observed after treatment with fibrates is reinstated, further supporting the potential therapeutic benefit in PBC ([Ali 2015](#)).

In addition to the biochemical improvement, significant pruritus relief has been observed in patients with PBC with inadequate response to UDCA following institution of fibrate therapy ([Lens 2014](#)). Patients experienced worsening of pruritus when bezafibrate was discontinued, and pruritus improved or completely disappeared after bezafibrate was reinstated. These data lend support to the use of fibrates in PBC patients, and suggest that fibrates could be used in the management of pruritus.

1.2. SUMMARY OF NONCLINICAL STUDIES

1.2.1. Safety Pharmacology

Any potential effects on the cardiovascular, respiratory, and central nervous system have been assessed and no safety issue was identified.

1.2.2. Absorption/Distribution/Metabolism/Excretion Studies (ADME)

In animal studies, elafibranor was well and rapidly absorbed although absolute bioavailability was moderate (about 20% to 40%). Elafibranor is extensively metabolized and the activity is mainly carried by the active metabolite GFT1007. In rat and dog, maximal plasma concentrations and exposure for both elafibranor and GFT1007 linearly increase with the dose after single or repeated administrations. Elafibranor and its metabolites are rapidly cleared from the plasma and they are totally excreted by both fecal and renal route within 48 hours. In the rat, elafibranor and/or its metabolites are rapidly excreted into the bile and undergo an extensive entero-hepatic cycle giving support for liver targeting of elafibranor and/or GFT1007. The distribution study in the rat supports the liver targeting of elafibranor and/or its metabolites.

In vitro, elafibranor does not inhibit cytochrome p450 (CYP)1A2, CYP3A4, and CYP2D6, with moderate inhibition of CYP2C9, and weak inhibition of CYP2C8, CYP2C19, and CYP4A11. GFT1007 does not produce any inhibition of the CYP450 isoforms 1A2, 3A4, 2C19, and 2D6, and only weak inhibition of CYP2C8 and CYP2C9. Both molecules also show weak inhibition of CYP3A4/5, but only with midazolam as substrate. Thus, the risk of drug-drug interaction due to an inhibition of the main cytochromes involved in drug metabolism should be limited. Potential interaction with CYP2C9 metabolized drugs has been assessed through a clinical study (GFT505-112-8) designed to evaluate potential pharmacokinetic (PK) interaction of elafibranor 120 mg administered for 14 days alone or with a single administration of warfarin. This study demonstrated that elafibranor administration did not affect the PK profile of warfarin (R-warfarin and S-warfarin).

A protein binding study showed that elafibranor and GFT1007 were highly bound to human serum albumin. The risk of drug-drug interaction due to albumin binding should be limited since this binding is not saturable.

In vitro studies have been performed to determine whether elafibranor (GFT505) and its principal metabolite GFT1007 are substrates and/or inhibitors of major drug transporters, in order to assess the potential for drug-drug interaction (DDI). Based on the results of the OATP1B3 transporter inhibition assay, elafibranor (GFT505) has recently been assessed in a follow-up clinical DDI study with the OATP1B3-sensitive substrate, atorvastatin.

For the other drug transporters studied, the interaction observed does not require follow-up studies based on current regulatory guidance.

The metabolic stability and metabolism pathways of elafibranor (GFT505) have been studied on liver microsomes and in primary hepatocytes from rat, dog, mouse, monkey, and human. There was no evidence of the formation of unique human metabolites or metabolites formed at disproportionately higher levels in human hepatocytes than in any other species.

An in vivo study has been performed to compare the bioavailability of ¹⁴C-GFT505 in the rat, dog, minipig, and monkey. This study showed that in all species ¹⁴C-GFT505 is rapidly absorbed, although absolute bioavailability was moderate (about 20% to 40%).

1.2.3. Toxicology

1.2.3.1. Mutagenicity and Genotoxicity

The toxicology program performed according to the International Council for Harmonisation (ICH) guidelines demonstrates that elafibranor has no genotoxic or mutagenicity potential.

1.2.3.2. Acute Toxicity

According to acute toxicity study results, it can be concluded that elafibranor is extremely safe when administered as single oral doses in rat and mouse, since no sign of toxicity was detected up to the dose of 1000 mg/kg.

1.2.3.3. Repeated Dose Toxicity Studies

The safety of elafibranor has been assessed in multiple preclinical toxicology studies with repeated-dose oral administration for up to 6 months in rats and 12 months in monkeys. Moreover, two-year repeated-dose carcinogenicity studies in mice and rats have been completed.

The only consistent safety concern raised by these studies is the expected PPAR α -associated hepatomegaly, hepatocellular hypertrophy, and liver carcinoma in rodent species (mice and rats). However, it is well known that, compared to nonhuman primates and humans, rodents are highly sensitive to PPAR α agonist induced peroxisome proliferation and associated liver side effects. Thus, available information on this class of drug which includes marketed fibrates together with the lack of any liver side effects in monkeys treated with high doses of elafibranor for 1 year support the nonrelevance to human ([Cattley 2008](#)). Overall, these studies did not reveal any other safety issues up to the highest doses tested. Notably, elafibranor did not have any of the known PPAR γ -related concerns such as excess weight gain, hemodilution, edema, cardiomegaly, adiponectin induction, or urinary bladder carcinoma. Importantly, the non clinical studies have demonstrated a reduced plasma ALP activity in monkeys treated for 3 or 12 months with elafibranor

1.2.3.4. Phototoxicity Studies

The phototoxic potential of elafibranor has been assessed by the in vitro 3T3 NRU phototoxicity test and the UV-Local Lymph Node Assay (LLNA) test in mice. Elafibranor (GFT505), but not its major metabolite GFT1007, showed UVA-dependent cytotoxicity in vitro. The UV-LLNA test was performed in mice with oral dosing for 3 days at up to 800 mg/kg/day elafibranor. Although a very conservative no observed effect level (NOAEL) was set at 400 mg/kg/day based on isolated findings at the highest dose, it is considered that data are more in favor of an absence of phototoxic effect, given the tissue distribution of elafibranor (GFT505), and absence of phototoxicity signal in the clinical studies.

1.3. CLINICAL STUDIES

1.3.1. Phase I Program

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.

The plasma concentrations of elafibranor and GFT1007 were determined using validated high-performance liquid chromatography tandem mass spectrometry methods. The PK parameters were calculated using a noncompartmental analysis.

In healthy volunteers, the PK of elafibranor and GFT1007 after single administration of elafibranor at rising dose levels were assessed in 2 distinct double-blind, placebo-controlled randomized trials from 10 mg to 120 mg (GFT505-106-1 and GFT505-108-4). The PK of elafibranor and GFT1007 after repeated doses of elafibranor at rising dose levels were assessed in 3 distinct double-blind, placebo-controlled randomized trials: GFT505-106-2 (5, 10, 20, and 30 mg/d), GFT505-108-4 (40, 60, 80, and 100 mg/d) and GFT505-113-9 (300 and 360 mg/d).

In overweight/obese but otherwise healthy volunteers, the PK of elafibranor and GFT1007 after single administration of elafibranor at rising dose levels from 180 mg to 300 mg were assessed in a double-blind, placebo-controlled randomized trial (GFT505-111-7). In the same trial, the PK of elafibranor and GFT1007 after repeated doses of elafibranor at dose levels from 120 mg to 240 mg, were also assessed in these overweight/obese but otherwise healthy volunteers. Another part of this trial assessed the PK of elafibranor and GFT1007 after repeated doses of elafibranor at 180 mg in type 2 diabetic patients.

The food effect on PK of elafibranor and GFT1007 was assessed in healthy volunteers at the dose of 30 mg elafibranor in a Phase I, randomized, crossover trial (GFT505-106-1).

The PK of elafibranor and GFT1007 obtained after administration of the different formulations used throughout clinical evaluation of elafibranor were compared in dedicated clinical trials in healthy volunteers: GFT505-108-3, GFT505-111-7, and GFT505-115-12. Comparable relative bioavailability was demonstrated.

The lack of PK DDI between elafibranor (80 mg/d) and simvastatin has been verified (GFT505-109-5).

The lack of effect of a concomitant administration of sitagliptin on elafibranor PK has been verified (GFT505-109-6).

The lack of effect of elafibranor administration (120 mg/d) on the PK and pharmacodynamics (PD) of warfarin has been verified (GFT505-112-8).

The lack of effect of elafibranor administration (180 mg/d) on the PK and PD of atorvastatin has been verified (GFT505-115-11).

The study GFT505-113-9 evaluated the effect of multiple oral doses of elafibranor on the QT/corrected QT (QTc) interval compared to placebo with moxifloxacin (400 mg in single oral dose) as a positive control, in healthy male and female volunteers. No effect of elafibranor on QT/QTc interval at both therapeutic and supratherapeutic doses for 14 days was observed.

The excretion balance of radiocarbon (ie, the sum of ¹⁴C-labeled elafibranor and its ¹⁴C-labeled metabolites) and the metabolite profiling and PK of elafibranor after a single oral dose of 120 mg ¹⁴C-labeled elafibranor have been assessed (GFT505-114-10). Most of the radiocarbon was excreted in feces (77.1%) and urine (19.3%), giving a recovery of 96.3% of the administered dose. The metabolite profile was assessed in plasma, urine, and feces, and did not highlight any new Phase I metabolite but allowed the identification of new glucuronated metabolites, one of them being the main urinary metabolite (12% of the administered dose).

The last part of the study GFT505-115-12 has been completed. The objective was to assess the dose linearity after single oral administration of 120, 180 and 240 mg of elafibranor, and if confirmed, to assess the time dependency of the PK parameters after single and multiple oral administration of therapeutic doses of elafibranor.

1.3.2. Phase II Program

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 also been completed (, and evaluated the efficacy and safety of elafibranor 80 mg and 120 mg on steatohepatitis in 274 patients with nonalcoholic steatohepatitis (NASH).

A Phase IIa pilot study (GFT505-207-1) was first conducted to evaluate the efficacy, safety, and tolerability of elafibranor at 30 mg/d for 28 days in patients with Fredrickson type IIb dyslipidemia. Thirty-seven randomized patients received elafibranor 30 mg (24 patients) or placebo (13 patients) over a 28-day treatment period. Although improvements were observed on primary lipid parameters, these trends were not statistically significant versus placebo.

The Phase IIa study (GFT505-208-3) assessed efficacy and safety in men and postmenopausal women with atherogenic dyslipidemia (high triglycerides, low HDL-C) and abdominal obesity treated once a day for 28 days with 80 mg/d of elafibranor. Ninety-four patients were randomized: 63 patients in the elafibranor 80 mg/d arm and 31 patients in the placebo arm.

The Phase IIa study (GFT505-209-4) assessed efficacy and safety in patients treated for 35 days with elafibranor at 80 mg/d. This study targeted patients with impaired fasting glucose and impaired glucose tolerance associated with abdominal obesity. Forty-seven patients were randomized: 23 patients in the elafibranor 80 mg/d arm and 24 patients in the placebo arm.

The Phase IIa study GFT505-210-5 assessed efficacy and safety in patients with type 2 diabetes mellitus. Patients were treated once a day for 12 weeks with 80 mg/d of elafibranor. Ninety-seven patients were randomized: 50 patients in the elafibranor 80 mg/d arm and 47 patients in the placebo arm.

The Phase IIa study (GFT505-210-6) was designed to evaluate the safety and efficacy of elafibranor on hepatic and peripheral insulin sensitivity using the gold standard glucose clamp technique in male patients with homeostasis model assessment of insulin resistance (HOMA-IR) > 3 and abdominal obesity. Patients were treated once daily (QD) with 80 mg/d of elafibranor or placebo for 8 weeks in a crossover design. In this study, after 8 weeks of treatment, elafibranor significantly improved the response of the liver to insulin action. Indeed, at the first level of insulin perfusion, the insulin-induced decrease in hepatic glucose production was $-49 \pm 4\%$ after elafibranor versus $-34 \pm 4\%$ after placebo ($p = 0.0016$). The insulin sensitivity of the muscles and other peripheral tissues measured at the second level of insulin perfusion was also increased by 28% with a significant effect on the glucose infusion rate (3.69 ± 0.31 mg/kg/min after elafibranor versus 3.21 ± 0.31 mg/kg/min after placebo, $p = 0.048$). Moreover, at the end of the treatment period, elafibranor significantly lowered the FFA levels measured at the first insulin level (FFA 0.21 mEq/L after elafibranor versus 0.27 mEq/L after placebo, $p = 0.006$).

The favorable effect of elafibranor on insulin sensitivity and glucose homeostasis was also observed in Studies GFT505-209-4 and GFT505-210-5. In prediabetic patients with impaired fasting glucose, impaired glucose tolerance, and abdominal obesity (Study GFT505-209-4), treatment with elafibranor 80 mg/d for 28 days led to a significant decrease in fasting plasma glucose (-5%, $p = 0.04$), fasting plasma insulin (-25%, $p = 0.009$), and consequently improvement of the insulin resistance index (HOMA-IR: -31%, $p = 0.027$). In diabetic patients treated for 3 months with 80 mg/d of elafibranor (study GFT505-210-5), oral glucose tolerance test-derived parameters, including area under the time-concentration curve for glycemia, insulinemia and FFA levels, significantly improved.

In all Phase IIa studies, patients treated with elafibranor at 80 mg/d for 1 to 3 months consistently experienced an improvement of the plasma lipid profile, with significant reduction of triglycerides (-20% to -35%), reduction in low density lipoprotein cholesterol (LDL-C) (-10% to -15% in prediabetic, insulin-resistant and diabetic patients) and increase in HDL-C (+10% in patients with atherogenic dyslipidemia). In addition, elafibranor treatment consistently increased the anti-atherogenic apolipoproteins (ApoAI and ApoAII) while reducing the pro-atherogenic apolipoproteins (ApoB, ApoCIII, ApoE).

In all Phase IIa studies, elafibranor treatment at 80 mg/d for 1 to 3 months also led to favorable reductions in inflammatory markers. Reduced haptoglobin levels were observed in all Phase IIa clinical trials with elafibranor, with the greatest effect obtained after 3 months of treatment in diabetic patients (-20% in the elafibranor group versus +6% in the placebo group, $p < 0.001$). Similarly, fibrinogen levels were consistently decreased by approximately 10% in all Phase IIa clinical trials with elafibranor, and high-sensitivity CRP levels were lowered after 3 months of treatment in diabetic patients (-17% in the elafibranor group versus +52% in the placebo group).

Finally, beneficial effects of elafibranor on liver function were consistently observed in all Phase IIa clinical trials of patients treated for 1 to 3 months with 80 mg/d elafibranor. Significant reductions in circulating levels of GGT and ALP were observed and reached up to -29% for GGT and -25% for ALP in elafibranor treated groups compared to placebo. In addition, in insulin-resistant patients, elafibranor treatment induced a significant reduction in ALT (-20% compared to placebo), while the level of aspartate aminotransferase (AST) was unchanged.

A Phase IIb study in nonalcoholic steatohepatitis (NASH) patients (GFT505-212-7) included 274 patients and involved a total of 56 centers in the US and in multiple European countries (France, Belgium, The Netherlands, Italy, UK, Germany, Spain, and Romania). The study evaluated the efficacy and safety of elafibranor at 80 and 120 mg QD for 52 weeks versus placebo in reversing histological steatohepatitis without worsening of fibrosis.

The study results showed that elafibranor at 120 mg demonstrates efficacy on the resolution of NASH without worsening of fibrosis in patients with an active disease (NAFLD Activity Score [NAS] score ≥ 4). Importantly, elafibranor at 120 mg concomitantly improved the cardiometabolic risk profile of NASH patients by decreasing plasma triglycerides, total and LDL-C, increasing HDL-C, and improving inflammation, insulin resistance and glucose homeostasis.

The safety profile of elafibranor was confirmed in this study. Elafibranor was well tolerated, at both doses. From the start to end of the study, regular safety reviews did not generate any comment or additional request from the Data Safety Monitoring Board (DSMB). The most frequent and expected adverse events were of gastrointestinal nature. Clinical adverse events were generally mild to moderate in severity and were similar in the placebo and treated groups for the most frequently reported treatment-related AEs. Leukocyturia, hypoglycemia, and diabetes mellitus inadequate control were more frequent in elafibranor arms as well as cutaneous rash, arthralgia, decrease in appetite, dizziness and renal impairment which were only reported in the elafibranor treated groups. Serious adverse events (SAE) were reported in 27 patients treated with elafibranor (13 with elafibranor 80 mg/d and 14 with elafibranor 120 mg/d). Of these, only 5 SAEs reported treated with elafibranor were considered by the sponsor as reasonably related to treatment after further analysis. Nineteen patients discontinued the study for safety reason with no imbalance between groups (6 in the placebo arm, 6 in the elafibranor 80 mg arm, and 7 in the elafibranor 120 mg arm).

1.4. CONCLUSION

In nonclinical studies, plasma ALP activity was reduced in monkeys treated for 3 or 12 months with elafibranor. Moreover, in the Phase 2a and 2b program, elafibranor has consistently shown a significant decrease in liver enzymes, notably in ALP. A decrease in ALP levels is recognized as a particularly relevant surrogate marker for the treatment of PBC, and was recently used as the basis for FDA approval of OCA in this indication. Elafibranor has also demonstrated significant anti-inflammatory properties in the phase 2a and 2b program.

The good safety profile of elafibranor was demonstrated through its development, including the therapeutic dose of 120 mg selected for the Phase 3 study in NASH.

Based on the mechanism of action of elafibranor, and on the relevant efficacy and safety data up to the phase 2B study, specifically the ALP decrease and inflammation markers, Genfit has decided to launch a phase 2 study in PBC patients, in order to validate the efficacy of elafibranor on ALP decrease, and to confirm its safety in this population.

Additional information can be found in the Investigator's Brochure.

2. TRIAL OBJECTIVES

2.1. PRIMARY OBJECTIVES

To evaluate the efficacy of elafibranor 80 and 120 mg with respect to relative change from baseline in serum ALP levels compared to placebo.

2.2. SECONDARY OBJECTIVES

To assess the following endpoints at Week 12:

- the response to treatment based on composite endpoints:
 - ALP < $1.67 \times$ upper limit of normal (ULN) and total bilirubin within normal limit and > 15% decrease in ALP
 - ALP < $2 \times$ 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
- ALP response rates of 10%, 20% and 40% decrease the response to treatment on normalization of ALP the response to treatment on normalization of bilirubin
- the response to treatment on normalization of albumin
- the change from baseline in ALT, AST, GGT, 5'nucleotidase, total bilirubin, conjugated bilirubin and albumin
- the change from baseline in lipid parameters
- the change from baseline in bile acids the change from baseline in C4, FGF19
- the change from baseline in IgM
- the change from baseline in inflammatory and liver fibrosis markers
- the change from baseline in pruritus (through 5D-itch scale and visual analogue score VAS)
- the changes from baseline in Quality of Life (using PBC 40 questionnaire)

2.3. EXPLORATORY OBJECTIVE

To determine PK parameters of elafibranor (GFT505) 80 and 120mg and its main active circulating metabolite, GFT1007, in patients with PBC and to explore an exposure-response relationship.

2.4. SAFETY SECONDARY OBJECTIVES

To assess the tolerability and safety of once a day administration of oral doses of elafibranor at 80 mg and 120 mg in patients with PBC:

- Serious adverse events (SAEs), adverse events (AEs), physical examination, vital signs, medical history, ECG
- Hematological parameters
- Liver markers
- Other biochemical safety markers

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).

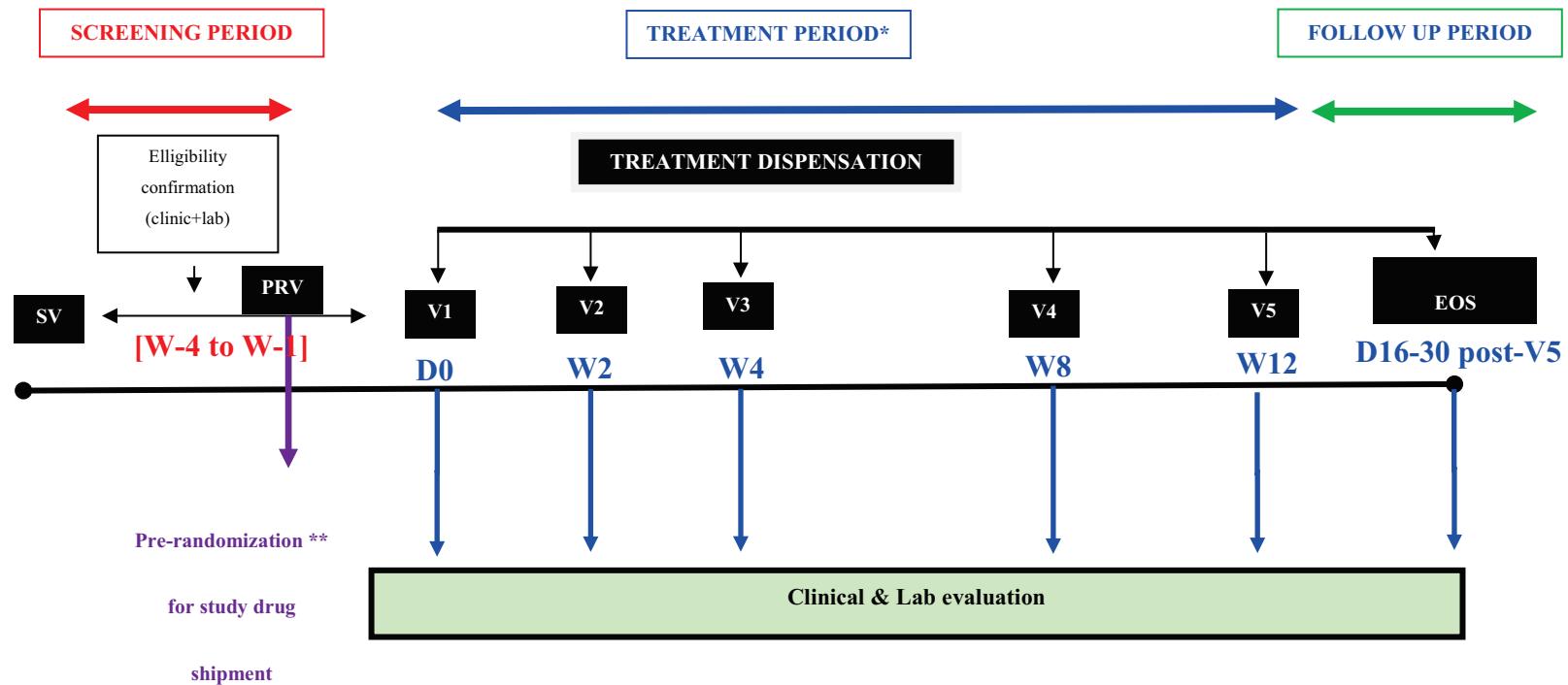
3.3. DOSE ADJUSTMENT CRITERIA

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. 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 SV potentially 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.

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](#)).

3.5.2.2. 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.

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.

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 |
| <i>Week</i> | <i>[-4, -1]</i> | <i>0</i> | | <i>2</i> | | <i>4</i> | <i>8</i> | <i>12</i> | <i>16 to 30 days after last drug intake</i> | <i>16 to 30 days after V5</i> |
| <i>Day</i> | <i>[-28, -7]</i> | <i>0</i> | | <i>14</i> | | <i>28</i> | <i>56</i> | <i>84</i> | | <i>100-114</i> |
| Permitted Margin | | 0 | | <i>14 +/- 1 day</i> | | <i>28 +/- 2 days</i> | <i>28 +/- 2 days</i> | <i>28 +/- 2 days</i> | | <i>16 + 14 days</i> |
| 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

Table 2: Study Biological Assessment Schedule

| Visit | Screening period SV SBx | Treatment period | | | | | | Follow-up period EOT ^c BEOT EOS |
|--|-------------------------------|------------------|-----------|-----------|-----------|-----------|---|---|
| | | V1 Bx1 | V2 Bx2 | V3 Bx3 | V4 Bx4 | V5 Bx5 | | |
| Week | [-4,-1] | 0 | 2 | 4 | 8 | 12 | | <u>16 to 30</u> days after last drug intake |
| 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), lysophosphatidic 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 (TCDC), deoxycholic acid (DCA), glycdeoxycholic acid (GDCA), taurodeoxycholic acid (TDCA), lithocholic acid (LCA), glycolithocholic acid (GLCA), taurolithocholic acid (TLCA), ursodeoxycholic acid (UDCA), glycoursoodeoxycholic 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:
 - o History of elevated ALP levels for at least 6 months
 - o 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
 - o Liver biopsy consistent with PBC
4. ALP $\geq 1.67 \times$ 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 oophorectomy, 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)

- 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 \geq 5x ULN; IgG \geq 2x ULN or smooth muscle antibody; interface hepatitis), and PBC (ALP \geq 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 m²,
 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 10³/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 \geq 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, thiazolidinediones (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)

- 12 months prior to inclusion visit and throughout the trial (up to 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 ½ 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.
21. Known hypersensitivity to the investigational product or any of its formulation excipients.
22. Evidence of any other unstable or untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease.

5. TRIAL PROCEDURES

The procedures performed at each visit are summarized in the study schedules ([Table 1](#) and [Figure 1](#)) and in [Section 3.5](#).

The Investigator will be asked, whenever possible, to schedule patient visits at the same time of the day for each patient. A patient may be seen at any time for reasons of safety.

During each visit, dietary, fluid and lifestyle and study recommendations will be repeated, vital signs will be measured, and the patient will be queried in the form of an open question regarding new or continuing events.

Procedures for premature discontinuation after SV are described in [Section 5.2](#).

5.1. STUDY RECOMMENDATIONS

5.1.1. Dietary, Fluid, and Lifestyle Restrictions

The following restrictions should be applied to patients in this trial from Screening through to the end of the study:

- Patients will be required to fast (no food or drink other than water) for at least 12 hours prior to all blood sampling (i.e., at each study visit). As such, patients should not consume any breakfast or take any medication (including study medication) in the morning prior to blood sampling. In case the patients do not fast before a visit, a new appointment will be scheduled within 2 days.
- Urine will be collected at each visit.
- On each study visit day, study treatment will be taken in fasted conditions after the blood sampling (which corresponds to the day of the visit).
- On visits with PK assessment, study treatment will be taken after the blood sampling for biological assessment and PK predose sampling. If possible, patient should remain fasting for 90 minutes after dosing.
- During the 48 hours preceding each study visit, patients should not perform strenuous exercise.
- Alcohol consumption should be limited during the study duration and registered in the eCRF. Alcohol consumption of more than 20 g per day for women and 30 g per day for men is considered abusive (see [Appendix IV](#)). A standard drink is equal to 14.0 grams (0.6 ounces) of pure alcohol. Generally, this amount of pure alcohol is found in:
 - 12 ounces/350 ml of beer (5% alcohol content)
 - 5 ounces/150 ml of wine (12% alcohol content)
 - 1.5 ounces/50 ml (40% alcohol content) distilled spirits or liquor (e.g., gin, rum, vodka, whisky).

Concomitant therapy is restricted and any change to treatment or introduction of a new treatment should be discussed with the Investigator before doing so (see [Section 7.12](#) and [Appendix III](#)).

5.2. PATIENT WITHDRAWAL AND PATIENT TREATMENT DISCONTINUATION RULES

5.2.1. Handling of Patient Withdrawal

Patients will be informed that they have the right to discontinue the study at any time, for any reason, without affecting future management and treatment.

5.2.2. Permanent Discontinuations of Study Drug

In some instances, it may be necessary for a patient to permanently discontinue study drug. The patient may be discontinued from study drug at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. In keeping with the ITT analysis, the patient will not be permanently discontinued from the study.

The reason for permanent discontinuation of study drug should be documented in the eCRF and the study Medical Monitor informed. If the discontinuation of study drug is due to an AE, the event should be documented in the eCRF.

Some possible reasons that may lead to permanent early study drug discontinuation include:

- In the opinion of the Investigator, any AE, SAE (described in [Section 8](#)), or significant change in a laboratory value that warrants permanent discontinuation of study drug therapy. Investigators are advised to call the study Medical Monitor prior to making such a decision
- Non-permitted concomitant medication (described in [Section 7.12](#) and [Appendix III](#))
- Female patients who are pregnant (see [Section 8.6.1](#)) or are breastfeeding or who do not agree to use a reliable method of birth control during the study will be permanently discontinued from study drug
- Non-compliance with the study treatment
- Uncooperative patient
- The patient requests to stop study drug permanently.

Patients permanently discontinued from study drug will be requested to stop taking study drug and attend an EOT Visit at least 16 days but no more than 30 days after the last administration of study drug (described in [Section 3.5.3](#)).

5.2.3. Patient Discontinuation From the Study

Patient discontinuation prior to the patient's completion of the study is expected to be low, occurring only if the patient withdraws consent, or if enrolling in any other clinical trial involving an IP, or enrolling in any other type of medical research judged not to be scientifically or medically compatible with this study.

At the time of discontinuing from the study, the Medical Monitor and IVRS/IWRS should be contacted, and, if possible, an EOT Visit should be conducted (see [Section 3.5.3](#)). The patient will be permanently discontinued from the study at that time with no further follow-up. The date the patient is withdrawn from the study and the reason for withdrawal should be appropriately documented in the eCRF. Where possible, patients withdrawn from the study will be followed until resolution of all their SAEs or until the unresolved SAEs are judged by the Investigator to have stabilized.

5.2.4. Patients Lost to Follow-Up

A patient would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Survival status will be collected within legal and ethical boundaries for all patients randomized, including those who did not get study drug. Survival status will be searched in public sources during the study close-out period. If survival status is determined, the patient will not be considered lost to follow-up.

5.2.5. Replacement

No patient replacements are permitted in this study.

5.2.6. Premature Discontinuation of the Study

Premature termination of this clinical trial may occur because of a Regulatory Authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of the study drug at any time.

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating patients within a reasonable period of time. As directed by the Sponsor, all trial materials must be collected and all eCRFs completed to the greatest extent possible.

Furthermore, the Investigator can decide to prematurely discontinue the study. In that event, the Investigator must notify the Sponsor immediately of his/her decision and give the reason in writing. Prompt compliance with this requirement is essential so that the Sponsor may comply with its regulatory obligations.

In all cases, ethics committee (IRB/IEC) and Health Authorities should be informed.

If the Investigator decides to prematurely discontinue the study, all test articles, eCRFs, and related study materials must be returned to the Sponsor.

5.3. PATIENT RESCREENING

Patient Rescreening is allowed in a screen failed patient if there is a change in the situation of the patient which allows him/her to fulfill inclusion/exclusion criteria. This will need sponsor approval. In case of rescreening, the patient will need to sign a new informed consent and will be entered as a new patient with a new patient number.

6. ASSESSMENTS

6.1. EFFICACY AND SAFETY ASSESSMENTS

6.1.1. Biological Assessments

All blood and urine samples for efficacy and/or for safety assessment (as described in [Table 2](#)) will be returned and analyzed by the central laboratory (BARC: Ghent – Belgium, or New York – USA).

A laboratory manual will be provided to each trial site.

The manual will outline the collection process and shipping requirements for the specific central laboratory. Blood sampling will be performed by trained personnel at each site. Blood samples will be processed and shipped as outlined in the laboratory manual. Refer to the laboratory manual for exact amounts of blood required for each test.

For all visits, reportable laboratory results (except serology) will be available at sites approximately 24 hours after receipt of samples. Final results will be sent to sites. Laboratory reports should be reviewed, signed, and dated by the Investigator as soon as they are received. The Investigator should comment upon out of range parameters and assess clinical significance.

The option to retest during the study is left to the Investigator's judgment. During Screening, retesting (to be performed at Retesting Screening visits) is limited to CPK, and HCV RNA (in case of positive HCV Ab at screening visit, or known cured HCV infection) as described [Section 3.5.5.1](#). Any other retest deemed necessary by the Investigator should be discussed with the Study Medical Monitors.

6.1.1.1. Laboratory Assessments

Clinical laboratory evaluations (including hematology, blood chemistry, and urinalysis) will be measured at every visit as described in [Table 2](#).

Hematology and urinalysis (dipstick done at central lab) will be measured at all visits. Both blood and urine sample will be transported to the central laboratory for testing and analysis.

At Screening, the Screening Visit chemistry panel will be measured.

The total chemistry panel and urine analysis will be measured at all visits from V1 to EOT or EOS visits respectively.

6.1.1.2. Urinary Pregnancy Tests

Urinary pregnancy tests will be supplied to each site to perform a pregnancy diagnostic at each visit during the study on WOCBP.

6.1.1.3. Serology (SB1)

Screening for a hepatitis panel and HIV antibodies will be performed at SV and include:

- HIV Ab I/II
- HBsAg

- 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 $-70^{\circ}\text{C}/-112^{\circ}\text{F}$ 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 $-80 \pm 10^{\circ}\text{C} (-112 \pm 50^{\circ}\text{F})$ 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 ($\geq 3 \times \text{ULN}$ and $\leq 5 \times \text{ULN}$), 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 ($\geq 3 \times \text{ULN}$ and $\leq 5 \times \text{ULN}$), 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 $>5 \times$ 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 $>3 \times$ ULN but $\leqslant 5 \times$ ULN: retest after 48 to 72 hours
 - If during the following retest:
 - ALT or AST remains $>3 \times$ ULN but $\leqslant 5 \times$ ULN: continue the drug with close serial monitoring (once a week)
 - ALT or AST increases to $>5 \times$ ULN: permanently discontinue patient from study drug and schedule EOT Visit
 - Increase in ALT or AST $>5 \times$ ULN: retest after 48 to 72 hours
 - If during the following retest:
 - ALT or AST remains $>5 \times$ ULN: permanently discontinue patient from study drug and schedule EOT Visit
 - ALT and AST reduces to $\leqslant 5 \times$ ULN: continue the drug with close serial monitoring (once a week).
 - Increase in ALT or AST $>3 \times$ ULN AND increase in total bilirubin > 2 ULN : permanently discontinue patient from study drug and schedule EOT Visit
 - Increase in ALT or AST $>3 \times$ ULN AND increase in INR >1.5 : permanently discontinue patient from study drug and schedule EOT Visit
 - Increase in ALT or AST $>3 \times$ 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 $>3 \times$ baseline value but $\leqslant 10 \times$ ULN: retest after 48 to 72 hours
 - ALT or AST remains $>3 \times$ baseline value but $\leqslant 10 \times$ ULN: continue the drug with close serial monitoring (once a week)
 - ALT or AST increases $> 5 \times$ baseline value or $>10 \times$ ULN: permanently discontinue patient from study drug and schedule EOT Visit
- Increase in ALT or AST $>3 \times$ baseline value AND increase in total bilirubin > 2 ULN: permanently discontinue patient from study drug and schedule EOT Visit
- Increase in ALT or AST $>3 \times$ baseline value AND increase in INR >1.5 : permanently discontinue patient from study drug and schedule EOT Visit

- 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

- Acute pancreatitis that occurred after 7 weeks of treatment in a patient treated with elafibranor 120 mg.
- Parkinson's disease in a patient treated for 12 months with elafibranor 120 mg, aged 76 years (in the risk group for Parkinson's disease, and with a family history of Parkinson's disease).

For 3 of the cases (atrial fibrillation, acute cholecystitis and pancreatitis, and Parkinson's disease) after later investigations, given the medical history of the patients or the time of occurrence of the event, relationship to elafibranor was judged as "no reasonable possibility" by the Sponsor.

For all completed studies to date with repeated administration of elafibranor (at least 14 days) from 80 mg/day up to 300 mg/day (MTD), numbers and percentages of frequency of non serious adverse drug reactions (AR, adverse events reported by investigators as possibly related or related to study drug) have been calculated compared to the total number of subjects treated with elafibranor and the total number of subjects treated with placebo.

Only non-serious adverse reactions with frequency $> 1\%$ are considered for reporting. Given the small numbers for each adverse reaction identified with a frequency $> 1\%$, an imbalance in frequency of occurrence compared to placebo is reported when the relative delta is $\geq 30\%$.

The common non-serious adverse drug reactions reported with repeated doses of at least 80 mg elafibranor per day are thus summarized in Table 3.

Table 3: Overview of the common non-serious adverse reactions ($> 1\%$ of patients treated with elafibranor) by system organ class (SOC) reported in completed elafibranor clinical studies with repeated administration of elafibranor (at least 14 days) from 80 mg/day up to 300 mg/day (MTD)

| System Organ Class | Adverse Reaction | Severity | Number of cases (Frequency %) |
|--|--|------------------|-------------------------------|
| Gastrointestinal disorders | Diarrhea | Mild to moderate | 17 (2.9%) |
| | Vomiting | Mild to moderate | 9 (1.5%) |
| General disorders and administration site conditions | Fatigue / Asthenia | Mild to moderate | 17 (2.9%) |
| Investigations | Hepatic enzymes increased (mainly transaminases) | Mild to severe | 11 (1.9%) |
| | Blood creatine phosphokinase increased | Mild to moderate | 6 (1.0%) |
| Musculoskeletal and connective tissue disorders | Myalgia | Mild to severe | 9 (1.5%) |
| Metabolism & nutrition disorders | Decreased appetite | Mild to severe | 9 (1.5%) |
| Skin and subcutaneous tissue disorders | Rash | Mild to moderate | 8 (1.4%) |
| Renal and urinary disorders | Renal failure/impairment | Mild to moderate | 7 (1.2%) |

Among the non-serious adverse reactions, the most frequent were gastro-intestinal disorders and general disorders. The first ones consisted mostly of diarrhea and vomiting. For general disorders, the main symptoms were fatigue / asthenia.

Other non-serious adverse reactions reported in more than 1% of patients concerned changes in biological parameters such as liver enzymes increase (mainly transaminases), CPK elevation, or increase of creatinine (reported by investigators as renal failure and/or impairment due to the calculation of creatinine clearance by MDRD based on creatinine). Myalgia, decrease of appetite and rash were also reported in more than 1% of patients but remain limited.

Regarding specific monitoring, although no signal for increase in CPK has been observed in the clinical trials, given the known effects of PPAR α agonists on the increase of CPK enzyme, this parameter is monitored in clinical trials. For this reason, it is recommended that investigators review these lab results in the course of clinical trials.

Other known effects of PPAR α agonists include the increase of creatinine, which was observed in our phase IIa and IIb trials, in a range of 5-10%. This increase was reversible at end of treatment. This should also be monitored in clinical trials.

Liver enzymes will also be monitored in clinical trials, with specific attention paid to drug induced liver injury (DILI).

Based on the findings of nonclinical reproductive and developmental toxicity studies performed to date, and in the absence of human pregnancy data, elafibranor may be classed in the “Possible human teratogenicity/fetotoxicity in early pregnancy” risk category according to the Clinical Trial

Facilitation Group (CTFG) document Recommendations related to contraception and pregnancy testing in clinical trials (September 2014).

As such, all clinical trials with elafibranor including WOCBP request a negative pregnancy test before Randomization, with effective contraceptive measures throughout the study. It is recommended to maintain the contraception up to 1 month after end of treatment. Pregnancy tests should be repeated as stated in each study protocol. In the absence of a clinical pharmacokinetic interaction study between elafibranor and contraceptive steroids, the exclusive use of hormonal contraceptive methods during clinical trials should be avoided, and they should be accompanied by barrier methods.

Conclusion

Based on the cumulative experience gathered to date, gastro-intestinal disorders such as diarrhea and vomiting, and asthenia or fatigue are considered common non serious adverse reactions reasonably associated with elafibranor. Most of them are of mild to moderate intensity. As previously, laboratory increases of serum creatinine or CPK should be monitored throughout clinical trials as this has been observed in Phase II trials, and is a known PPAR α agonist effect. Elevation of AT will be monitored as well as DILI. In the absence of human pregnancy data, double contraception should be maintained for women of childbearing potential participating in clinical trials with elafibranor treatment, up to 1 month after end of study treatment.

7. TREATMENTS

7.1. DESCRIPTION OF STUDY MEDICATIONS

Elafibranor (propanoic acid, 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl]phenoxy]-2-methylpropanoic acid) will be supplied as 80 mg or 120 mg white to off-white round coated tablets (of different size) with no printed inscription. The tablet contains elafibranor and inactive ingredients (microcrystalline cellulose, povidone, croscarmellose, anhydrous colloidal silica, magnesium stearate, Opadry II HP 85F18422).

Two Placebo tablets (each one of same size as corresponding active tablet) to match elafibranor 80 mg or 120 mg will be provided as a white to off-white round coated tablet with no printed inscription.

For additional information see Investigator's Brochure.

7.2. PACKAGING AND LABELING

7.2.1. Packaging

Elafibranor/placebo:

The primary packaging is composed of opaque polyamide/aluminum/PVC complex and aluminum foil blisters. This has been shown to be a suitable primary packaging for tablets.

Blisters will be packed in child proof wallets.

Each childproof wallet will contain 2 tablets (one of each size), containing either one active tablet and one placebo tablet or two placebo tablets to ensure the blind between the treatment arms.

Thirty-five wallets of two tablets will be packaged inside a period box. Three period boxes will be packaged into a carton.

7.2.2. Labeling

All labels for study drugs will meet all applicable requirements of the US Food and Drug Administration (FDA) and the EU annex 13 of Good Manufacturing Practices: Manufacture of Investigational Medicinal Products (February 2010) and /or other local regulations, as applicable.

Distribution of study drug will be performed according to the Good Distribution Practices.

Product cartons will be labeled with the protocol number, Sponsor's name and address, description of contents, storage conditions, expiry date, dosage instructions, and any other applicable items required by national and regional guidelines/regulations. The label will contain the statements "For clinical trial use only" or other similar/appropriate statements as well as the following instructions "Please return empty packaging and unused products to your doctor at your next visit." Details of carton and wallet labels are detailed in [Appendix V](#).

7.3. DOSAGE AND ADMINISTRATION OF ELAFIBRANOR AND PLACEBO

Patients will be informed to take two tablets per day of elafibranor 80 mg or 120 mg or placebo orally before breakfast with a glass of water each morning.

7.4. METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

If the patient fulfills all criteria to enter the treatment period, the Investigator or authorized, designated study coordinator/research nurse will register the patient in the IVRS/IWRS system to pre-randomize him/her (at least 1 week before V1).

The IVRS/IWRS will check if the Investigator or authorized, designated study coordinator/research nurse is authorized to use the system (identification number and access code). The IVRS/IWRS will then allocate the patient to a treatment group (placebo or elafibranor 80 mg or 120 mg) through a treatment number and will immediately forward the information to the Drug Distribution Centre which will be responsible to send to the site the corresponding treatment package allocated to the patient for the 12-week period, within 1 week at most. This labeled package will include 3 period boxes, one for each period [V1-V3], [V3-V4], and [V4-V5]. A confirmatory email will also be sent to the Investigator or authorized, designated study coordinator/research nurse, and to the Sponsor. The pharmacy will acknowledge receipt of the study drug in the IVRS/IWRS.

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

The randomization list will be generated by the IVRS/IWRS partner and will be kept under blinded condition to the study participants until the Blind-Review Meeting and the Sponsor authorization to unblind the trial.

7.5. STORAGE CONDITIONS

Elafibranor and placebo should be stored between +15°C and +25°C (59°F and 77°F). Storage conditions are specified on the label.

7.6. DISPENSING OF TREATMENT

The Investigator will receive one package per randomized patient, each package covering the full treatment period:

- Upon pre-randomization of each patient: the Investigator will receive a 1st package containing 3 period boxes (one for each of periods V1-V3, V3-V4 and V4-V5)

Each randomized patient will be given at each visit from V1 to V4 (except at V2) the study medication containing the adequate number of tablets to cover the drug administration over the entire period (i.e. covering at least 4 weeks of treatment + 5 days margin for each period):

- At Visit 1: the Investigator will dispense 1 labeled period boxes of 35 wallets of 2 tablets
- At Visit 3: the Investigator will dispense 1 labeled period boxes of 35 wallets of 2 tablets
- At Visit 4: the Investigator will dispense 1 labeled period boxes of 35 wallets of 2 tablets
- The patient will be instructed to take the treatment orally (2 tablets per day before breakfast) with a glass of water.

The Investigator will confirm each study drug dispensation in the IVRS/IWRS. A specific IVRS/IWRS procedure manual will be provided to the Investigator.

7.7. TREATMENT REPLACEMENT

Treatment replacement, if needed, will be explained in details in a specific IVRS/IWRS procedure manual which will be provided to the Investigator.

7.8. PROCEDURE FOR BLINDING

The Investigator, patient, and study personnel will be blinded to the treatment. Both elafibranor and placebo tablets and packaging are indistinguishable.

Identification numbers will be assigned to a patient at the Screening Visit. The number will also be reported in the eCRF. Upon completion of the Screening Visit, eligible patients will be randomly assigned to active treatment (elafibranor 80 or 120 mg) or placebo at the pre-randomization visit.

7.9. PROCEDURE FOR UNBLINDING

The randomization code may be broken by the Investigator when urgent action is required for the clinical management of the patient. For each patient, the list of treatment numbers allocated to the patient will be stored in the IVRS/IWRS. The Investigator will be able to unblind any treatment carton that was dispensed to the patient by connecting to the IVRS/IWRS (**24-hour and 7-day access**) and entering their identification number and access code. A back-up phone Interactive Response Technology (IRT) module will also be available should the site be unable to access the internet. The IVRS/IWRS will verify the authorization to unblind the entered treatment carton number and the screen will then display the treatment group. When completed, a blinded confirmatory e-mail will be sent to the Investigator and the Sponsor.

The reason for unblinding should be clearly and fully documented by the Investigator.

7.10. STUDY DRUG COMPLIANCE

From Visit 1 and at every subsequent visit while the patient is being treated with study drug, the patient will be directed to bring back all used and unused cartons and blisters. Compliance will be checked by the Investigator during those visits and recorded in the eCRF.

If treatment is interrupted, whatever the cause, duration and reason of the interruption should be documented.

7.11. TREATMENT ACCOUNTABILITY, RETRIEVAL AND DESTRUCTION.

The Investigator or pharmacist will acknowledge receipt for each study treatment on the day of receipt. A drug accountability record should be maintained by the person responsible for dispensing the trial medication to the patient.

All partially used or unused treatments will be inventoried by the monitor during and at the conclusion of the study.

On Sponsor request, the Drug Distribution Center will organize the retrieval of all treatments (used or unused) and will proceed to their destruction only after the Sponsor provides written authorization.

If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used and unused study drugs in accordance with the site SOP and always after the drug accountability has been performed by the monitor.

If drug is destroyed at the site, the Investigator must maintain accurate records for treatment cartons destroyed recording:

- Treatment carton (kit) number (see [Appendix V](#))
- Quantity destroyed
- Method of destruction
- Person who disposed of the drug
- Date of destruction

7.12. OTHER MEDICATION

7.12.1. Handling of Concomitant Medication

In a general manner, patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose. Similarly, any qualitative or quantitative change in concomitant therapy should be avoided, when possible (see [Table 4](#) and [Appendix III](#)). In the event such a change becomes necessary during the study, it should be recorded by the Investigator in the eCRF (including concomitant medications taken within 30 days prior to Screening) and information should be communicated to the Medical Monitor in order to evaluate the risk of DDIs. This includes drugs used on a chronic as well as on an “as needed” basis.

7.12.2. Non-Permitted Medication

See [Table 4](#) and [Appendix III](#).

The following medications are not allowed within the timeframe given in [Appendix III](#):

- Thiazoledinediones (glitazones [pioglitazone & rosiglitazone])
- Obeticholic acid
- Fibrates
- Budesonide and other systemic corticosteroids
- Azathioprine
- Colchicine
- Cyclosporine
- Methotrexate
- Mycophenolate mofetil/Pentoxyfilline
- Potentially hepatotoxic drugs (alpha-methyl-dopa, sodium valproic acid, isoniazide, nitrofurantoin)
- Antibodies or immunotherapy directed against interleukins or other cytokines or chemokines
- Indomethacin (NOTE: Other NSAIDs are allowed)

If it is identified after Randomization that these non-permitted drugs have been administered to a patient within the excluded timeframes, the patient will be permanently discontinued from the study drug (see [Section 5.2.2](#)).

7.12.3. Permitted Medication Under Conditions

See [Table 5](#) and [Appendix III](#).

The following medications are permitted under the condition of steady dosage prior to Screening:

- Ursodeoxycholic acid if taken for at least 12 months (and stable dose for ≥ 6 months) prior to screening visit
- Statins and ezetimibe provided the dosage is kept stable for at least 2 months prior to Screening
- Rifamycin and other anti-pruritis medication, if taken for at least 6 months prior to screening, and at stable dose for the 3 months prior to screening.

7.12.4. Permitted Medication

Any medications other than those listed above are permitted. However, the dosage of a current medication for a chronic disease should remain unchanged as far as possible in order to reduce the risk of unknown Drug-Drug Interactions.

In the event that additional concomitant therapy becomes necessary during the study (treatment and follow-up periods), it should be recorded by the Investigator in the eCRF. This includes drugs used on a chronic as well as on an “as-needed” basis. Patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose.

8. ADVERSE EVENT AND TOXICITY MANAGEMENT

8.1. DEFINITIONS

8.1.1. Adverse Events

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical (investigational) product and which does not necessarily have to have a causal relationship with this treatment will be considered as an AE. The term AE is synonymous with the term “adverse experience” as used by the Food and Drug Administration (FDA).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal product.

Examples of AE include (but are not limited to): abnormal test findings; clinically significant symptoms and signs; changes in physical examination findings; hypersensitivity; progression/worsening of pre-existing condition or underlying disease; recurrence of a pre-existing condition; lack of effect, complication, and termination of pregnancy.

Additionally, they may include the signs or symptoms resulting from: drug overdose, drug withdrawal, drug abuse, drug misuse, drug interactions, drug dependency, extravasation, exposure in utero.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to a change in trial dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be an AE by the Investigator or Sponsor.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

An AE does not include the following:

- Medical or surgical procedures performed; the condition that leads to the procedure may be an AE if applicable
- Pre-existing disease, condition or laboratory abnormalities present or detected before the Screening Visit that do not worsen
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset before the consent form is signed. Such a medical condition is considered to be pre-existing and should be documented on the medical history of the eCRF
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether

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.

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.

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.

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 < $1.67 \times \text{ULN}$ and total bilirubin within normal limit and > 15% decrease in ALP
 - ALP < $2 \times \text{ULN}$ 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)

- 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:

$$[(\text{End-point value} - \text{Baseline Value}) / \text{Baseline value}] \times 100.$$

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 $\alpha=0.05$.

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: AUC_{0→24} and C_{max} 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 be 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.

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.

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

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. QUALITY CONTROL & MONITORING PROCEDURES

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Good Clinical Practice (ICH topic E6), applicable regulatory requirements, and the current Declaration of Helsinki ([Appendix I](#)) and that valid data are entered into the eCRFs.

To achieve this objective, the Study Monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well-organized, and easily retrievable data.

Before enrolling any patients in this study, the Study Monitor will review the protocol, the brochure for clinical investigators, the eCRFs and instructions for their completion and return, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs with the Investigator. In addition, the Study Monitor will explain the Investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the study drug.

The Investigator will permit the representatives of Sponsor to monitor the study as frequently as the Sponsor deems is necessary to determine that data recording and protocol adherence are satisfactory. A Study Monitor from the CRO will be responsible for monitoring this clinical trial. To this end, the Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The eCRFs and related source documents, as well as drug accountability will be reviewed in detail by the monitor at each visit, in accordance with relevant SOPs and Good Clinical Practice (GCP; ICH topic E6) regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRFs, such as past medical history and secondary diagnoses.

Further details can be found in the Monitoring Plan.

It is essential that the Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Study Monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the Monitoring Visit to answer questions, and to provide any missing information.

All monitoring activities will be reported and archived in the Trial Master File.

11.2. ETHICAL PRINCIPLES

This protocol complies with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies ([Appendix I](#)), and the GCP guideline.

This trial also complies with applicable local regulatory requirements and laws of each country in which the study is performed, as well as any applicable guidelines.

11.3. QUALITY ASSURANCE

For the purpose of ensuring compliance with the protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by the Sponsor and/or designee and inspection by applicable regulatory authorities. The Investigator agrees to allow the

auditorsinspectors to have direct access to his/her study records for review, being understood that these personnel will adhere to all requirements for patient confidentiality, and as such will not disclose any personal identity or personal medical information.

As soon as the Investigator is notified of a future inspection by the Authorities, he/she will inform the Sponsor and authorize the Sponsor to participate at this inspection.

The confidentiality of the data verified and the anonymity of the patients should be respected during these inspections.

Clinical data associates from the Sponsor's representative will review the data for completeness and logical consistency. Additionally, the clinical data associates will use automated validation programs to help identify missing data, selected protocol violations, out of range data, and other data inconsistencies. Requests for data clarification or correction will be electronically provided to the investigative site for resolution. Clinical data associates will assure that corrections have been applied properly.

12. ETHICS AND REGULATORY

12.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The GCP guidelines and the US CFR Title 21 Section 56 (21 CFR 56) require that approval must be obtained from an Independent Ethics Committee (IRB/IEC) prior to participation of human patients in research studies. Prior to the study onset, the protocol, ICF, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient's legally acceptable representative must be approved by the IRB/IEC. The Sponsor will supply relevant material for the Investigator to submit to the IRB/IEC for the protocol's review and approval. Verification of the IRB's unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator. Documentation of the relevant IRB/IEC approval and of the IRB/IEC compliance with GCP guideline will be maintained by the site and will be available for review by the Sponsor or its designee or by the authorized members of regulatory agencies.

The Applicant must supply the Sponsor with written documentation of the initial favorable opinion of the clinical research before the start of the trial.

The study will not commence until favorable opinion has been obtained from the appropriate IRB/IEC.

If any alterations, other than changes of administrative nature only, are made to the study protocol, a formal protocol amendment will be issued. The IRB/IEC will be informed by the Investigator of subsequent protocol amendments and of SUSARs. Approval for protocol amendments will be transmitted in writing to the Investigator.

The amendment will not be implemented until IRB/IEC approval, except in cases where immediate implementation is necessary to eliminate or prevent imminent hazard to the patients. A protocol change intended to eliminate an apparent immediate hazard must be documented in an amendment, reported to the IRB/IEC within 5 working days, and submitted to the appropriate regulatory agencies in the required time frame.

If requested, the Investigator will permit audits by the IRB/IEC and regulatory inspections by providing direct access to source data/documents.

The Investigator will provide the IRB/IEC with progress reports at appropriate intervals (not to exceed one year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

12.2. COMPETENT AUTHORITY

In the same way as for IRB/IEC (see [Section 12.1](#)), when required by national regulation, approval from Competent Authorities (CA) should be granted before the beginning of the study. If applicable, Amendments will also be submitted to CA for approval.

12.3. PATIENT INFORMATION AND CONSENT

Written informed consent for the study will be obtained from each patient before protocol-specific procedures are carried out. The ICF used by the Investigator for obtaining the patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC). The ICF will be approved (along with the protocol) by the IRB/IEC.

In the case of any exploratory sub-studies, specific study documents will be prepared and IRB/IEC and authority approvals shall be obtained when applicable.

The Investigator or a person designated by the Investigator (according to applicable regulatory requirements), will explain the nature of the study and the action of the test product. The patients will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the designated IRB/IEC and will be signed and personally dated by the patient or by the patient's legally acceptable representative and by the person who conducted the informed consent discussion prior to protocol-specific procedures being performed. The Investigator must maintain the original, dated and signed ICF. A copy of the signed ICF must be given to the patient.

12.4. PATIENT CONFIDENTIALITY

The Sponsor will affirm and uphold the principle of the patient's right to protection against the invasion of privacy. Throughout this study and any subsequent data analyses, all data will be identified only by protocol number and patient number.

All unpublished information that the Sponsor gives to the Investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

The Investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor unless otherwise specified in the CSA.

12.5. DEFINITION OF THE END OF THE RESEARCH

End of the research corresponds to the end of participation (EOS or EOT Visit respectively) of the last patient participating in the research.

13. FINANCING AND INSURANCE

13.1. FINANCIAL ISSUES

Financial contracts will be signed between the Sponsor and the Investigator/Institution before initiation of the study.

13.2. INSURANCE AND PATIENT INJURY

The patients taking part in the trial will be covered by the insurance taken by the Sponsor for this trial, if they were to suffer any prejudice as a result of taking part in the trial.

In general, if a patient is injured as a direct result of the study drug, the Sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the patient's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the trial is taking place require additional payment of expenses, the Sponsor shall comply with such law or regulation.

The Sponsor certifies to have taken out an insurance policy to cover the financial consequences of its civil liability and that of everyone involved in the research, and notably that of the Investigators and their colleagues with regard to any accidents or damage concerning the administration of the drug or paraclinical examinations directly linked to the performance of the trial.

14. STUDY RESULTS AND PUBLICATION POLICY

14.1. STUDY REPORT

The final report will be written in ENGLISH upon completion of study and statistical analysis according to ICH E3 guideline. The report or part of it must be submitted to relevant authorities if applicable.

The CRO will prepare an integrated clinical and safety report. Prior to issuing the final CSR, the CRO will prepare a draft report for approval by the Sponsor. The report will be in accordance with the ICH E3 Guideline for Industry: Structure and Content of CSRs. The draft report will be submitted for Quality Assurance audit, the findings of which will be incorporated into the final version.

An electronic copy of the final CSR will be made available to the Sponsor. The study report will be provided in PDF and MS Word formats unless agreed otherwise by the CRO. Reports requiring specialized Sponsor formats/alternative computer software packages may be possible on request from the Sponsor but may involve extra time and cost. Electronic datasets will also be provided to the Sponsor on issuance of the final report.

After review by the Sponsor, a final CSR will be submitted to the Sponsor which incorporates the Sponsor's comments.

14.2. CONFIDENTIALITY AND OWNERSHIP OF DATA, USE OF THE STUDY RESULTS AND PUBLICATION

All materials, information (oral or written), and unpublished documentation provided to the Investigators (or any company/institution acting on their behalf), including this protocol, the patient CRFs, and the Investigator's Brochure, are the exclusive property of the Sponsor and may not be published, given, or disclosed, either in part or in whole, by the Investigator or by any person under his/her authority to any third party without the prior express consent of the Sponsor.

However, the submission of this protocol and other necessary documentation to the ethics committee (IRB/IEC) and the Competent Authority is expressly permitted, their members having the same obligation of confidentiality.

The Investigator shall consider all information, results, discoveries, records (accumulated, acquired, or deduced) in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, or records to any third party without the Sponsor's prior written consent.

The Sponsor retains exclusive ownership of all data, results, reports, findings, discoveries, and any other information collected during this study. Therefore, the Sponsor reserves the right to use the data from the present study, either in the form of CRFs (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the Health Authorities of any country.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

Furthermore, in the event that the study generates patentable results, the Investigator (or entity acting on his/her behalf according to local requirements) shall refrain from filing patent

application(s) on such results, which will be filed by the Sponsor or its designees in its own name and at its expense.

Clinical study will be registered on the open access website <http://www.clinicaltrials.gov> before the screening of the first patient in the study.

It is the policy of the Sponsor to encourage the presentation and/or publication of the results of their studies, using only clean, checked, and validated data in order to ensure the accuracy of the results.

The publication of study results will be agreed between the Sponsor and the Investigators.

At least 45 days in advance of proposed submission, the Investigator should forward a copy of the manuscript or abstract for review by the Sponsor, and, if necessary, delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein. The Sponsor may also request that the Sponsor's name and/or names of one or several of its employees appear or not appear in such publication.

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APPENDICES

APPENDIX I: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI



WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

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19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

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publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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APPENDIX III: PERMITTED/NON-PERMITTED MEDICATION

Table 3: Non-Permitted Medication and Condition

| Medications | When |
|--|--|
| Medication that may interact with absorption, metabolism, etc | |
| Indomethacin | From Pre-randomization up to EOT or EOS Visit |
| Same pharmacological class (PPAR agonists) | |
| Thiazoledinediones (glitazones) | From 2 months prior to screening visit up to EOT or EOS Visit |
| Fibrates | From 2 months prior to screening visit up to EOT or EOS Visit |
| Therapies for treatment of PBC | |
| Obeticholic acid | From 2 months prior to screening visit up to EOT or EOS Visit |
| Other Medications | |
| Budesonide and other systemic Corticosteroids | From 3 months prior to screening visit up to EOT or EOS Visit |
| Azathioprine | |
| Colchicine | |
| Cyclosporine | |
| Methotrexate | |
| Mycophenolate Mofetil | |
| Pentoxyfilline | |
| Alpha-methyl-dopa | |
| Sodium valproic acid | |
| Isoniazide | |
| Nitrofurantoin | |
| Antibodies or immunotherapy directed against interleukins or other cytokines or chemokines | From 12 months prior to screening visit up to EOT or EOS Visit |

Table 4: Permitted Medication and Condition

| Medications | When |
|---|---|
| Therapies for treatment of PBC | |
| Ursodeoxycholic acid | Taken for at least 12 months prior to the screening visit with Dose stability required from at least 6 months prior to Screening |
| Therapies for management of pruritus in PBC patients | |
| Rifamycin | Taken for at least 6 months prior to the screening visit Dose stability for at least 3 months prior to the screening visit, and the intent of maintaining that stable dose throughout the study up to EOT or EOS visit. |
| Lipid lowering therapy | |
| Statins | Dose stability required from at least 2 months prior to Screening |
| Ezetimibe | |

APPENDIX IV: ALCOHOL COMPARISON TABLE

| Alcohol type | Alcohol by volume (ABV) | Volume | | Amount of alcohol | |
|---|----------------------------|-------------|-----|--------------------|-------|
| | | Fluid ounce | mL | Units ² | grams |
| Beer | 3.5% | 12 | 350 | 0.7 | 9.8 |
| Beer | 5% | 12 | 350 | 1 | 14 |
| Cider | 7% | 12 | 350 | 1.4 | 19.6 |
| Distilled spirits or liquor ¹ | 40% | 1.5 | 45 | 1 | 14 |
| Wine | 12% | 5 | 150 | 1 | 14 |

¹ e.g., gin, rum, vodka, whiskey.

² Units calculated using the cleave Books calculator for units of drink, using the US definition of 1 unit of alcohol as 17.7 mL (14.0 g) of pure alcohol (<http://www.cleavebooks.co.uk/scol/ccalcoh3.htm>).

APPENDIX V: PRODUCT CARTON AND WALLET LABELING

| | Carton | Period box | Wallet |
|--|--------|------------|--------|
| Protocol number | X | X | X |
| Sponsor details | X | X | X |
| Site number | X | | |
| Subject ID | X | X | |
| Kit number | X | X | X |
| Visit number | - | X | |
| Lot number | X | X | X |
| Expiry date | X | X | X |
| Contents | X | X | X |
| Route of administration | X | X | X |
| Administration instructions | X | X | X |
| “For Clinical Trial Use only.” | X | X | X |
| “Keep out of reach of Children.” | X | X | X |
| Storage details | X | X | X |
| Instructions for product and package return at next visit | X | X | X |