CLINICAL PROTOCOL – PHASE 3

Protocol N° *GFT505B-319-1*

EudraCT *N°2019-004941-34*

IND number: *132202*

Version 6.0 – *13 February 2024*

A Double-blind, Randomized, Placebo-Controlled Study and Open-label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 mg in Patients with Primary Biliary Cholangitis with Inadequate Response or Intolerance to Ursodeoxycholic Acid

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Sponsor Signatory:

PPD

Claudia O. Zein, MD, MSc
Senior Medical Development Director
Rare Diseases Therapeutic Area

PPD

Date

Principal Investigator Signature Page

I have read and agree to Protocol N° GFT505B-319-1 Version 6.0 with Amendment 5 entitled 'A Double-blind, Randomized, Placebo-Controlled Study and Open-label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 mg in Patients with Primary Biliary Cholangitis with Inadequate Response or Intolerance to Ursodeoxycholic Acid'. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:

TITLE: [PRINCIPAL] INVESTIGATOR SIGNATURE:

DATE:

OFFICE: [ ]
[ ]
[ ]
[ ]
[ ]

STUDY CONTACTS

Protocol N°: GFT505B-319-1 / EudraCT N° 2019-004941-34 / IND n° 132202

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

	DOCUMENT HISTORY		
Document	**Version**	**Date**	**Status**
Amendment 5	6.0	13 February 2024	Effective
Amendment 4	5.0	20 December 2022	Superseded, Replaced by V6.0
Amendment 3	4.0	20 September 2022	Superseded, Replaced by V5.0
Amendment 2	3.0	18 March 2022	Superseded, Replaced by V4.0
Amendment 1	2.0	11 December 2020	Superseded, Replaced by V3.0
Original Protocol	1.0	22 July 2020	-

Amendment 5 (13 February 2024)

This amendment is considered to be non-substantial based on the criteria set forth in applicable regulations because it neither significantly impacts the safety or rights of participants nor the reliability and robustness of the data generated in the clinical trial.

Overall Rationale for the Amendment:

The protocol was amended to incorporate the information from the local addendum #1 for Germany dated 30 May 2023 and the typographical errors in the protocol version 4.0 dated 20 September 2022 until now mentioned separately in an erratum to the protocol.

Summary change table from previous version of the protocol

Any new or amended text in the protocol is indicated in bold (IS column). Deletions are marked in strikeout text (WAS column). Minor formatting and editing are not included.

Section	Was (Version 5.0, 20 December 2022)	Is (Version 6.0, 13 February 2024)	Rationale
All pages (header)	Protocol version 5.0 20 December 2022	Protocol version **6**.0 **13 February 2024**	
Clinical study protocol – Investigator signature page	**Principal Investigator Signature Page** I have read and agree to Protocol N° GFT505B-319-1 Version ~~5~~.0 entitled 'A Double-blind, Randomized, Placebo-Controlled Study and Open-label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 mg in Patients with Primary Biliary Cholangitis with Inadequate Response or Intolerance to Ursodeoxycholic Acid'. (…)	**Principal Investigator Signature Page** I have read and agree to Protocol N° GFT505B-319-1 Version **6**.0 **with Amendment 5** entitled 'A Double-blind, Randomized, Placebo-Controlled Study and Open-label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 mg in Patients with Primary Biliary Cholangitis with Inadequate Response or Intolerance to Ursodeoxycholic Acid'. (…)	
Clinical Study Synopsis	**Table 1: Study General Assessment Schedule - Footnote "l".** l. If premature study drug discontinuation during DB period, end of treatment (EOT) DB Visit should be performed between 16 and 30 days after last drug intake, and patients will continue in the study until V8, or until the last completed ~~V6~~ whichever occurs first. In case the EOT DB visit occurs within the time window of the next scheduled visit, EOT DB visit replaces the scheduled visit. If premature study drug discontinuation occurs during LTE period, an EOT LTE visit will be performed between 16 and 30 days after last drug intake	**Table 1: Study General Assessment Schedule - Footnote "l".** l. If premature study drug discontinuation during DB period, end of treatment (EOT) DB Visit should be performed between 16 and 30 days after last drug intake, and patients will continue in the study until V8, or until the last completed **V5** whichever occurs first. In case the EOT DB visit occurs within the time window of the next scheduled visit, EOT DB visit replaces the scheduled visit. If premature study drug discontinuation occurs during LTE period, an EOT LTE visit will be performed between 16 and 30 days after last drug intake**.**	Correction of a typo error: This footnote "l" is not in line with the period instruction mentioned in the footnote "j" indicating that the Last Visit in the double-blind period (DBP) for the other patients is anchored to Last Visit 5 completed in the study as opposed to Last Visit 6.

Section	Was (Version 5.0, 20 December 2022)	Is (Version 6.0, 13 February 2024)	Rationale
1. Introduction and rationale	Elafibranor has been developed by Genfit for the treatment of PBC. In December 2021, Genfit and IPSEN ("the partner") entered into an exclusive licensing agreement for elafibranor, which gives the partner, the exclusive worldwide license for the future development of elafibranor in PBC, with the exception of China, Taiwan, Hong-Kong and Macau. The transfer of sponsorship from Genfit to Ipsen ~~is anticipated to take~~ place within approximately 30 days of top line results for the double-blind portion of the study (part A).	Elafibranor has been developed by Genfit for the treatment of PBC. In December 2021, Genfit and IPSEN ("the partner") entered into an exclusive licensing agreement for elafibranor, which gives the partner, the exclusive worldwide license for the future development of elafibranor in PBC, with the exception of China, Taiwan, Hong-Kong and Macau. The transfer of sponsorship from Genfit to Ipsen **took** place **on 8th August 2023,** within approximately 30 days of top line results for the double-blind portion of the study (part A).	Integration of this information from the local protocol addendum #1 for Germany dated 30May2023
1. Introduction and rationale 1.3.1. Phase 1 Program	A Phase 1 program to assess the safety and the tolerability, as well as the PK profile, of elafibranor currently comprises ~~13~~ completed ~~and 4 ongoing~~ clinical studies. ~~As of 31 July 2022 (the date of the most recent Development Safety Update Reports (DSUR) update (Development Safety Update Reports, 2019), 755 volunteers had been randomized in these studies, including 650~~ healthy and lean subjects, ~~60~~ overweight or obese but otherwise healthy subjects, ~~12~~ subjects with type 2 diabetes, 13 with renal impairment (ESRD) and 20 with hepatic impairment (Child-Pugh class A, B or C). Elafibranor daily doses ranged between 5 mg and 360 mg, with a maximum treatment duration of ~~14 to 16~~ days. *Additional information can be found in the IB.*	A Phase 1 program to assess the safety and the tolerability, as well as the PK profile, of elafibranor currently comprises **19** completed clinical **pharmacology** studies. **At least 732** healthy and lean subjects, **90** overweight or obese but otherwise healthy subjects, **59** subjects with type 2 diabetes, 13 with renal impairment (ESRD) and 20 with hepatic impairment (Child-Pugh class A, B or C). Elafibranor daily doses ranged between 5 mg and 360 mg, with a maximum treatment duration of **18** days. *Additional information can be found in the IB.*	Updated status, number and exposure of clinical pharmacology studies with elafibranor

Section	Was (Version 5.0, 20 December 2022)	Is (Version 6.0, 13 February 2024)	Rationale
3. Study Design 3.5.2. DB period (Week 0 to max Week 104)	(…) In case of premature study drug discontinuation prior to visit 8 during DB period, EOT DB visit should be performed between 16 and 30 days after last drug intake. The patients will continue in the study until V8, or until the last completed ~~V6~~ whichever occurs first, and will complete all visit procedures except liver biopsy and PK (if not done prior to study drug discontinuation). (…)	(…) In case of premature study drug discontinuation prior to visit 8 during DB period, EOT DB visit should be performed between 16 and 30 days after last drug intake. The patients will continue in the study until V8, or until the last completed **V5** whichever occurs first, and will complete all visit procedures except liver biopsy and PK (if not done prior to study drug discontinuation). (…)	Correction of a minor typographical error pertaining to the timing of the end of the DBP for the end of treatment (EOT) participants. This instruction is not in line with the period instruction mentioned in the same section where it is noted "(…). *The last V5 completed for all randomized patients will trigger the switch to open-label LTE for all patients still in DB.* (…)", meaning that the Last Visit in the DBP for the randomized patients is anchored to Last Visit 5 completed in the study as opposed to Last Visit 6.
5. Study Procedures 5.2.1. Permanent discontinuation of study drug/withdrawal from study	(…) Patients permanently discontinued from study drug during the DB period will perform an EOT DB visit within 16-30 days after the last drug intake and will continue to attend all scheduled visits until the visit 8 (without undergoing histology or PK assessment, if applicable), or until the last completed ~~V6~~ whichever occurs first. (…)	(…) Patients permanently discontinued from study drug during the DB period will perform an EOT DB visit within 16-30 days after the last drug intake and will continue to attend all scheduled visits until the visit 8 (without undergoing histology or PK assessment, if applicable), or until the last completed **V5** whichever occurs first. (…)	Correction of a minor typographical error pertaining to the timing of the end of the DBP for the EOT participants. This instruction is not in line with the period instruction for the Last Visit in the DBP for the randomized patients that is anchored to Last Visit 5 completed in the study as opposed to last Visit 6

Section	Was (Version 5.0, 20 December 2022)	Is (Version 6.0, 13 February 2024)	Rationale
5. Study Procedures 5.2.1. Permanent discontinuation of study drug/withdrawal from study	(...) Some possible reasons that may lead to permanent early study drug discontinuation include: • At the discretion of the Investigator, any AE, AESI, SAE (described in Section 8.1.1 and 8.1.2), or significant change in a laboratory value or worsening or disease progression that would require in the patient's best interest, initiation of any standard of care prohibited in the study. Investigators are advised to call the Medical Monitor prior to making such a decision • Non-permitted concomitant medication (described in Section 7.12 and 16.2) • 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 • Non-compliance with the study treatment • Uncooperative patient • The patient requests to stop study drug permanently. (...)	(...) Some possible reasons that may lead to permanent early study drug discontinuation include: • At the discretion of the Investigator, any AE, AESI, SAE (described in Section 8.1.1 and 8.1.2), or significant change in a laboratory value **(described in Section 6.3.1, 6.3.2, 6.3.3, 6.3.4 and 6.3.5)** or worsening or disease progression that would require in the patient's best interest, initiation of any standard of care prohibited in the study. Investigators are advised to call the Medical Monitor prior to making such a decision • Non-permitted concomitant medication (described in Section 7.12 and 16.2) • 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 • Non-compliance with the study treatment • Uncooperative patient • The patient requests to stop study drug permanently. (...)	Addition of a cross-reference to the rules described in section 6.3 "Important Specific Biological Considerations And Patient Discontinuation Rules".

Section	Was (Version 5.0, 20 December 2022)	Is (Version 6.0, 13 February 2024)	Rationale
6. Assessments 6.4.1. Summary of safety data	(...) A Phase 1 program has been conducted to assess the safety and tolerability, as well as the PK profile, of elafibranor. Elafibranor daily doses ranged between 5 mg and 360 mg, with a treatment duration up to ~~16~~ days. (...) Based on the cumulative experience gathered to date, gastro-intestinal disorders (nausea~~-~~, vomiting ~~renal and urinary disorders, and pruritus~~ are considered common non-serious adverse reactions reasonably associated with elafibranor; most of them are of mild to moderate severity. ~~Of note~~, these AEs are to be monitored as AESIs (see Section 8.1.2) as well as other AESIs which could be considered as class effect AEs. (...)	(...) A Phase 1 program has been conducted to assess the safety and tolerability, as well as the PK profile, of elafibranor. Elafibranor daily doses ranged between 5 mg and 360 mg, with a treatment duration up to **18** days. (...) Based on the cumulative experience gathered to date, gastro-intestinal disorders (**abdominal pain,** nausea, vomiting, **diarrhoea, constipation)** are considered common non-serious adverse reactions reasonably associated with elafibranor; most of them are of mild to moderate severity. **In addition**, these AEs are to be monitored as AESIs (see Section 8.1.2) as well as other AESIs which could be considered as class effect AEs. ***Additional details are provided in IB.*** (...)	Update of the maximum treatment duration in Phase 1 program Update of the most common non-serious adverse reactions based on the cumulative experience gathered to date

Amendments to be implemented in the following documents

Informed consent form	Yes ☐ No ☒
Case report form (CRF)	Yes ☐ No ☒
Statistical analysis plan (SAP)	Yes ☐ No ☒

LIST OF ABBREVIATIONS

Ab	Antibody
ABV	alcohol by volume
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AFP	Alfa-fetoprotein
AIH	autoimmune hepatitis
ALCOA	attributable, legible, contemporaneous, original and accurate
ALD	alcoholic liver disease
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMA	anti-mitochondrial antibodies
ANA	antinuclear antibodies
AST	aspartate aminotransferase
AT	aminotransferase
AUCss	Area Under Curve steady state
BP	blood pressure
BUN	blood urea nitrogen
C4	serum 7α-hydroxy-4-cholesten-3-one
CA	cholic acid
CCl4	carbon tetrachloride
CDCA	chenodeoxycholic acid
CEC	clinical events committee
CFR	Code of Federal Regulations
CI	confidence interval
CK-18	cytokeratin-18
CKD-EPI	Chronic Kidney Disease - Epidemiology Collaboration
CPK	creatine phosphokinase
CRF	case report form
CRO	clinical research organization
CSR	clinical study report
CT	computed tomography
CTA	Clinical Trial Agreement
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
DB	double blind
DCA	deoxycholic acid
DDI	drug-drug interaction
DEXA	dual-energy X-ray absorptiometry
DILI	drug-induced liver injury
DSMB	data safety monitoring board
DSUR	development safety update report
EAIR	exposure adjusted incidence rates
EASL	European Association for the Study of the Liver

ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EOT	end of treatment
ePRO	electronic patient-reported outcomes
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FGF19	fibroblast growth factor 19
FPG	Fasting plasma glucose
GCA	glycocholic acid
GCDCA	glycochenodeoxycholic acid
GCP	Good Clinical Practice
GDCA	glycodeoxycholic acid
GGT	gamma-glutamyl transferase
GLCA	glycolithocholic acid
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HCV Ab	hepatitis C virus Antibody
HDL-C	High-density lipoprotein cholesterol
hHSC	human hepatic stellate cells
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
hsCRP	high sensitivity C-reactive protein
IB	Investigator’s Brochure
ICE	Intercurrent event
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IXRS	interactive voice/web response system
LCA	lithocholic acid
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
LTE	long term extension
LVDB	last visit double blind

MAR	missing at random
MCP	monocyte chemotactic protein
MDR3	multidrug resistance protein type 3
MDRD	modification of diet in renal disease
MedDRA	medical dictionary for regulatory activities
MELD-Na	Model for End-Stage Liver Disease-Sodium
MMRM	mixed model with repeated measurement
MRI	magnetic resonance imaging
NA	not applicable
NASH	nonalcoholic steatohepatitis
NF-κB	nuclear factor kappa B
NOAEL	no observed adverse effect level
NRS	numeric rating scale
OATP1B3	organic anion transporting polypeptide 1B3
OCA	obeticholic acid
PAI	Plasminogen activator inhibitor
PBC	Primary biliary cholangitis
PBI	placebo-based multiple imputation
PDGF	platelet-derived growth factor
PGIC	patient global impression of change
PGIS	patient global impression of severity
PK	pharmacokinetics
PKS	pharmacokinetics set
PP	per-protocol
PPAR	peroxisome proliferator-activated receptor
PRO	patient reported outcome
PROMIS	Patient Reported Outcome Measurement Information System
PSC	Primary sclerosing cholangitis
PT	prothrombin time
QoL	quality of life
RNA	ribonucleic acid
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDV	Source data verification
SMA	smooth muscle antibodies
SOP	standard operating procedure
SS	safety set
SUSAR	suspected unexpected serious adverse reaction
SV	screening visit
TB	total bilirubin
TC	total cholesterol
TCA	taurocholic acid
TCDCA	taurochenodeoxycholic acid
TDCA	taurodeoxycholic acid

TE	transient elastography
TG	triglycerides
TGF-β	transforming growth factor beta
TIPS	transjugular intrahepatic portosystemic shunts
TLCA	taurolithocholic acid
TNFα	tumor necrosis factor-alpha
UDCA	ursodeoxycholic acid
UK	United Kingdom
ULN	upper limit of normal
Urine ACR	Urine albumin to creatinine ratio
UV-LLNA	UV- local lymph node assay
VLDL	very low density lipoprotein
WBC	white blood count
WOCBP	women of childbearing potential

CLINICAL STUDY SYNOPSIS

Sponsor:	Study Drug:	Protocol Number:
IPSEN PHARMA SAS	Elafibranor	GFT505B-319-1

Title of the study:

A Double-blind, Randomized, Placebo-Controlled Study and Open-label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 mg in Patients with Primary Biliary Cholangitis with Inadequate Response or Intolerance to Ursodeoxycholic Acid

Phase: 3

Indication: Primary Biliary Cholangitis (PBC)

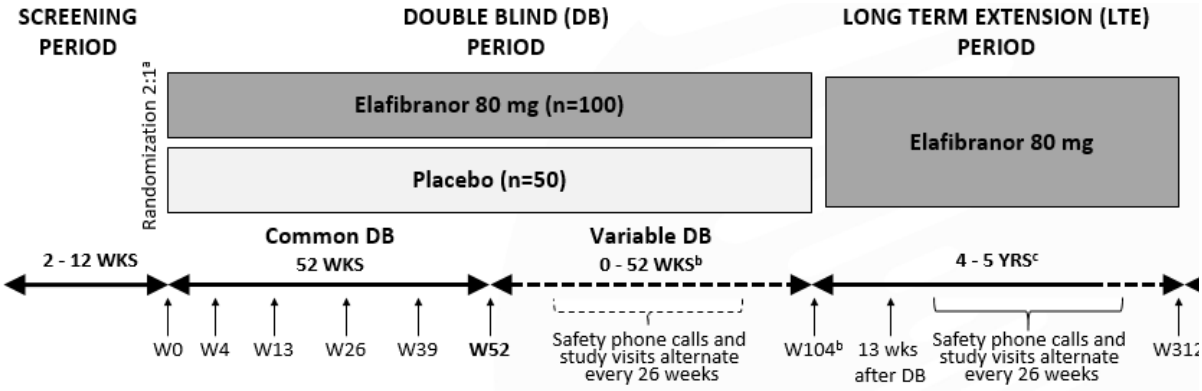
Study Design and dose levels:

This is a phase 3 double-blind (DB), randomized, placebo-controlled study with an open-label long term extension (LTE) evaluating the efficacy and safety of Elafibranor 80 mg once daily versus placebo in patients with PBC and inadequate response or intolerance to ursodeoxycholic acid (UDCA).

In the DB period, patients will be randomized in a 2:1 ratio to receive Elafibranor 80 mg or placebo, once daily. The DB period will last until the last completed week 52 (V6) or until a maximum of 104 weeks DB period, whichever happens first, to further collect safety and clinical outcomes data in a DB manner. After the DB period, all patients will receive Elafibranor 80 mg daily for up to 5 years during the LTE period.

When applicable, patients should continue their pre-study dose of UDCA throughout the study participation.

Schema 1: GFT505B-319-1 Study Design



Footnotes:

a. If receiving UDCA at randomization, continue throughout study participation
b. The Variable DB duration is an additional 52 weeks after end of Common DB (W104) or until the last completed V6 (W52), whichever occurs first
c. The LTE duration is up to 5 years after end of the DB period or until the patient's total treatment duration is 6 years, whichever occurs first
d. Safety follow-up 4 weeks after last dose of study drug

For exploratory purposes, all patients enrolled will be invited to participate in the following voluntary procedures, which will require separate informed consent:

- collection of biobank samples for additional research on biomarkers associated with PBC
- collection of liver biopsy samples (at baseline and week 52)

Route of Administration: Oral

Primary Objective:

To evaluate the effect of Elafibranor (80 mg/day) on cholestasis as defined by the primary endpoint over 52 weeks of the treatment compared to placebo

Key Secondary Objectives:

To evaluate the effect of Elafibranor (80 mg/day) on normalisation of alkaline phosphatase (ALP) over 52 weeks of the treatment compared to placebo

To evaluate the effect of Elafibranor (80 mg/day) on pruritus through 52 weeks of the treatment compared to placebo in patients with baseline PBC Worst Itch NRS score ≥4

To evaluate the effect of Elafibranor (80 mg/day) on pruritus through 24 weeks of the treatment compared to placebo in patients with baseline PBC Worst Itch NRS score ≥4

Secondary Objectives:

1) To evaluate the effect of Elafibranor (80 mg/day) over 52 weeks of treatment compared to placebo on:
    a) Hepatobiliary injury and liver function markers
    b) Inflammation and hepatic fibrosis
    c) Lipid parameters
    d) Bile acids
    e) Pruritus Patient Reported Outcomes (PROs)
    f) Patient-reported Fatigue
    g) Patient-reported Sleep
    h) Health-related Quality of Life (HRQoL)
    i) Health utility
    j) Markers of bone turnover and bone density
    k) Safety and tolerability
2) To determine the pharmacokinetics (PK) parameters of elafibranor and its active metabolite GFT1007, at steady state following daily oral administration at 80 mg in PBC patients
3) To evaluate the effect of Elafibranor (80 mg/day) during the LTE period on:
    a) Safety and tolerability
    b) Maintenance of efficacy from the DB period

Exploratory objectives (for the patients having consented to participate):

1) To constitute a biobank for discovery and validation of biomarkers associated with PBC
2) Based on histology:
    a) To assist the interpretation of efficacy and safety results of elafibranor
    b) To explore the correlation of fibrosis scores with non-invasive markers of fibrosis (liver stiffness, ELF test and ProC3)

Patient Population: Patients with PBC and inadequate response or intolerance to UDCA

Number of Randomized Patients (Approximately): 150

Number of Participating Centers (Approximately): 120

Number of Participating Countries (Approximately): 15

Study Duration per Patient: Up to approximately 6 years, or 328 weeks (2 to 12 weeks for the screening period, 52 to 104 weeks for the DB period, 208 to 260 weeks for the LTE period, and 4 weeks for safety follow-up).

Inclusion Criteria:

Patients must meet all of the following inclusion criteria to be eligible for randomization into the study:

1) Must have provided written informed consent and agree to comply with the study protocol
2) Males or females age of 18 to 75 years inclusive at first Screening Visit (SV)
3) PBC diagnosis as demonstrated by the presence of ≥ 2 of the following 3 diagnostic criteria:
   a. History of elevated ALP levels for ≥ 6 months prior to randomization (V1)
   b. 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 (ANA)
   c. Liver biopsy consistent with PBC
4) ALP ≥ 1.67x upper limit of normal (ULN) (based on two values – see section 3.5.1)
5) Total bilirubin (TB) ≤ 2x ULN

   To ensure inclusion of a relevant ratio of patients with substantial risk of long-term clinical outcomes or moderate disease stage, approximately 10% of randomized patients will be moderately advanced per Rotterdam Criteria (TB > ULN or Albumin < lower limit of normal [LLN]) and approximately 20% will have a TB > 0.6 x ULN (patients at risk of progression)
6) Must have at least 4 available values for PBC Worst Itch Numeric Rating Scale (NRS) during each of the 7 day intervals in the 14 days prior to randomization (V1), for a total of at least 8 values for PBC Worst Itch NRS in the last 14 days prior to randomization (V1)
7) UDCA for at least 12 months (stable dose ≥ 3 months) prior to screening, or unable to tolerate UDCA treatment (no UDCA for ≥ 3 months) prior to screening (per country standard-of-care dosing)
8) If on colchicine must be on a stable dose for ≥ 3 months prior to screening
9) Medications for management of pruritus (e.g., cholestyramine, rifampin, naltrexone or sertraline) must be on a stable dose for ≥ 3 months prior to screening
10) Patients taking statins or ezetimibe must be on a stable dose for ≥ 2 months prior to screening
11) Females participating in this study must be of non-child bearing potential or must be using highly effective contraception for the full duration of the study and for 1 month after the last drug intake:
    - Non-child bearing potential: cessation of menses for at least 12 months due to ovarian failure or surgical sterilization such as bilateral oophorectomy, or hysterectomy
    - Highly effective contraception includes:
      a. Combined (estrogen and progrestogen containing) hormonal contraception associated with inhibition of ovulation, oral, intravaginal or transdermal
      b. Progestogen-only hormonal contraception associated with inhibition of ovulation, oral, injectable or implantable
      c. Intrauterine device (IUD)
      d. Intrauterine hormone release system (IUS)
      e. Bilateral tubal occlusion
      f. Vasectomized partner

g. Sexual abstinence, if required by local IRB/IEC regulations and/or considered adequate by National laws (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient)

12) For patients who consent to have liver biopsy samples collected, patients in whom it is safe and practical to proceed with a liver biopsy, and who agree to have:
    - 1 liver biopsy during the Screening Period (if no historical biopsy within 6 months before screening is available)
    - 1 liver biopsy after 52 weeks of treatment

Exclusion Criteria:

Patients presenting any of the following exclusion criteria will not be eligible for randomization into the study:

1) History or presence of other concomitant liver disease including:
    a) Positive anti-hepatitis A virus (HAV) immunoglobulin M (IgM) antibodies or positive hepatitis B surface antigen (HBsAg) or positive anti-hepatitis C virus (HCV) ribonucleic acid (RNA) (tested for in case of known cured HCV infection or positive HCV Ab at screening)
    b) Primary sclerosing cholangitis (PSC)
    c) Alcoholic liver disease (ALD)
    d) Autoimmune hepatitis (AIH) or if treated for an overlap of PBC with AIH, or if there is suspicion and evidence of overlap AIH features, that cannot be explained alone by insufficient response to UDCA
    e) Nonalcoholic steatohepatitis (NASH)
    f) Gilbert's Syndrome (exclusion due to interpretability of bilirubin levels)
    g) Known history of alpha-1 antitrypsin deficiency
2) Clinically significant hepatic decompensation, including:
    a) History of liver transplantation, current placement on a liver transplant list, current Model for End-Stage Liver Disease-Sodium (MELD-Na) score ≥ 12 linked to hepatic impairment
    b) Patients with cirrhosis/portal hypertension complications, including known esophageal varices, ascites, history of variceal bleeds or related interventions (e.g., insertion of variceal bands or transjugular intrahepatic portosystemic shunts [TIPS]), and hepatic encephalopathy, history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma
    c) Hepatorenal syndrome (type I or II)
3) Medical conditions that may cause non-hepatic increases in ALP (e.g., Paget's disease) or which may diminish life expectancy to < 2 years, including known cancers
4) Patient has a positive test for Human Immunodeficiency Virus (HIV) Type 1 or 2 at screening, or patient is known to have tested positive for HIV
5) Evidence of any other unstable or untreated clinically significant immunological, endocrine, hematologic, gastrointestinal, neurological, or psychiatric disease as evaluated by the investigator; other clinically significant medical conditions that are not well controlled

6) 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 screening visit (SV1)
7) For female patients: known pregnancy, or has a positive serum pregnancy test, or lactating
8) Administration of the following medications are prohibited as specified below:
    a) 2 months prior to screening: fibrates and glitazones
    b) 3 months prior to screening: azathioprine, cyclosporine, methotrexate, mycophenolate, pentoxifylline, budesonide and other systemic corticosteroids (parenteral and oral chronic administration only); potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid isoniazid, or nitrofurantoin)
    c) 12 months prior to screening: antibodies or immunotherapy directed against interleukins (ILs) or other cytokines or chemokines
    d) For patients with previous exposure to OCA, OCA should be discontinued 3 months prior to screening
9) Patients who are currently participating in, plan to participate in, or have participated in an investigational drug study or medical device study containing active substance within 30 days or five half-lives, whichever is longer, prior to screening; for patients with previous exposure to seladelpar, seladelpar should be discontinued 3 months prior to screening.
10) Patients with previous exposure to elafibranor
11) SV value of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 5x ULN
12) For patients with AT or TB values >ULN at SV1, Variability of AT or TB > 40% (see section 3.5.1)
13) SV value of albumin < 3.0 g/dL
14) Severely advanced patients according to Rotterdam criteria (TB > ULN and albumin < LLN)
15) SV value of international normalized ratio (INR) > 1.3 due to altered hepatic function
16) SV value of creatine phosphokinase CPK > 2X ULN
17) Screening serum creatinine > 1.5 mg/dL
18) Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney failure damage or estimated glomerular filtration rate [eGFR] < 60 mL/min/1,73 m2) calculated by modification of diet in renal disease (MDRD)
19) Platelet count < 150 X 10^3/µL
20) Alfa-fetoprotein (AFP) > 20 ng/mL with 4-phase liver computed tomography (CT) or magnetic resonance imaging (MRI) suggesting presence of liver cancer
21) Known hypersensitivity to the investigational product or to any of the formulation excipients of the elafibranor or placebo tablet
22) Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain

Randomization:

Patients who satisfy all eligibility criteria will be randomized in a 2:1 ratio to one of the following groups:

- Elafibranor 80 mg
- Placebo

A central randomization system (Interactive Voice/Web Response system (IXRS)) will be used.

The randomization will be stratified on two factors (ALP > 3 x ULN or bilirubin > ULN **and** Worst Itch score averaged - over the 14 days preceding baseline - ≥ 4) at baseline (V1). During the LTE period, all patients will receive Elafibranor 80 mg, once daily, for up to 5 years.

To ensure inclusion of a relevant ratio of patients with substantial risk of long term clinical outcomes or moderate disease stage, approximately 15 patients (approximately10% of the total randomized patients) will present a TB above ULN or albumin below LLN and approximately 30 patients (approximately 20% of the total randomized patients) will present a TB above 0.6x ULN.

Criteria for Evaluation:

Primary Endpoint:

Response to treatment at week 52 defined as ALP < 1.67 x ULN and TB ≤ ULN and ALP decrease ≥ 15%.

Secondary Endpoints:

Key Secondary Endpoints:

1) Response to treatment based on ALP normalization at week 52.

2) Change in pruritus from baseline through week 52 on PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4.

3) Change in pruritus from baseline through week 24 based on PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4

Other Secondary Endpoints:

1) Change from baseline in ALP at 4, 13, 26, 39 and 52 weeks
2) ALP response defined as 10%, 20% and 40% ALP reduction from baseline at week 52
3) Response to treatment at week 52 according to:
   a) ALP < 1.5x ULN, ALP decrease ≥ 40% and TB ≤ ULN
   b) ALP < 3x ULN, AST <2x ULN and TB < 1 mg/dL (Paris I)
   c) ALP ≤ 1.5x ULN, AST ≤ 1.5x ULN and TB ≤ ULN (Paris II)
   d) TB response rate of 15% change
   e) Normalization of abnormal TB and/or albumin (Rotterdam)
   f) TB ≤ 0.6 x ULN
   g) ALP ≤ 1.67x ULN and TB ≤ 1 mg/dL [1]
   h) No worsening of TB defined as level of TB ≤ ULN at week 52 or no increase from baseline of more than 0.1XULN at week 52
   i) Complete biochemical response defined as normal ALP, TB, AST, ALT, albumin and INR
4) PBC risk scores at week 52: United Kingdom (UK) PBC score [2] and GLOBE score [3]

5) Response based on bilirubin normalization (TB ≤ ULN) at week 52
6) Response based on albumin normalization at week 52
7) Change from baseline to week 52 in hepatobiliary injury and liver function as measured by AST, ALT, gamma-glutamyl transferase (GGT), 5' NT, total and conjugated bilirubin, albumin, INR and ALP fractionated (hepatic)
8) Change from baseline to week 52 in biomarkers of inflammation as measured by high-sensitivity C-Reactive Protein (hsCRP), fibrinogen, haptoglobin and tumor necrosis factor-alpha (TNF-α)
9) Change from baseline to week 52 in immune response as measured by immunoglobulin G (IgG) and IgM
10) Change from baseline to week 52 in biomarkers, and non-invasive measures of hepatic fibrosis as measured by enhanced liver fibrosis (ELF)(HA, PIINP, TIMP-1), plasminogen activator inhibitor-1 (PAI-1), transforming growth factor beta (TGF-β), cytokeratin-18 (CK-18) (M65 and M30), Pro-C3 and liver stiffness measured by Transient Elastography (TE) (continuous)
11) Change from baseline to week 52 in lipid parameters as measured by total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), calculated VLDL-C and TG
12) Change from baseline to week 52 in fasting plasma glucose (FPG)
13) Change from baseline to week 52 in bile acids and biomarkers of bile acid synthesis as measured by bile acids, serum 7α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF-19)
14) Proportion of patients with no worsening of pruritus from baseline through week 52 and through week 24 as measured by the PBC Worst Itch NRS
15) Proportion of responders in PBC Worst Itch NRS according to clinically meaningful change; at least 30% reduction; and one point, two points or three points decrease in score from baseline through week 52 and through week 24 in patients with a baseline NRS score≥ 4
16) Change from baseline to week 52 in 5D-Itch
17) Change from baseline to week 52 in Patient Reported Outcome Measurement Information System (PROMIS) Fatigue Short Form 7a
18) Change from baseline to week 52 in the Epworth Sleepiness Scale (ESS)
19) Change from baseline to week 52 in PBC-40
20) Change from baseline to week 52 in health utility as measured by the EQ-5D-5L
21) Change from baseline to week 52 in serum markers of bone turnover and in bone density (hip and lumbar) assessed by DEXA scanning
22) Onset of clinical outcomes described as a composite endpoint composed of:
    a) MELD-Na > 14 for patients with baseline MELD-Na <12
    b) Liver transplant
    c) Uncontrolled ascites requiring treatment
    d) Hospitalization for new onset or recurrence of any of the following:
        i) variceal bleed
        ii) hepatic encephalopathy defined as West-Haven/Conn score of 2 or more
        iii) spontaneous bacterial peritonitis
    e) Death
23) Safety and tolerability as assessed by

a) Serious adverse events (SAEs), adverse events (AEs), adverse events of special interest (AESIs), physical examination, vital signs, medical history, electrocardiogram (ECG)

b) Chemistry and hematology

c) Liver markers

d) Renal biomarkers (including urinalysis)

e) Other biochemical safety markers

24) PK assessed by GFT505 and GF1007 concentrations measurement in plasma

Additionally, apart from histology (if applicable) and PK assessments, the same endpoints as for the DB period will be collected over the LTE period to assess the maintenance of efficacy and safety of the treatment.

Exploratory Endpoints (related to histological assessements):
1) Change from baseline in the histological scores:
   a) Fibrosis stage according to Nakanuma scoring
   b) Bile duct loss score
   c) Cholangitis activity
   d) Interface Hepatitis activity
   e) Stage of disease (Sum of Fibrosis stage by Nakanuma and Bile duct loss score)
   f) Other exploratory scores (Fibrosis according to Ishak scoring, portal inflammation, ductular reaction, cholestasis, concentric periductal fibrosis)
2) Correlation between histological fibrosis scores and non-invasive markers of fibrosis (liver stiffness, ELF test, proC3)

Data Safety Monitoring Board (DSMB):

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review (including review of the adjudication reports issued from the clinical events committee (CEC) on a regular basis during the study to protect patient welfare and preserve study integrity.

The DSMB will consist of at least 5 experienced physicians (1 endocrinologist, 1 cardiologist, 1 hepatologist, 1 oncologist, and 1 nephrologist) and 1 statistician, all of whom will be independent from the conduct of the study. The DSMB Charter will define the membership, role, responsibilities, rules, and tasks of the DSMB.

Clinical Event committee (CEC)

The CEC will conduct adjudication of the clinical outcomes and DILI (Drug Induced Liver Injury) events. The CEC assessment and adjudication will occur in a blinded (during DB period) and consistent and unbiased manner throughout the course of the study to determine whether the event meets the protocol specified criteria. The CEC will be comprised of 3 hepatologists; all of them will be independent from the conduct of the study.

Statistical considerations:

Determination of the sample size

The assumptions used for the determination of the sample size are:

- an expected response rate in the placebo group slightly higher than that in the phase 3 pivotal study supporting the regulatory approval of OCA (10%) [4],
- an expected response rate in the elafibranor group at least similar to OCA (47%).

The response rates from phase 3 pivotal study supporting the regulatory approval of OCA has been estimated after imputation of missing data as non-response.

One hundred and fifty patients (100 elafibranor and 50 placebo) allow to achieve at least 90% power to demonstrate a statistically significant between group difference of 35% (47% in elafibranor group vs 12% in placebo group) in the response rate at week 52 of the primary efficacy endpoint with a two-sided alpha of 0.05 and using an exact Fisher test.

In addition, assuming 1/50 (2.0%) patient in the placebo group with ALP normalization at week 52 (key secondary endpoint), 150 patients (100 elafibranor vs 50 placebo) provide at least 80% power to detect a statistically significant between group difference of 20.0% at a two-sided 0.05 alpha level.

Assuming a pooled standard deviation (SD) of 2.3 points, 60 patients (40 Elafibranor vs 20 placebo) with baseline PBC Worst Itch NRS score ≥4 provide at least 80% power to detect a statistically significant between group difference of 1.8 points in mean change from baseline in PBC Worst Itch NRS score (second key secondary endpoint) at a two-sided 0.05 alpha level. It is assumed that the same assumptions would apply to the two key secondary endpoints for pruritus (through week 52 and through week 24).

Analysis sets:

- Screened set: all patients who sign informed consent. This set will be used to summarize disposition.
- Intent-to-treat (ITT) set: All randomized subjects.
- Per-protocol (PP) set: All subjects from the ITT set without any major protocol deviation affecting the primary efficacy endpoint.
- Safety set (SS): All subjects who were administered at least one dose of study drug.
- Pharmacokinetics set (PKS): All patients who were administered at least one dose of study drug and have at least one post-dose PK sample. Moreover, patients of the PK set must have data for time of dosing, time of sampling and amount of drug administered. Whereas all patients are sampled in order to maintain the blind, the pharmacokinetics set applies only to patients under elafibranor.
- Exploratory (Histological) set: All subjects from the ITT set who consent to have liver biopsy samples collected at baseline and/or week 52.

Efficacy analysis:

DB treatment period

The primary and secondary efficacy analyses will be performed primarily on the ITT set and secondarily on the PP set. Each efficacy endpoint will be evaluated up to week 52. For patients who completed additional visits during the DB period, descriptive statistics will be presented up to the end of the DB period.

- Primary efficacy endpoint

The response rates (ALP < 1.67 x ULN and TB ≤ ULN and ALP decrease ≥ 15%) at week 52 will be compared between the treatment groups using the exact Cochran-Mantel-Haentzel test stratified by the randomization strata. Patients who stopped prematurely the study treatment will be considered as non-responders.

A sensitivity analysis to the statistical model will be performed using an exact logistic regression model with treatment group and randomization strata as factors.

Three supplementary/sensitivity analyses will be assessed using relevant multiple imputation methods to manage missing data. One will assume Missing At Random (MAR) and use multiple imputation to

impute values as if subjects would follow their initial treatment. A second one will impute values using the information from the placebo group. The third one will be a tipping point analysis to explore a number of scenarios about the missing outcomes.

A last supplementary analysis will use outcome value at week 52 regardless of treatment discontinuation or use of rescue therapy.

- Key secondary endpoints

The response rates (proportion of patients with ALP normalization) at week 52 will be compared between the treatment groups using the same method as for the primary efficacy endpoint, including sensitivity and supplementary analyses.

The change from baseline in PBC Worst Itch NRS score through week 52 will be summarized by treatment group and will be compared using a Mixed Model with Repeated Measurement (MMRM) with stratification factors as fixed factors. A supplementary analysis based on treatment policy will use outcome values at week 52 regardless of treatment discontinuation or use of rescue therapy. The same analyses will be repeated for the change from baseline in PBC Worst Itch NRS score through week 24.

- Other secondary endpoints

The continuous endpoints will be compared between the treatment groups using the MMRM.

The categorical endpoints will be analyzed using the exact Cochran-Mantel-Haentzel test stratified by the randomization strata. As for the primary endpoint, the subject who do not complete the study will be considered as non-responders/treatment failures.

- Control of type I error rate

The fixed-sequence testing approach will be used to control the overall Type I error rate at a two-sided 0.05 level. If the primary endpoint is statistically significant at a two-sided 0.05 level, the first key secondary endpoint (ALP normalization) will be tested at the same level. If the first key secondary endpoint is statistically significant at a two-sided 0.05 level, the second key secondary endpoint (change in pruritus through week 52) will be tested at the same level. If the second key secondary endpoint is statistically significant at a two-sided 0.05 level, the third key secondary endpoint (change in pruritus through week 24) will be tested at the same level.

LTE period

All the efficacy endpoints (apart from histology – if applicable - and PK) considered for the DB period will be summarized using descriptive statistics by DB treatment group and overall on both ITT and PP sets.

Safety analysis:

Descriptive statistics will be provided on the SS according to the treatment groups and an overall summary will be produced. In addition, for AEs, exposure adjusted incidence rates (EAIR) will be compared between treatment groups presenting estimates with their confidence intervals (CIs). No formal significance testing is planned. Safety analyses will be performed for both DB treatment period and LTE period.

Pharmacokinetic analysis:

The PK analysis will be performed on the PKS using a PK pop model approach.

PK parameters of elafibranor and GFT1007 will be calculated at steady state and summarized by geometric mean, SD, coefficient of variation, minimum and maximum, and median.

Exploratory analysis (related to histological assessments):

Descriptive statistics on the histological scores and the non invasive markers of fibrosis (liver stiffness, ELF test and ProC3) will be provided by DB treatment groups and overall in the Exploratory (Histological) set.

For assessing the correlation between the histological fibrosis endpoints (Nakanuma and Ishak scores) and the non invasive markers of fibrosis, the correlation coefficients and their CIs will be estimated depending on the nature and distribution of the endpoints considered.

Table 1: Study General Assessment Schedule

Study Period	Screening			Double Blind (DB)									If applicable	Safety contact in variable DB & LTE[l]	Long-term Extension (LTE)		
				Common DB						Variable DB							
Visit number	SV1	SV2	SV3	V1	V2	V3	V4	V5	V6	V7	V8	LVDB[j]	EOT DB[k]		LT1	LT2 to LTn	EOT-LTE[k]
Weeks	-12 to -2			0	4	13	26	39	52	78	104	At max. 13 weeks after last V5 for the last patient	Safety Follow-up: 16 to 30 days after last drug intake	DB period: -Week 65 -Week 91 LTE: - 13 weeks after LT2 then every 26 weeks	13 weeks after last DB visit	LT2 13 weeks after LT1 then every 26 weeks	Safety Follow-up: 16 to 30 days after last study drug intake
Days				1	29	92	183	274	365	547	729	NA	NA	Week 65: 456 days Week 91: 638 days LTE: 91 d after LT2 then every 182 d	V6 or V8 or LVDB + 91 d	LT2: 91 days after LT1 then every 182 days up to 2185	NA
Tolerances (Days)					+/- 7	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	NA	NA	+/- 14	+/- 14	+/- 14	NA
STUDY PROCEDURES[a]																	
Obtain Informed Consent	X																
Medical and Disease History	X																
Inclusion/Exclusion Criteria	X			X													
Physical Examination (Height at SV1 only)	X			X	X	X	X	X	X	X	X	X	X		X	X	X
Vital Signs and Weight	X			X	X	X	X	X	X	X	X	X	X		X	X	X
12-lead Electrocardiogram	X			X			X		X		X	X				X	
PRO questionnaires [b]																	
PBC Worst Itch NRS	X[f] →																
PBC Worst Itch NRS-Past Week										X	X	X	X			X	
PGIC					X	X	X	X	X	X	X	X	X			X	
PGIS	X[g]			X	X	X	X	X	X	X	X	X	X			X	

Study Period	Screening			Double Blind (DB)								If applicable	Safety contact in variable DB & LTE[l]	Long-term Extension (LTE)		
				Common DB						Variable DB						
Visit number	SV1	SV2	SV3	V1	V2	V3	V4	V5	V6	V7	V8	LVDB[j]	EOT DB[k]		LT1	LT2 to LTn	EOT-LTE[k]
Weeks	-12 to -2			0	4	13	26	39	52	78	104	At max. 13 weeks after last V5for the last patient	Safety Follow-up: 16 to 30 days after last drug intake	DB period: -Week 65 -Week 91 LTE: - 13 weeks after LT2 then every 26 weeks	13 weeks after last DB visit	LT2 13 weeks after LT1 then every 26 weeks	Safety Follow-up: 16 to 30 days after last study drug intake
Days				1	29	92	183	274	365	547	729	NA	NA	Week 65: 456 days Week 91: 638 days LTE: 91 d after LT2 then every 182 d	V6 or V8 or LVDB + 91 d	LT2: 91 days after LT1 then every 182 days up to 2185	NA
Tolerances (Days)					+/- 7	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	NA	NA	+/- 14	+/- 14	+/- 14	NA
5-D Itch				X	X	X	X	X	X	X	X	X	X			X	
PROMIS Fatigue Short Form 7a				X	X	X	X	X	X	X	X	X	X			X	
ESS				X	X	X	X	X	X	X	X	X	X			X	
PBC-40				X	X	X	X	X	X	X	X	X	X			X	
EQ-5D-5L				X	X	X	X	X	X	X	X	X	X			X	
Transient Elastography (TE) (Fibroscan)				X			X		X	X	X	X				X	
Liver Biopsy (optional)		X[h]							X								
Ultrasound exam (liver & bladder)[c]		X							X		X					X	
Hip and lumbar DEXA scanning[d]		X							X							X	
PK					X[i]												
Adverse Events (AEs)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Outcomes				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	Screening			Double Blind (DB)									If applicable	Safety contact in variable DB & LTE[l]	Long-term Extension (LTE)		
				Common DB						Variable DB							
Visit number	SV1	SV2	SV3	V1	V2	V3	V4	V5	V6	V7	V8	LVDB[j]	EOT DB[k]		LT1	LT2 to LTn	EOT-LTE[k]
Weeks	-12 to -2			0	4	13	26	39	52	78	104	At max. 13 weeks after last V5for the last patient	Safety Follow-up: 16 to 30 days after last drug intake	DB period: -Week 65 -Week 91 LTE: - 13 weeks after LT2 then every 26 weeks	13 weeks after last DB visit	LT2 13 weeks after LT1 then every 26 weeks	Safety Follow-up: 16 to 30 days after last study drug intake
Days				1	29	92	183	274	365	547	729	NA	NA	Week 65: 456 days Week 91: 638 days LTE: 91 d after LT2 then every 182 d	V6 or V8 or LVDB + 91 d	LT2: 91 days after LT1 then every 182 days up to 2185	NA
Tolerances (Days)					+/- 7	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	NA	NA	+/- 14	+/- 14	+/- 14	NA
Randomization				X													
Treatment Assignment[e]				X					X								
Dispense Study Drug				X		X	X	X	X	X	X	X				X[m]	
Study Drug Accountability/Compliance					X	X	X	X	X	X	X	X	X			X	X
EOS registration				To be completed in study system(s) as applicable													

Footnotes:

a. Procedures/assessments should be conducted in the following order during study visits: PROs (when completed at the study center), investigator assessments, safety and laboratory assessments, administration of study drug

b. Refer to Table 3 (Schedule of PRO Questionnaires) for details

c. At baseline, US exam can be performed before randomization after the patient has been otherwise confirmed as eligible and up to randomization visit. Ultrasound exam to be performed every year and for any visit post baseline, US exam can be performed with a tolerance of +/ 7 days around the planned visit date.

d. Hip and lumbar DEXA scanning to be performed in all patients where the exam is accessible to sites at baseline, at V6, and then 2 years later. At baseline, the exam can be performed before randomization after the patient has been otherwise confirmed as eligible and up to randomization visit. For exam post baseline, DEXA exam can be performed with a tolerance of +/ 7 days around the planned visit date.

e. The switch to elafibranor treatment will happen either at V8 or at LVDB (either V7 or V8, depending on when the last patient in the study completes his/her V5) .

f. During the screening period and DB period up to week 52 (V6), the PBC Worst Itch NRS score will be collected every evening via an eDiary. The mean score of the 14 days prior to randomization (V1) will be used for stratification. Patients must have at least 4 available values for PBC Worst Itch NRS during each of the 7 day intervals in the 14 days prior to V1, for a total of at least 8 values in the 14 days prior to V1

g. Patient Global Impression of Severity (PGIS) will be collected at SV1 only during the screening period
h. For patients who have consented to have liver biopsy samples collected, Liver biopsy at inclusion to be done at any SV preferably in patients already confirmed as eligible and if at all possible 2 to 4 weeks prior to randomization. LB at week 52 can be performed with a tolerance of +/- 2 weeks around the planned visit V6.
i. PK assessment will include the following timepoints: predose, 0.5h, 1.5h, between 2 and 3h, 4h, and 6h
j. Until the last patient in the study completes his/her V5, patients between V6 and V8, will complete LVDB according to Table 1 General Assessment Schedule. After the last patient in the study completes his/her V5, patients between V6 and V8, will complete LVDB at the next scheduled visit (either V7 or V8). LVDB will replace V7 or V8. The same procedures as for V8 will be performed for LVDB (except US exam). For patients who have not yet had V6 at the time the last patient completes his/her V5, LVDB will be scheduled at the latest 13 weeks after the date on which V5 was completed for the last patient. For those patients, LVDB will coincide with V6, and patients will complete V6 and associated procedures to facilitate transition to the open-label elafibranor treatment phase in the long-term extension study, in a timely manner. .
k. Safety contact by phone call every alternating 26 weeks starting 13 weeks after V6 in the DB period and starting after LT2 during LTE to check AEs and concomitant medications
l. If premature study drug discontinuation during DB period, end of treatment (EOT) DB Visit should be performed between 16 and 30 days after last drug intake, and patients will continue in the study until V8, or until the last completed V5 whichever occurs first. In case the EOT DB visit occurs within the time window of the next scheduled visit, EOT DB visit replaces the scheduled visit. If premature study drug discontinuation occurs during LTE period, an EOT LTE visit will be performed between 16 and 30 days after last drug intake
m. Drug dispensation will be done up to LT10. There will be no drug dispensation at LT11

Table 2: Study Biological Assessment Schedule

Study Period	Screening			Double Blind (DB)									If applicable	Long-term Extension (LTE)		
				Common DB						Variable DB						
Visit number	SV1	SV2	SV3	V1	V2	V3	V4	V5	V6	V7	V8	LVDB	EOT DB[i]	LT1	LT2 to LTn	EOT-LTE[i]
Weeks	-12 to -2			0	4	13	26	39	52	78	104	At max. 13 weeks after last V5 for the last patient	Safety Follow-up: 16 to 30 days after last drug intake	13 weeks after last DB visit	LT2 13 weeks after LT1 then every 26 weeks	Safety Follow-up: 16 to 30 days after last study drug intake
Days				1	29	92	183	274	365	547	729	NA	NA	V6 or V8 or LVDB + 91 d	LT2: 91 days after LT1 then every 182 days up to 2185	NA
Tolerances (Days)					+/- 7	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	NA	NA	+/- 14	+/- 14	NA
Serum Hematology *Hemoglobin, hematocrit, WBC with differential, platelet count, prothrombin time (PT) , INR, reticulocytes/RBC*	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Screening Serum Chemistry [a] *ALP, ALT, AST, GGT, CPK, total and conjugated bilirubin, albumin, creatinine, sodium, AFP, eGFR (MDRD formula & CKD-EPI formula), MELD-Na*	X															
Screening serum hCG pregnancy test [b]	X															
Serum Chemistry *Sodium, potassium, chloride, calcium, albumin, BUN, creatinine, TB , conjugated bilirubin, AST, ALT, ALP, GGT, 5'NT, total proteins, lipase, amylase, TC, LDL-C, HDL-C, VLDL-C, TG, CPK , FPG, eGFR, MELD-Na*				X	X	X	X	X	X	X	X	X	X	X	X	X
ALP fractionated				X					X							

Study Period	Screening			Double Blind (DB)									If applicable	Long-term Extension (LTE)		
				Common DB						Variable DB						
Visit number	SV1	SV2	SV3	V1	V2	V3	V4	V5	V6	V7	V8	LVDB	EOT DB[i]	LT1	LT2 to LTn	EOT-LTE[i]
Weeks	-12 to -2			0	4	13	26	39	52	78	104	At max. 13 weeks after last V5 for the last patient	Safety Follow-up: 16 to 30 days after last drug intake	13 weeks after last DB visit	LT2 13 weeks after LT1 then every 26 weeks	Safety Follow-up: 16 to 30 days after last study drug intake
Days				1	29	92	183	274	365	547	729	NA	NA	V6 or V8 or LVDB + 91 d	LT2: 91 days after LT1 then every 182 days up to 2185	NA
Tolerances (Days)					+/- 7	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	NA	NA	+/- 14	+/- 14	NA
Serology *HIV Ab I/II, Anti- HAV IgM , HBs, HCV*	X															
Serum Bile Acids and Biomarkers of Bile Acid Synthesis *Bile acids (cholic acid (CA), glycocholic acid (GCA), taurocholic acid (TCA), chenodeoxycholic acid (CDCA), glycochenodeoxycholic acid (GCDCA), taurochenodeoxycholic acid (TCDCA), deoxycholic acid (DCA), glycodeoxycholic acid (GDCA), taurodeoxycholic acid (TDCA), lithocholic acid (LCA), glycolithocholic acid (GLCA), taurolithocholic acid (TLCA)), C4, FGF-19*				X			X		X	X	X	X			X	
Biomarkers of Hepatic Fibrosis and/or Inflammation *HsCRP, fibrinogen, haptoglobin, TNF-α , IL-6, ELF (HA, PIINP, TIMP-1), PAI-1, TGF-β, CK-18 (M65 and M30), Pro-C3*				X			X		X	X	X	X			X	

Study Period	Screening			Double Blind (DB)									If applicable	Long-term Extension (LTE)		
				Common DB						Variable DB						
Visit number	SV1	SV2	SV3	V1	V2	V3	V4	V5	V6	V7	V8	LVDB	EOT DB[i]	LT1	LT2 to LTn	EOT-LTE[i]
Weeks	-12 to -2			0	4	13	26	39	52	78	104	At max. 13 weeks after last V5 for the last patient	Safety Follow-up: 16 to 30 days after last drug intake	13 weeks after last DB visit	LT2 13 weeks after LT1 then every 26 weeks	Safety Follow-up: 16 to 30 days after last study drug intake
Days				1	29	92	183	274	365	547	729	NA	NA	V6 or V8 or LVDB + 91 d	LT2: 91 days after LT1 then every 182 days up to 2185	NA
Tolerances (Days)					+/- 7	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	NA	NA	+/- 14	+/- 14	NA
Additional Safety Markers *Cystatin C, urine albumin to creatinine ratio (urine ACR) , AFP[c]*				X			X		X	X	X	X	X		X	X
Immunoglobulins *IgG, IgM*				X			X		X	X	X	X			X	
Serum Bone markers[d] CTX, P1NP				X		X	X		X							

Visit number	SV1	SV2	SV3	V1	V2	V3	V4	V5	V6	V7	V8	LVDB	EOT DB[i]	LT1	LT2 to LTn	EOT-LTE[i]
Weeks	-12 to -2			0	4	13	26	39	52	78	104	At max. 13 weeks after last V5 for the last patient	Safety Follow-up: 16 to 30 days after last drug intake	13 weeks after last DB visit	LT2 13 weeks after LT1 then every 26 weeks	Safety Follow-up: 16 to 30 days after last study drug intake
Days				1	29	92	183	274	365	547	729	NA	NA	V6 or V8 or LVDB + 91 d	LT2: 91 days after LT1 then every 182 days up to 2185	NA
Tolerances (Days)					+/- 7	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	NA	NA	+/- 14	+/- 14	NA
Urinalysis (dipstick) [e,] *Specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocytes*	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Urine-based β-human chorionic gonadotropin (hCG) Pregnancy Test [f]				X	X	X	X	X	X	X	X	X		X	X	
urinary myoglobin, serum IgG and SMA [g]				----------X----------												
Biobank (optional) [h]				X			X		X	X	X	X			X	

Footnotes:

a. Repeated measured for AST, ALT, ALP and TB to be collected (See 3.5.1)
b. Serum pregnancy test must be performed at screening in all females of childbearing potential and may be repeated within one month prior to randomization in case the screening period lasts more than 4 weeks.
c. AFP to be evaluated at V1, V6, and then every year, as well as at LVDB, if applicable (see section 6.3.5)
d. Serum bone markers to be assessed at baseline, week 13, week 26, and week 52
e. Microscopic evaluation will be performed if dipstick urinalysis indicated presence of any significant abnormality
f. In all females of childbearing potential, urine-based β-hCG pregnancy tests at any site visits from V1. In between site visits, a home pregnancy test is to be performed every 4 weeks, starting after V1. If the urine-based test is positive, a confirmatory serum pregnancy test must be performed at site
g. Assessment of presence of myoglobin in urine (or blood myoglobin) to be done locally only in case of clinically significant CPK elevation; assessment of IgG and SMA to be done locally in case of suspicion of AIH
h. Additional blood samples will be collected from patients, who have given their consent, to be used to discover or validate biomarkers in PBC and related diseases
i. If premature study drug discontinuation during DB period, EOT DB Visit should be performed between 16 and 30 days after last drug intake, and patients will continue in the study until V8. In case the EOT DB visit occurs within the time window of the next scheduled visit, EOT DB visit replaces the scheduled visit. If premature study drug discontinuation occurs during LTE period, an EOT LTE visit will be performed between 16 and 30 days after last drug intake

Table 3: Schedule of Patient Reported Outcomes (PROs) Questionnaires

eDiary devices will be provided to patients at SV1 for daily completion throughout the study. eDiary devices will be collected at V6.

Platform	Assessment	Frequency and Duration of Assessment	Time of Assessment
eDiary	PBC Worst Itch NRS	Once daily during screening[a] and the Common DB periods (up to V6)	Evening
eTablet	PBC Worst Itch NRS-Past Week	Throughout the Variable DB and LTE periods	During study visit[b]
eTablet	PGIC	Throughout the DB period (starting at V2) and LTE periods	During study visit[b]
eTablet	PGIS	Throughout the screening, DB, and LTE periods	During study visit[b]
eTablet	5-D Itch	Throughout the DB and LTE periods	During study visit[b]
eTablet	PROMIS Fatigue Short Form 7a	Throughout the DB and LTE periods	During study visit[b]
eTablet	ESS	Throughout the DB and LTE periods	During study visit[b]
eTablet	PBC-40	Throughout the DB and LTE periods	During study visit[b]
eTablet	EQ-5D-5L	Throughout the DB and LTE periods	During study visit[b]

Footnotes:
The mean PBC Worst Itch NRS score of the 14 days prior to randomization (V1) will be used for stratification. Patients must have at least 4 available values for PBC Worst Itch NRS during each of the 7 day intervals in the 14 days prior to V1, for a total of at least 8 values in the 14 days prior to V1
Administered on-site

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1 INTRODUCTION AND RATIONALE

Elafibranor has been developed by Genfit for the treatment of PBC. In December 2021, Genfit and IPSEN ("the partner") entered into an exclusive licensing agreement for elafibranor, which gives the partner, the exclusive worldwide license for the future development of elafibranor in PBC, with the exception of China, Taiwan, Hong-Kong and Macau. The transfer of sponsorship from Genfit to IPSEN took place on 8th August 2023, within approximately 30 days of top line results for the double-blind portion of the study (part A).

1.1. BACKGROUND AND RATIONALE FOR ELAFIBRANOR IN PRIMARY BILIARY CHOLANGITIS

Characterization of the disease

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 [5, 6]. 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 [7]. 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 [8]. 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 [6].

. Patients with PBC progress at varying rates, some experiencing liver decompensation over a period of several years while others over decades [9, 10]. PBC is one of the leading indications for liver transplantation. Despite its rarity, PBC remains an important cause of morbidity in the Western world. PBC has also been identified as an important risk factor for hepatocellular carcinoma [11].

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 ALP levels, a hallmark of the disease. Antimitochondrial antibody and IgM are specific immunological hallmarks of PBC, and antimitochondrial antibody is a diagnostic marker of the disease in approximately 90% of patients [12]. 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) [13-15]. 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 [15].

As PBC advances, the transaminases ALT and AST may also be elevated due to hepatocellular damage secondary to cholestasis. While GGT lacks specificity, elevation of this enzyme in the presence of elevated ALP is confirmatory of a cholestatic condition such as PBC [16].

The most common symptoms of PBC are fatigue and pruritus [17]. The mechanisms underlying these symptoms are not well elucidated and neither correlates with disease stage or clinical outcomes.

Current Treatment Options

UDCA, an epimer of the primary human bile acid UDCA, 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 [18]. 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 [19] and the European Association for the Study of the Liver (EASL) [20]. While UDCA has had a marked impact on clinical outcomes in PBC, a large proportion of patients have an inadequate response. It is estimated [11] that up to 40% of UDCA-treated patients have a suboptimal response to UDCA. Lammers et al. found that ALP remains elevated in up to 70% of patients who are currently being treated or are intolerant to UDCA [15]. Such patients remain at risk of disease progression and longer term adverse clinical outcomes.

Ocaliva (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 achieving a primary endpoint. The primary endpoint was defined as a composite endpoint of an ALP level of less than 1.67 times the ULN range, with a reduction of at least 15% from baseline, and a TB level at or below the ULN range at 12 months. On a background of standard of care, the rate of the primary endpoint was higher in the 5-10 mg group (46%) and in the 10 mg group (47%) compared to the placebo group at month 12 ($p<0.001$ for both comparisons). Pruritus was the most common AE across all groups, with a higher incidence reported in the 5-10 mg group (56%) and the 10 mg group (68%) than in the placebo group (38%) [4].

A 24-month, DB, placebo-controlled, phase 3 study of bezafibrate, a pan-peroxisome proliferator-activated receptor (PPAR) agonist, demonstrated efficacy in patients who had an inadequate response to UDCA. In this study the primary outcome was the percentage of patients with a complete biochemical response, which was defined as normal serum levels of ALP, AST, ALT, total bilirumin and albumin, as well as a normal prothrombin index at 24 months. The result was the primary outcome occurred in 31% of the patients assigned to bezafibrate and in 0% assigned to placebo ($p<0.001$). Results regarding changes in pruritus, fatigue, and noninvasive measures of liver fibrosis, including liver stiffness and ELF score, were consistent with the results of the primary outcome [21].

Rationale for Evaluation of Elafibranor in PBC

Elafibranor is being developed by Ipsen for the treatment of PBC, based on its pharmacological properties as a PPARα/δ agonist. Activation of PPARα 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. PPARα and PPARδ receptor activation also has anti-inflammatory effects by acting on different pathways of inflammation (nuclear factor kappa B [NF-κB] and B-cell lymphoma 6 [BCL6] pathways).

Ligand-activated PPARα contributes to a range of actions, including cholesterol and bile acid homeostasis. PPARα primarily downregulates bile acid synthesis. PPARα 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 multidrug resistance protein type 3 (MDR3) [22].

1.2. SUMMARY OF NON CLINICAL STUDIES

1.2.1. Nonclinical Pharmacology

1.2.1.1. In Vitro Pharmacology

1.2.1.1.1. Activity on Human and Murine PPAR isoforms

In Gal4- PPAR reporter gene assays, elafibranor (GFT505) and its main metabolite GFT1007 are PPAR agonists with a similar selectivity profile on both the human and murine PPAR isoforms. Both (GFT505) and GFT1007 activate the PPARα subtype with a 5-fold selectivity over PPARδ.

In human hepatocytes, elafibranor and GFT1007 induce the expression of mitochondrial genes (pyruvate dehydrogenase kinase [PDK]4, carnitine palmitoyltransferase [CPT]1a) but not peroxisomal PPAR target genes (acylCoA-oxidase [ACOX]1, enoyl-CoA hydratase/3-hydroxyacyl CoA dehydrogenase [EHHADH]), likely via PPARδ activation.

In stimulated human monocytes, elafibranor decreases the secretion of inflammatory markers (monocyte chemotactic protein (MCP)-1 and tumor necrosis factor [TNF-α]) through combined PPARα and PPARδ activation and parallel PPAR-independent mechanisms.

1.2.1.1.2. Anti-fibrotic Activity

Anti-fibrotic properties of (GFT505) were demonstrated in primary human hepatic stellate cells (hHSC). (GFT505) inhibits hHSC proliferation induced by either fetal calf serum or platelet-derived growth factor (PDGF)-BB. Moreover, (GFT505) specifically inhibited PDGF-BB-induced PDGF receptor β phosphorylation in vitro. (GFT505) also inhibited hHSC activation (gene expression of fibrosis markers: α-smooth muscle actin [αSMA], collagen [Col] 1α1 and Col4α1) induced by TGF β1.

1.2.1.2. In Vivo Pharmacology

1.2.1.2.1. Rat Model of CCl4-induced Hepatic Fibrosis

The liver-protective effects of (GFT505) have also been demonstrated in a rat model of carbon tetrachloride (CCl4)-induced hepatic fibrosis. When administered concomitantly with CCl4, (GFT505) totally prevented the development of liver fibrosis evaluated by macroscopic and microscopic examination. In addition, (GFT505) significantly reduced CCl4-induced macro- and micro- steatosis and liver inflammation. (GFT505) treatment prevented the CCl4-induced increase in liver expression of genes involved in the inflammatory ([IL]-1β, RANTES) and pro-fibrotic (collagens [Col1α1, Col1α2], TGFβ1, TIMP-2, αSMA) response.

1.2.1.3. Safety Pharmacology

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

1.2.1.4. Absorption/distribution/metabolism/excretion Studies (ADME)

In animal studies, elafibranor (GFT505) was well and rapidly absorbed although absolute bioavailability was moderate (about 20% to 40%). (GFT505) 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 (GFT505) and GFT1007 linearly increase with the dose after single or repeated administrations. (GFT505) 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, (GFT505) and/or its metabolites are rapidly excreted into the bile and undergo an extensive entero-hepatic cycle giving support for liver targeting of (GFT505) and/or GFT1007. The distribution study in the rat supports the liver targeting of (GFT505) and/or its metabolites.

In vitro, (GFT505) 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 (DDI) 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 PK interaction of (GFT505) 120 mg administered for 14 days alone or with a single administration of warfarin. This study demonstrated that (GFT505) administration did not affect the PK profile of warfarin (R-warfarin and S-warfarin). A protein binding study showed that (GFT505) and GFT1007 were highly bound to human serum albumin. The risk of DDI due to albumin binding should be limited since this binding is not saturable.

In vitro studies have been performed to determine whether GFT505 and its principal metabolite GFT1007 are substrates and/or inhibitors of major drug transporters, in order to assess the potential for DDI. Based on the results of the OATP1B3 (organic anion transporting polypeptide 1B3) transporter inhibition assay, 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 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%).

1.2.1.5. Toxicology

1.2.1.5.1. Mutagenicity and Genotoxicity

The toxicology program performed according to the International Conference on Harmonisation (ICH) guidelines demonstrates that (GFT505) has no genotoxic or mutagenicity potential.

1.2.1.5.2. Acute Toxicity

According to acute toxicity study results, it can be concluded that (GFT505) 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.

1.2.1.5.3. Repeated Dose Toxicity Studies

The safety of (GFT505) 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 PPARα-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 PPARα 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 (GFT505) for 1 year support the non-relevance to human [23]. Overall, these studies did not reveal any other safety issues up to the highest doses tested. Notably, (GFT505) did not have any of the known PPARγ-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 (GFT505).

1.2.1.5.4. Phototoxicity Studies

The phototoxic potential of elafibranor has been assessed by the in vitro 3T3 Neutral Red Uptake (NRU) phototoxicity test and the UV-Local Lymph Node Assay (UV-LLNA) test in mice. 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 (GFT505). Although a very conservative No Observed Adverse 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 GFT505, and absence of phototoxicity signal in the clinical studies.

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

1.3. CLINICAL STUDIES

1.3.1. Phase 1 Program

A Phase 1 program to assess the safety and the tolerability, as well as the PK profile, of elafibranor currently comprises 19 completed clinical pharmacology studies. At least 732 healthy and lean subjects, 90 overweight or obese but otherwise healthy subjects, 59 subjects with type 2 diabetes, 13 with renal impairment (ESRD) and 20 with hepatic impairment (Child-Pugh class A, B or C). Elafibranor daily doses ranged between 5 mg and 360 mg, with a maximum treatment duration of 18 days.

Additional information can be found in the IB.

1.3.2. Phase 2 Program

One phase 2 study with elafibranor was completed in PBC patients. Study GFT-505B-216-1 was a 12-week, DB, randomized, parallel group, placebo-controlled, proof-of-concept study in PBC. A total of 45 adult patients were randomized to one of 3 treatments arms in a 1:1:1 ratio: elafibranor 80 mg, elafibranor 120 mg, or placebo. In both elafibranor-treated groups, a significant decrease in mean ALP was achieved: -48% for the 80 mg dose and -41% for 120 mg dose, compared to a mean 3% increase in ALP for subjects receiving placebo. This resulted in a highly significant treatment effect versus

placebo: -52% (95% CI: [-62.5;-41.5]) (p<0.001) for 80 mg and -43.9% (95% CI: [-55.7;-32.1]) (p< 0.001) for 120 mg elafibranor. There was no apparent difference in the magnitude of improvement between the 2 elafibranor doses suggesting a plateau of the dose exposure-response. The effect was observed from the first visit following baseline (Visit 2 [Week 2]) and was maintained and reinforced up to the end of the active treatment period. A composite endpoint composed of ALP <1.67xULN and ALP decrease >15% and TB <ULN, was achieved in 66.7% subjects at 80 mg and 78.6% of subjects at the 120 mg elafibranor dose (p= 0.002 and p< 0.001, respectively) as compared to 6.7% subjects on placebo.

Additional information can be found in the IB.

1.4. CONCLUSION

In summary, elafibranor may provide an effective therapeutic option for patients with PBC who are inadequately responding to or unable to tolerate UDCA. As a result, elafibranor will be further evaluated in this larger Phase 3 study with an open-label extension.

1.5. RATIONALE FOR STUDY POPULATION

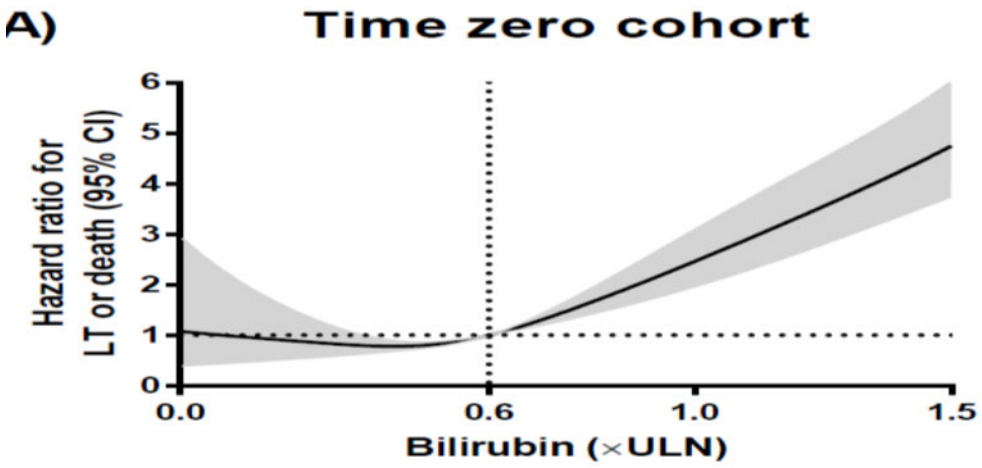
Partial or suboptimal responders constitute up to 40% of UDCA-treated PBC patients [11]. This group of patients along with patients intolerant to UCDA treatment will be randomized in this study.

This study targets patients with mild and moderately advanced disease and excludes patients with advanced cirrhosis. ALP reduction is not a good predictive marker of long term benefit in the advanced disease population [15]. Patients with moderately advanced disease are identified per Rotterdam Criteria (TB > ULN or Albumin < LLN), liver stiffness measurement by Fibroscan *[EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis –2021 update, J Hep 2021]*, or histology among those who undergo liver biopsy. Patients with cirrhosis will be identified by elastography [24] or histology among those who undergo liver biopsy.

In addition, a recent publication has shown that in UDCA-treated and untreated patients with TB levels $\leqslant 1\times$ULN at baseline or 1 year, the TB threshold with the highest ability to predict LT or death at 1 year was 0.6×ULN. The risk for LT or death was stable below TB levels of 0.6×ULN and yet increased beyond this threshold [25] and Figure 1.

To ensure inclusion of a relevant ratio of patients with substantial risk of long-term clinical outcomes or moderate disease stage, approximately 10% of randomized patients will be moderately advanced per Rotterdam Criteria. Patients will also be categorized as early or advanced disease stage based on liver stiffness measurement at the baseline Fibroscan examination (LSM<=10 kPa or LSM >10 kPa), and based on histology (absent or mild fibrosis vs. presence of bridging fibrosis or cirrhosis) among those who undergo liver biopsy *[EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis –2021 update, J Hep 2021]*. Additionally, approximately 20% will have a TB > 0.6 x ULN (patients at risk of progression).

Figure 1: Hazard Ratio for LT or Death (95% CI) vs. Bilirubin (×ULN)



1.6. JUSTIFICATION OF THE SELECTED DOSE

There was no apparent difference in the magnitude of improvement of cholestatic paramaters (ALP, GGT and 5′ NT) between the two elafibranor doses (80 and 120 mg) in Study GFT-505B-216-1 suggesting a plateau of the dose-exposure-response. In addition, both doses were generally well-tolerated. As a result, elafibranor 80 mg was selected for this study.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1. OBJECTIVES

2.1.1. DB Period

2.1.1.1. Primary Objective

To evaluate the effect of elafibranor (80 mg/day) on cholestasis as defined by the primary endpoint over 52 weeks of treatment compared to placebo.

2.1.1.2. Key Secondary Objectives

To evaluate the effect of elafibranor (80mg/day) over 52 weeks of treatment compared to placebo on:

- Normalization of ALP
- Pruritus based on change from baseline through week 52 in PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4
- Pruritus based on change from baseline through week 24 in PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4

2.1.1.3. Secondary Objectives

To evaluate the effect of elafibranor (80 mg/day) over 52 weeks of treatment compared to placebo on:

a) Hepatobiliary injury and liver function markers
b) Inflammation and hepatic fibrosis
c) Lipid parameters
d) Bile acids
e) Pruritus Patient Reported Outcomes (PROs)
f) Patient-reported Fatigue
g) Patient-reported Sleep
h) HRQoL
i) Health utility
j) Bone markers and bone density
k) Safety and tolerability

To determine the PK parameters of elafibranor and its active metabolite GFT1007, at steady state following daily oral administration at 80 mg) in PBC patients.Of note, and in order to further collect safety and clinical outcomes data in a DB manner, placebo controlled treatment will be maintained until the last completed week 52 visitor until a maximum of 104 weeks, whichever occurs first. When this time point is reached, every patient will be switched to open-label Elafibranor 80 mg.

2.1.1.4. Exploratory Objectives (related to histological assessements)

For the patients having consented to participate:

1) To constitute a biobank for discovery and validation of biomarkers associated with PBC
2) Based on histology:
   a) To assist the interpretation of efficacy and safety results of elafibranor
   b) To explore the correlation of fibrosis scores with non-invasive markers of fibrosis (liver stiffness, ELF test and ProC3)

2.1.2. LTE Period

To evaluate the effect of elafibranor (80 mg/day) during the LTE period on:

a) Safety and tolerability
b) Maintenance of efficacy from the DB period

2.2. ENDPOINTS

2.2.1. DB Period

2.2.1.1. Primary Endpoint

Response to treatment at week 52 defined as ALP < 1.67 x ULN and TB ≤ ULN and ALP decrease ≥ 15%.

2.2.1.2. Secondary Endpoints

Key Secondary Endpoints

1) Response to treatment based on ALP normalization at week 52.

2) Change in pruritus from baseline through week 52 based on PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4.

3) Change in pruritus from baseline through week 24 based on PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4

Other Secondary Endpoints

1) Change from baseline in ALP at 4, 13, 26, 39 and 52 weeks
2) ALP response defined as 10%, 20% and 40% ALP reduction from baseline at week 52
3) Response to treatment at week 52 according to:
   a) ALP < 1.5 x ULN, ALP decrease ≥ 40% and TB ≤ ULN
   b) ALP < 3 x ULN, AST <2x ULN and TB < 1 mg/dL (Paris I)
   c) ALP ≤ 1.5 x ULN, AST ≤ 1.5x ULN and TB ≤ ULN (Paris II)
   d) TB response rate of 15% change
   e) Normalization of abnormal TB and/or albumin (Rotterdam)
   f) TB ≤ 0.6 x ULN
   g) ALP ≤ 1.67 x ULN and TB ≤ 1 mg/dL [1]
   h) No worsening of TB defined as level of TB at week 52 < ULN or no increase from baseline of more than 0.1XULN at week 52
   i) Complete biochemical response defined as normal ALP; TB; AST; ALT; albumin; and INR
4) PBC risk scores at week 52: UK PBC score [2] and GLOBE score [3]
5) Response based on the normalization of bilirubin at week 52
6) Response based on the normalization of albumin at week 52
7) Change from baseline to week 52 in hepatobiliary injury and liver function as measured by AST, ALT, GGT, 5' NT, total and conjugated bilirubin, albumin, INR and ALP fractionated (hepatic)

8) Change from baseline to week 52 in biomarkers of inflammation as measured by hsCRP, fibrinogen, haptoglobin and TNF-α
9) Change from baseline to week 52 in immune response as measured by IgG and IgM
10) Change from baseline to week 52 in biomarkers, and non-invasive measures of hepatic fibrosis as measured by ELF (HA, PIINP, TIMP-1), PAI-1, TGF-β, CK-18 (M65 and M30), Pro-C3 and liver stiffness measured by TE (continuous)
11) Change from baseline to week 52 in lipid parameters as measured by TC, LDL-C, HDL-C, calculated VLDL-C and triglycerides (TG)
12) Change from baseline to week 52 in FPG
13) Change from baseline to week 52 in bile acids and biomarkers of bile acid synthesis as measured by bile acids, C4 and FGF-19
14) Proportion of responders in PBC Worst Itch NRS according to clinically meaningful change; at least 30% reduction; and one point, two points or three points decrease in score from baseline through week 52 and through week 24 in patients with a baseline NRS score ≥ 4
15) Proportion of patients with no worsening of pruritus from baseline through week 52 and through week 24 as measured by the PBC Worst Itch NRS
16) Change from baseline to week 52 in 5D-Itch
17) Change from baseline to week 52 in PROMIS Fatigue Short Form 7a
18) Change from baseline to week 52 in ESS
19) Change from baseline to week 52 in PBC-40
20) Change from baseline to week 52 in health utility as measured by the EQ-5D-5L
21) Change from baseline to week 52 in serum markers of bone turnover and in bone mineral density (hip and lumbar) assessed by DEXA scanning
22) Onset of clinical outcomes described as a composite endpoint composed of:
    a) MELD-Na >14 for patients with baseline MELD-Na <12
    b) Liver transplant
    c) Uncontrolled ascites requiring treatment
    d) Hospitalization for new onset or recurrence of any of the following:
        i) variceal bleed
        ii) hepatic encephalopathy defined as West-Haven score of 2 or more
        iii) spontaneous bacterial peritonitis
    e) Death
23) Safety and tolerability as assessed by:
    a) SAE, AE, AESI, physical examination, vital signs, medical history, ECG
    b) Chemistry and hematology
    c) Liver markers
    d) Renal biomarkers (including urinalysis)
    e) Other biochemical safety markers
24) PK assessments by GFT505 and GF1007 concentrations measurement in plasma

2.2.1.3. Exploratory Endpoints

Exploratory endpoints associated with Histological assessment (for patients who have consented to having liver biopsy)

1) Change from baseline in the histological scores
   a) Fibrosis stage according to Nakanuma scoring
   b) Bile duct loss scores
   c) Cholangitis activity
   d) Interface Hepatitis activity
   e) Stage of disease (Sum of Fibrosis stage by Nakanuma and Bile duct loss score)
   f) Other exploratory scores (Fibrosis according to Ishak scoring, portal inflammation, ductular reaction, cholestasis, concentric periductal fibrosis)
2) Correlation of Fibrosis scores with non-invasive markers of fibrosis (Liver stiffness, ELF test and ProC3)

2.2.2. LTE Period

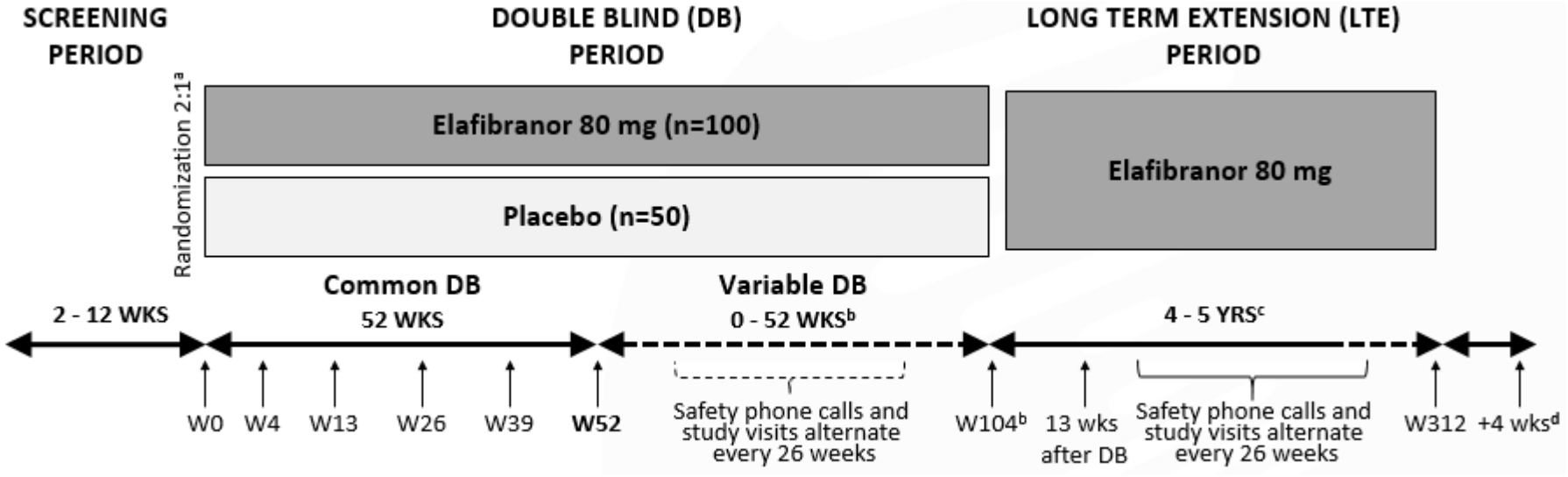
Additionally, apart from histology (if applicable) and PK assessments, the same endpoints as for the DB period will be collected over the LTE period to assess the maintenance of efficacy and safety of the treatment. The endpoints will be described using descriptive statistics by DB treatment group and overall on both ITT and PP sets.

3 STUDY DESIGN

This is a phase 3, randomized, DB, placebo-controlled, parallel group study followed by an open-label LTE that evaluates the efficacy and safety of elafibranor in patients with PBC and inadequate response or intolerance to UDCA.

In the DB period, approximately 150 patients will be randomized in a 2:1 ratio to receive elafibranor 80 mg or placebo, once daily, for maximum 104 weeks or until the last completed week 52 visit (V6), whichever happens first. Placebo control will be maintained after week 52 notably to further collect safety and clinical outcome data in a DB manner. At the end of the DB period, all patients will receive elafibranor 80 mg, once daily, for up to 5 years or until the patient's total treatment duration is 6 years, whichever occurs first. When applicable, patients should continue their pre-study dose of UDCA throughout the study participation.

Schema 2: GFT505B-319-1 Study Design



Footnotes:
a. If receiving UDCA at randomization, continue throughout study participation
b. The Variable DB duration is an additional 52 weeks after end of Common DB (W104) or until the last completed V6 (W52), whichever occurs first
c. The LTE duration is 5 years after end of the DB period or until the patient's total treatment duration is 6 years, whichever occurs first
d. Safety follow-up 4 weeks after last dose of study drug

3.1. NUMBER OF PATIENTS

The study is projected to randomize approximately 150 patients, including approximately 15 patients (10% of the total randomized patients) with a TB above ULN or albumin below LLN and approximately 30 patients (20% of the total randomized patients) with a TB above 0.6 x ULN.

3.2. TREATMENT GROUPS

The treatment groups will be allocated, in a 2:1 ratio, to receive either elafibranor 80 mg or placebo during the DB period.

3.3. DOSE ADJUSTMENT CRITERIA

N/A

3.4. DURATION OF STUDY PARTICIPATION

Up to approximately 6 years, or 328 weeks (2 to 12 weeks for the screening period, 52 to 104 weeks for the DB period, 208 to 260 weeks for the LTE period, and 4 weeks for safety follow-up). The full treatment period for each patient will last 312 weeks, with a variable number of weeks in the DB Period and in the LTE Period depending the time point of the visit V8 or LVDB completed.

3.5. STUDY PERIODS AND SCHEDULE OF ASSESSMENTS

The study will be comprised of 3 periods: a screening period, a DB period and a LTE period.

A schedule of assessments by visit is presented in Table 1 and Table 2.

3.5.1. Screening Period

As a first step, patients will be asked if they agree to participate in the study and sign the Informed Consent Form (ICF). Each patient who has signed the ICF will perform procedures listed on Table 1 and Table 2. Screening visits (SV1, SV2 or SV3) should be performed within 2 to 12 weeks of randomization. At SV1, preliminary eligibility criteria will be reviewed.

For the purpose of establishing relevant baseline chemistries for suspected DILI, repeated measures of AST, ALT and TB will be collected (see Laboratory Manual) **ONLY** if the first measure (M1) collected at SV1 is > ULN. M1 and another value either a historical value (M0), collected at least 4 weeks and up to 12 weeks apart before SV1, or a second measure (M2) will be collected at SV2 (4 to 6 weeks after SV1). This applies to only the analyte above ULN.

- If variability between M1 and either M0 or M2 is ≤ 40% the patient is eligible
- If variability between M1 and either M0 or M2 is > 40% a third measure (M3) will collected at SV3 (4 to 6 weeks after SV1 (if M0 compared) or SV2 (if M2 compared)):
    - If variability between M1 and M3 is ≤ 40% the patient is eligible
    - If variability between M1 and M3 is > 40% the patient is ineligible for the study

To assess the ALP eligibility criterion, two ALP values will be required. One value is the M1 collected at SV1, and the other value is M0 collected at least 4 weeks and up to 12 weeks apart before SV1 or M2 collected at SV2 (4 to 6 weeks after SV1).

- If M1 is < 1.67 x ULN, the patient will be excluded and no further assessment will be performed
- If M1 is ≥ 1.67 x ULN, and the mean of M1 and either M0 or M2 is ≥ 1.67 x ULN, and variability is ≤ 40% the patient is eligible
- If M1 is ≥ 1.67 x ULN, and the mean of M1 and either M0 or M2 is < 1.67 x ULN or variability is > 40%, M3 collected at SV3 (4 to 6 weeks after SV1 (if M0 compared) or SV2 (if M2 compared)) will be required:
    - If the mean of M1 and M3 is ≥ 1.67 x ULN and variability is ≤ 40%, the patient is eligible
    - If the mean of M1 and M3 is < 1.67 x ULN or variability is > 40%, the patient is ineligible for the study

NOTE: M2 and M3 values for AST, ALT, TB and ALP can be obtained at local laboratory. Comparison between M1 and local value(s) will be done on normalized values according to ULN.

For patients having consented to have liver biopsy samples collected and in absence of valid historical liver biopsy, the liver biopsy can be performed at any visits during the screening period, preferably in patients already confirmed as eligible and if at all possible 2 to 4 weeks prior to randomization.

Screening is a minimum duration of 2 weeks to help ensure the stability of the PBC Worst Itch NRS daily scores for the calculation of the baseline score.

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

3.5.2. DB period (Week 0 to max Week 104)

At the Randomization visit 1 (week 0), all eligibility criteria will be reviewed for inclusion including lab assessments obtained during the screening period.

Randomization in IXRS will be stratified based on central lab assessments obtained for ALP & TB at SV1, as well as on the mean PBC Worst Itch NRS Score over the 14 days preceding the visit 1.

At least 4 values of the PBC Worst Itch NRS during each of the 7-day intervals in the 14 days prior to randomization (V1), for a total of at least 8 values for PBC Worst Itch NRS in the last 14 days prior to randomization (V1) are required for randomizing the patients. In case this number is not achieved, the screening period may be extended in order to obtain the expected number of NRS values.

To ensure inclusion of a relevant ratio of patients with substantial risk of long-term clinical outcomes or moderate disease stage, approximately 10% of randomized patients will be moderately advanced per Rotterdam Criteria (TB> ULN or Albumin < LLN) and approximately 20% will have a TB > 0.6 x ULN (patients at risk of progression). Patients will also be categorized as early or advanced disease stage based on liver stiffness measurement at the baseline Fibroscan examination (LSM<=10 kPa or LSM >10 kPa), and based on histology (absent or mild fibrosis vs. presence of bridging fibrosis or cirrhosis) among those who undergo liver biopsy *[EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis –2021 update, J Hep 2021]*.

The DB period will last until the last completed week 52 (V6) visit or until a maximum of 104 weeks DB period, whatever happens first.

During the DB period the patients will return to the site every 13 weeks (±2 weeks) from V1 up to V6 (week 52) except for the V2 (4 weeks after V1) and if applicable post V6, every 26 weeks up to V8; Between V6 and V8, safety contacts will be performed by phone call between on site visits, every alternating 26 weeks (+/-14 days), to collect information related to AEs, concomitant medications, pregnancy, and study drug compliance. The first phone safety contact will start 13 weeks after V6 as applicable.

Any patient completing V8 will be automatically switched to open-label LTE. The last V5 completed for all randomized patients will trigger the switch to open-label LTE for all patients still in DB. The switch will be operated either at V6 or at an additional onsite visit (LVDB). Until the last patient in the study completes his/her V5, patients between V6 and V8, will complete LVDB according to Table 1 General Assessment Schedule. After the last patient in the study completes his/her V5, patients between V6 and V8, will complete LVDB at the next scheduled visit (either V7 or V8). LVDB will replace V7 or V8. The same procedures as for V8 will be performed for LVDB (except US exam). For patients who have not yet had V6 at the time the last patient completes his/her V5, LVDB will be scheduled at the latest 13 weeks after the date on which V5 was completed for the last patient. For those patients, LVDB will coincide with V6, and patients will complete V6 and associated procedures to facilitate transition to the open-label elafibranor treatment phase in the long-term extension study, in a timely manner.

In case of premature study drug discontinuation prior to visit 8 during DB period, EOT DB visit should be performed between 16 and 30 days after last drug intake. The patients will continue in the study until V8, or until the last completed V5 whichever occurs first, and will complete all visit procedures except liver biopsy and PK (if not done prior to study drug discontinuation). In case the EOT DB visit occurs within the time window of the next scheduled visit, EOT DB visit replaces the scheduled visit. For any EOT patients, their EOS status will be registered in relevant study system(s) as applicable.

Patients will be contacted at least 1 week before each onsite visit to be reminded of procedures and study drug return.

The study scheduled assessments will be performed as per Table 1 and Table 2.

3.5.3. LT period

After the last DB visit, patients will continue to the LTE period (open label). During the LTE period, all patients will receive elafibranor 80 mg for up to 5 years after the DB period or until the patient's total treatment duration is 6 years, whichever occurs first.

Apart from the first 2 visits in this LTE period which will occur at 13 weeks interval starting after the last visit in the double-blind period (V6, V7, V8), patients will return to the site every 26 weeks (+/-14 days) for procedures listed on Table 1 and Table 2, and safety contacts by phone call will be performed, every alternating 26 weeks (+/-14 days) after LT2, to collect information related to AEs, concomitant medications, pregnancy, and study drug compliance. The Investigator may subsequently decide to perform an unscheduled visit (see Section 3.5.5.2).

If premature study drug discontinuation occurs during LTE period, an EOT LTE visit will be performed between 16 and 30 days after last drug intake.

For any patients in the LTE, their EOS status will be registered in relevant study system(s) as applicable.

3.5.4. Safety Follow up

An EOT DB or EOT LTE visit will be performed between 16 to 30 days after the last drug intake for any subjects who received the study drug. The study procedures will be assessed as per the Table 1 and Table 2.

3.5.5. Optional Visits

3.5.5.1. Retesting and/or additional screening visits

- If CPK value is >2xULN at SV1, it can be repeated within 1 to 2 weeks, but prior to V1

If HCV Ab test is positive at SV1, a patient's HCV infection status needs to confirmed by HCV RNA testing prior to V1Any other 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 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.).

3.5.6. Off-site study procedures in case of crisis situation

In cases of emergency (e.g., pandemic, political strife, natural disasters), to continue to ensure patient safety and minimize risks to study integrity, certain study procedures may be completed remotely (e.g., not on-site) for patients already randomized in the study. Any temporary changes to study conduct will be defined based on a risk assessment specific to the crisis, and regulatory agencies and ethics committees will be informed in accordance with local laws and regulations.

The temporary study conduct changes might include:

- Study visits conducted with the patient via phone
- Laboratory testing performed in the patient's local lab
- Study drug shipped from the site or supplier to the patient, or delivered by the site study staff to the patient

Certain changes may be applied on a case-by-case basis depending on the investigator's judgment.

The investigator will confirm a patient's agreement before implementing any temporary study conduct changes.

4 PATIENT SELECTION

A patient will be eligible for the study only if all of the following criteria apply:

4.1 INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for randomization into the study:

1) Must have provided written informed consent and agree to comply with the study protocol
2) Males or females age of 18 to 75 years inclusive at SV1
3) PBC diagnosis as demonstrated by the presence of ≥ 2 of the following 3 diagnostic criteria:
   a. History of elevated ALP levels for ≥ 6 months prior to randomization (V1)
   b. Positive AMA titers (> 1:40 on immunofluorescence or M2 positive by ELISA or positive PBC-specific ANA
   c. Liver biopsy consistent with PBC
4) ALP ≥ 1.67 x ULN (based on two values - see section 3.5.1)
5) TB ≤ 2 x ULN

   To ensure inclusion of a relevant ratio of patients with substantial risk of long-term clinical outcomes or moderate disease stage, approximately 10% of randomized patients will be moderately advanced per Rotterdam Criteria (TB > ULN or Albumin < LLN) and approximately 20% will have a TB > 0.6 x ULN (patients at risk of progression)
6) Must have at least 4 available values for PBC Worst Itch NRS during each of the 7 day intervals in the 14 days prior to randomization (V1), for a total of at least 8 values for PBC Worst Itch NRS in the last 14 days prior to randomization (V1)
7) UDCA for at least 12 months (stable dose ≥ 3 months) prior to screening, or unable to tolerate UDCA treatment (no UDCA for ≥ 3 months) prior to screening (per country standard-of-care dosing)
8) If on colchicine must be on a stable dose for ≥ 3 months prior to screening
9) Medications for management of pruritus (e.g., cholestyramine, rifampin, naltrexone or sertraline) must be on a stable dose for ≥ 3 months prior to screening
10) Patients taking statins or ezetimibe must be on a stable dose for ≥ 2 months prior to screening
11) Females participating in this study must be of non-child bearing potential or must be using highly effective contraception for the full duration of the study and for 1 month after the last drug intake:
    - Non-child bearing potential: Cessation of menses for at least 12 months due to ovarian failure or surgical sterilization such as bilateral oophorectomy, or hysterectomy
    - Highly effective contraception methods include:
      a. Combined (estrogen and progrestogen containing) hormaonal contraception associated with inhibition of ovulation, oral, intravaginal or transdermal
      b. Progestogen-only hormonal contraception associated with inhibition of ovulation, oral, injectable or implantable

c. Intrauterine device (IUD)

d. Intrauterine hormoine release system (IUS)

e. Bilateral tubal occlusion

f. Vasectomized partner

g. Sexual abstinence, if required by local IRB/IEC regulations and/or considered adequate by National laws (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient)

12) For patients who consent to have liver biopsy samples collected, patients in whom it is safe and practical to proceed with a liver biopsy, and who agree to have:

a. 1 liver biopsy during the Screening Period (if no historical biopsy within 6 months before screening is available)

b. 1 liver biopsy after 52-weeks of treatment

4.2 EXCLUSION CRITERIA

Patients presenting any of the following exclusion criteria will not be included in the study:

1) History or presence of other concomitant liver disease including:
   a) Positive anti-HAV IgM antibodies or positive HBsAg or positive HCV RNA (tested for in case of known cured HCV infection or positive HCV Ab at screening)
   b) PSC
   c) ALD
   d) AIH or if treated for an overlap of PBC with AIH, or if there is suspicion and evidence of overlap AIH features, that cannot be explained alone by insufficient response to UDCA
   e) NASH
   f) Gilbert's Syndrome (exclusion due to interpretability of bilirubin levels)
   g) Known history of alpha-1 antitrypsin deficiency
2) Clinically significant hepatic decompensation, including:
   a) History of liver transplantation, current placement on a liver transplant list, current MELD-Na score ≥ 12 linked to hepatic impairment
   b) Patients with cirrhosis/portal hypertension complications, including known esophageal varices, ascites, history of variceal bleeds or related interventions (e.g., insertion of variceal bands or TIPS, and hepatic encephalopathy, history or presence of spontaneous bacterial peritonitis, hepatocellular carcinoma
   c) Hepatorenal syndrome (type I or II)
3) Medical conditions that may cause non-hepatic increases in ALP (e.g., Paget's disease) or which may diminish life expectancy to < 2years, including known cancers
4) Patient has a positive test for HIV Type 1 or 2 at screening, or patient is known to have tested positive for HIV
5) Evidence of any other unstable or untreated clinically significant immunological, endocrine, hematologic, gastrointestinal, neurological, or psychiatric disease as evaluated by the investigator; other clinically significant medical conditions that are not well controlled

6) 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 screening visit (SV1)
7) For female patients: known pregnancy, or has a positive serum pregnancy test, or lactating
8) Administration of the following medications are prohibited as specified below:
    a) 2 months prior to screening: fibrates and glitazones
    b) 3 months prior to screening: OCA, azathioprine, cyclosporine, methotrexate, mycophenolate, pentoxifylline, budesonide and other systemic corticosteroids (parenteral and oral chronic administration only); potentially hepatotoxic drugs (including α-methyl-dopa, sodium valproic acid isoniazid, or nitrofurantoin)
    c) 12 months prior to screening: antibodies or immunotherapy directed against ILs or other cytokines or chemokines
    d) For patients with previous exposure to OCA, OCA should be discontinued 3 months prior to screening
9) Patients who are currently participating in, plan to participate in, or have participated in an investigational drug study or medical device study containing active substance within 30 days or five half-lives, whichever is longer, prior to screening; for patients with previous exposure to seladelpar, seladelpar should be discontinued 3 months prior to screening
10) Patients with previous exposure to elafibranor
11) SV value ALT and/or AST > 5 x ULN
12) For patients with AT or TB>ULN at SV1, variability of AT or TB > 40% (see section 3.5.1)
13) SV value albumin<3.0 g/dl
14) Severely advanced patients according to Rotterdam criteria (TB > ULN and albumin < LLN)
15) SV value INR > 1.3 due to altered hepatic function
16) SV value CPK > 2 x ULN
17) Screening serum creatinine > 1.5 mg/dl
18) Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney failure damage or eGFR < 60 mL/min/1,73 m2) calculated by MDRD
19) Platelet count < 150 x 10^3/µL
20) AFP > 20 ng/mL with 4-phase liver CT or MRI imaging suggesting presence of liver cancer
21) Known hypersensitivity to the investigational product or to any of the formulation excipients of the elafibranor or placebo tablet
22) Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain

5 STUDY PROCEDURES

The procedures performed at each visit are summarized in the study schedules (Table 1 and Table 2 and Table 3) 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, vital signs will be measured, and the patient will be queried in the form of an open question regarding new or continuing events.

During any study visit during which PROs are performed, it is recommended to be completed by the patient prior to the site performing any invasive procedures.

Procedures for premature discontinuation after randomization are described in Section 5.2.

5.1. SCREEN FAILURES

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who screen failure because of a specified modifiable factor may be rescreened.

5.2. PATIENT WITHDRAWAL AND PATIENT TREATMENT DISCONTINUATION RULES

5.2.1. Permanent discontinuation of study drug/withdrawal from study

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.

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.

The reason for permanent discontinuation of study drug should be documented in the electronic case report form (eCRF) and the 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:

- At the discretion of the Investigator, any AE, AESI, SAE (described in Section 8.1.1 and 8.1.2), or significant change in a laboratory value (described in Section 6.3.1, 6.3.2, 6.3.3, 6.3.4, and 6.3.5) or worsening or disease progression that would require in the patient's best interest, initiation of any standard of care prohibited in the study. Investigators are advised to call the Medical Monitor prior to making such a decision
- Non-permitted concomitant medication (described in Section 7.12 and 16.2)
- 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
- Non-compliance with the study treatment
- Uncooperative patient
- The patient requests to stop study drug permanently.

Patients permanently discontinued from study drug during the DB period will perform an EOT DB visit within 16-30 days after the last drug intake and will continue to attend all scheduled visits until the visit 8 (without undergoing histology or PK assessment, if applicable), or until the last completed V5 whichever occurs first. Patients permanently discontinuing study drug during the LTE period will attend the EOT LTE Visit within 16 to 30 days after the last administration of study drug (as described in Section 3.5.4).

5.2.2. 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.

5.2.3. Replacement

No patient replacements are permitted in this study.

5.2.4. Premature Discontinuation of the Study

Premature termination of this clinical study may occur because of a Regulatory Authority decision, change in opinion of the institutional review board/independent ethics committee (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 treatment at any time.

The Sponsor reserves the right to discontinue the study 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 study materials must be collected and all case report forms (CRFs) 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.

In all cases 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.

6 ASSESSMENTS

6.1. EFFICACY AND SAFETY ASSESSMENT

6.1.1. Biological assessment

All blood samples for efficacy and/or for safety assessment will be returned and centralized by the central laboratory.

A Laboratory Manual will be provided to each 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 24-48 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 received. The Investigator should comment upon out of range parameters and assess clinical significance.

In order to maintain the blind, ALP, GGT and 5' NT obtained from blood samples from V2 to V8 / LVDB/or last V6 whichever occurs first (up to end of DB period) will be kept in blinded condition during the DB treatment period for each patient. Similarly, the same rule will apply to ALP, GGT and 5'-NT obtained from blood samples until the first visit in the LTE period (LT1), including EOT LTE and unscheduled visits. The Investigator will not be informed of these values until the database lock at the end of the DB period.

The option to retest during the study is left to the Investigator's judgment. During Screening, retesting (to be performed at Retesting and/or additional SVs) is limited to CPK, and HCV RNA (in case of positive HCV Ab at SV) as described Section 3.5.5 and in Table 2.

At visits for which blood samples will be drawn, patients must be fasting for at least 12 hours. These visits should be scheduled in the morning.

Both blood and urine dipstick samples will be transported to the central laboratory for testing and analysis except for urinary/blood myoglobin that should be tested at local laboratory when applicable.

Local laboratory assessments are allowed for repetition of assessment of ALT, AST, TB and ALP during the screening period as well as for any required retest for liver function monitoring and assessment of urinary/blood myoglobin, when applicable.

Local laboratory results will be entered in eCRF including corresponding normal ranges.

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) will be measured at all visits. Both blood and urine dipstick samples will be transported to the central laboratory for testing and analysis.

6.1.1.2. Urinary Pregnancy Tests

For WOCBP, serum pregnancy test will be performed at screening (and may be repeated within one month prior to randomization in case the screening period lasts more than 4 weeks) while urinary pregnancy tests will be administered at each visit from V1. Notably, the urine pregnancy test performed at V1 is to occur on site prior to randomization. If such test is unclear, a follow-up serum pregnancy test should also be performed prior to dosing. In addition, monthly urine home pregnancy test kits will be provided during scheduled visits for use during non-visit months. In case of positive urinary test, a confirmatory serum pregnancy test must be performed at site.

6.1.1.3. Serology

Screening for hepatitis and HIV will be performed during screening and will include:

- HIV Ab I/II
- Anti-HAV IgM
- HBsAg
- HCV Ab (If positive, a HCV RNA test will be performed to determine infection status)

6.1.1.4. Other Parameters

All other parameters will be measured according to the schedule described on Table 2.

6.1.2. Constitution of biobank

In order to be able to test other specific parameters which could be of interest regarding the elafibranor development program or regarding diagnosis, prevention, or treatment of PBC or other related diseases, an additional amount of blood will be sampled from patients who have given their consent for these additional analyses by signature of the biobank ICF.

These samples will be destroyed 3 years after final study results at the latest.

6.1.3. Bone density by DEXA scanning

DEXA scanning (hip and lumbar) will be performed in patients at study sites at which DEXA scan equipment is available and has been approved for use in this study. Study participants will have this exam at baseline (before randomization after the patient has been otherwise confirmed as eligible and up to randomization visit), at week 52 and then 2 years later as described in Table 1.

6.1.4. Histological assessment

For patients who consent to have liver biopsy samples collected, a liver biopsy (see Section 6.1.4.1 for recommendations) will be performed:

- During the Screening period (unless an historical liver biopsy within 6 months before screening is available)
- At 52 weeks of treatment

In addition, for any patient randomized in the study, a liver biopsy can be requested at any time in case of suspicion of auto-immune hepatitis or for safety monitoring at the discretion of the investigator (section 6.3.2 & 6.3.3).

A Laboratory Manual will be provided to each study site. The manual will outline the collection process, and shipping requirements for the specific central laboratory.

6.1.4.1. Recommendations related to liver biopsy

The patient's platelet count and PT should be checked according to local hospital standards before the date of liver biopsy. Local guidelines and thresholds for hemostatic parameters should be used as they are in everyday clinical practice. Usually a platelet count >80,000/mm^3, a PT >60% or longer by no more than 4 seconds over the control, and a normal bleeding time are acceptable for performing percutaneous liver biopsy in a patient that has stopped taking any antiaggregant therapy for >5 days. If these conditions are not all respected, a safer option would be to perform the liver biopsy by transjugular route, when available.

Sedation is recommended to be given for percutaneous liver biopsy, and should be given with caution in liver disease.

The recommended biopsy procedure to be applied is:

- Needle core biopsy
- Biopsy obtained with a 16 or lower gauge needle
- A tissue core ≥2 cm long (≥10 portal tracts) represents optimal biopsy length
- Preferably obtain biopsy from the right lobe. If left lobe biopsy is used for inclusion, a left lobe biopsy should be used for future biopsies.

Post-biopsy observation: It is recommended that the patient should remain in hospital at least for 6 hours after the procedure.

The biopsies will be sent to the central laboratory and then stained and digitalized, before being transfered for central reading. Biopsy slides will be blinded for patient and visit identification prior to central reading.

In case the liver biopsy fragment is too small or of bad quality, thereby precluding adequate reading, other available slides or new slides to be prepared from an available block of tissue may be requested to the site.

6.1.4.2. Liver biopsy reading

Liver biopsy samples will be sent to the central laboratory where they will be stained and digitalized.

Liver biopsy slides will be assessed and scored by at least two pathologists. Scores for fibrosis, bile duct, cholangitis activity, interface hepatitis activity, will be evaluated and agreed. A liver biopsy management plan will detail the process of management of the liver biopsy samples from collection to final assessment. A liver biopsy assessment protocol will detail the reading methodology to be implemented.

6.1.5. Pharmacokinetic assessment

Elafibranor (GFT505) and GFT1007 plasma concentrations PopPK analysis is to be done at steady-state. Thus the PK blood collection will be at steady state after repeated administration of elafibranor in order to assess its PK and the one of its main active metabolites, GFT1007, in PBC patients. GFT505 and GFT1007 will both be included in the PopPK analysis.

6.1.5.1. Pharmacokinetic blood sampling timepoints

Elafibranor and its main active metabolite GFT1007 plasma concentrations will be evaluated at steady-state after 4 weeks of treatment (V2).

The collection of PK blood samples is to be performed at the first visit post randomization (V2) in order to limit as much as possible treatment compliance issues. Prior to sampling the patient, the investigator will have to check the patient compliance over the preceding 16 days.

All patients (including patients under placebo in order to maintain the blind of the study) will be sampled with 6 sampling timepoints: predose, 0.5h, 1.5h, between 2 and 3h, 4h, and 6h.

The following restrictions should be applied to patients for the visit V2 where PK sampling are planned:

- Study treatment will be taken at site under fasting conditions after the blood sampling for biological assessment (see section 6.1.1) and predose PK sampling and before further PK samplings, in this strict order.
- The time of study drug intake (T0) should be at least 24h after the previous dosing.
- The date and time of study drug intake the day before the visit (V2) has to be recorded as well as the day of the visit (V2).
- The predose PK sampling has to be collected as close as possible to the study drug intake (T0) (within max 1h prior to T0).

Samples should be collected as close as possible to the therotical timepoints. Exact time of sampling will be recorded in the eCRF.

6.1.5.2. Pharmacokinetic blood handling procedures

At each time point (predose, 0.5h, 1.5h, between 2 and 3h, 4h, and 6h), 1 tube of 6 mL blood sample should be drawn into lithium heparin Vacutainer® tube protected from light with foil. Plasma will be separated, stored and shipped as described in the laboratory manual, first to the central laboratory (as for all the other blood samples collected) where they will be stored until shipped to a specialized laboratory for analysis.

The exact time of sample collection will be recorded in the source documents and reported in the eCRF.

6.1.5.3. Bioanalytical analysis

The bioanalysis part will be conducted at a specialized laboratory in compliance with its Standard Operating Procedures (SOPs) in use.

Elafibranor and GFT1007 will be assayed by measuring concentrations according to an analytical method previously developed and validated as detailed in the Bioanalytical Study Plan.

6.1.5.4. Description of pharmacokinetic evaluation parameters

PK parameters (AUCss, clearance, volumes of distribution, etc.) will be determined from elafibranor and GFT1007 plasma concentrations using a popPK model. A dedicated software for nonlinear mixed models will be used for the analysis.

The population PK analyses will be described in a separate data analysis plan and reported in a standalone report.

An exploratory analysis will be performed to assess the relationship between PK and PD (efficacy or safety endpoints). If a trend is shown, an attempt to build a PKPD model using a population approach will be performed. Those analyses (population PK and, if applicable, population PKPD) will be described in a separate data analysis plan and reported in a standalone report..

PK parameters of elafibranor and GFT1007 will be summarized by geometric mean, SD, coefficient of variation, minimum and maximum, and median.

6.1.6. Liver stiffness by transient elastography (FibroScan®)

FibroScan® TE device (Echosens, Paris, France) is a non-invasive technique used to measure liver stiffness, which correlates with fibrosis. This assessment will be performed on all patients as illustrated by the Study General Assessment Schedule (Table 1). All sites must have designated staff trained in the use of the device.

This assessment will be done the day of the visit. Failing this, it can be performed within 7 days of the visit.

To ensure reliability of the assessments patients must be in a fasted state for at least 3 hours before the examination. Additional instructions will be provided in a separate manual.

As presented in the paper from Corpechot et al [24], the threshold for classification of cirrhosis is ≥ 16.9 KPa.

6.1.7. Patient Reported Outcomes Questionnaires

The following PROs will be assessed:

a) The PBC Worst Itch NRS (Appendix 16.3.7) is a simple, self-administered PRO questionnaire that measures itch intensity. It uses 24-hour and 7-day recall periods and asks patients to rate the intensity of their Worst Itch on an 11-point scale ranging from 0 (no itch) to 10 (Worst Itch imaginable). Patients will record their scores once daily (24-hour recall) using the eDiary during the screening and Common DB periods and during study visits (7-day recall; PBC Worst Itch NRS-Past Week) during the Variable DB and LTE periods as outlined in Table 3. At randomization, the patient's daily scores (24-hour recall) over the previous 14 days will be averaged to determine the baseline score for stratification and analysis; at least 4 available values for PBC Worst Itch NRS during each of the 7 day intervals in the 14 days prior to randomization (for a total of at least 8 values for PBC Worst Itch NRS in the last 14 days prior to randomization) are required for the baseline score to be calculated.

b) The 5-D Itch scale (Appendix 16.3.3) is a questionnaire that has been validated in several different diseases. It assesses symptoms in terms of 5 domains: degree, duration, direction, disability and distribution [27]. Patients rate their symptoms over the preceding 2-week period on a 1 to 5 scale, with 5 being the most affected. Patients will complete the 5-D Itch scale as outlined in Table 3.

c) The PBC-40 (Appendix 16.3.1) is a validated, PBC-specific, HRQoL 40 question questionnaire that assesses symptoms across six domains: fatigue, emotional and social, cognitive function, general symptoms and itch [28]. Patients respond on a verbal response scale, depending on the section options range from 'never' / 'not at all' / 'strongly disagree' to 'always' / 'very much' / 'strongly agree'. Five items (3/3 in the itch domain and 2/10 in the social domain) also include a 'does not apply' option. A score for each domain is provided (but a total score is not calculated), with each verbal response scale correlating to a score of 1-5 per item (0-5 on items with a 'does not apply' option) with 5 being the most affected. The PBC-40 has a 4-week recall period (Appendix 16.3.1). Patients will complete the PBC-40 as outlined in Table 3.

d) The Euro quality of life (EuroQol) EQ-5D-5L (Appendix 16.3.8) is a 6-item, standardized questionnaire that assesses mobility, self-care, usual activities, pain / discomfort, anxiety / depression, and overall health state.

e) The ESS [29, 30] (Appendix 16.3.2) is a short, self-administered questionnaire that consists of eight questions asking to rate how likely it is to fall asleep in everyday situations (each question can be scored from 0 to 3 points; '0' indicates no sleepiness, '3' indicates significant sleepiness). It provides a total score which has been shown to relate to the patient's level of daytime sleepiness (total score range 0–24 points). Patients will be asked to complete the ESS with regard to the level of sleepiness they experienced over approximately the past 7 days as outlined in Table 3.

f) The PROMIS Fatigue Short Form 7a (Appendix 16.3.4) consists of seven items that measure both the experience of fatigue and the interference of fatigue on daily activities over the past week (National Institute of Health, 2007). Patients will complete the PROMIS Fatigue Short Form 7a as outlined in Table 3.

g) The Patient Global Impression of Change (PGIC) (Appendix 16.3.5) is a single item 5 point scale designed to assess the change in overall itch intensity since the baseline visit. PGIC-Itch scores will be captured as outlined in Table 3.

h) The PGIS (Appendix 16.3.6) is a 1-item 5-point scale designed to assess patient's impression of itch severity. The PGIS-Itch scores will be captured as outlined in Table 3.

Of note, PGIC and PGIS are collected as anchors to facilitate the derivation of a clinically meaningful threshold but will not be used to measure any treatment effect.

In order to avoid bias in the patients' responses to the questionnaires, it is recommended that site based assessments be completed before any other evaluations or study procedures on the day of the study visit and prior to discussions with the investigator or study site staff. Site procedures and assessments should be conducted in the following order: PROs, investigator assessments, safety and laboratory assessments, administration of study drug.

6.2. OTHER SAFETY ASSESSMENTS AND ONGOING SAFETY MONITORING

6.2.1. Physical Examination

A physical examination including neurological exam will be performed at the time points specified in the study general assessment schedule of events (Table 1). Height will be measured at the SV only. The physical examination will include the following: General appearance, weight, hair and skin, lymph nodes, head, eyes/ears/nose, throat, neck, respiratory system, cardiovascular system, abdominal region, musculoskeletal system, mental status and neurological system.

6.2.2. Vital Signs and Weight

Blood pressure (BP), heart rate, respiratory rate and temperature will be measured [26]. Weight will be measured in pounds or kilograms. All measurements will be recorded in eCRF.

6.2.3. 12 Lead ECG

ECGs will be analyzed by the Investigator or designee. Patients are to be supine position for at least 5 minutes prior to ECG assessments. A minimum of 3 cycles will be recorded per lead. 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 eCRF.

6.3. IMPORTANT SPECIFIC BIOLOGICAL CONSIDERATIONS AND PATIENT DISCONTINUATION RULES

6.3.1. Creatine Phosphokinase

If at any visit during the treatment period, a patient experiences diffuse myalgia, muscle tenderness, and/or marked increase in muscle CPK values between 3 x and 5 x ULN (≥ 3 x ULN and ≤ 5 ULN), an additional visit and test must be performed within 48 to 72 hours, and an assessment of myoglobinuria/myoglobinemia should be done locally. If, during that visit, the patient still experiences diffuse myalgia, muscle tenderness and/or marked increase in muscle CPK values between 3 x and 5 x ULN (≥ 3 x ULN and ≤ 5 ULN), myopathy must be considered and the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.1.

If at any visit during the treatment period, a patient experiences marked increase in muscle CPK values >5 x ULN, the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.1.

6.3.2. Liver Function Monitoring

Patients will be closely monitored and evaluated for other causes of liver injury and for the potential of DILI. Relevant assessment for suspected DILI includes:

- Establishing baseline values (by at least two samples obtained at least 4 weeks and no more than 12 weeks apart)
- Obtaining a more detailed history of symptoms and prior or concurrent disease
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Ruling out acute viral hepatitis types A, B, C, D and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatotoxicity; and biliary tract disease
- Obtaining a history of exposure to environmental chemical agents
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin)
- Considering gastroenterology or hepatology consultations

In addition, guidelines for management of any sign of liver function deterioration are given in the several subsequent sections below.

For any of the cases below, if a patient lives in a remote area from the site, laboratory testing can be performed in a local lab. The results should be promptly communicated to the investigator site.

Liver function monitoring will be done with respect to Liver Function Tests baseline values. Of note, in the absence of large prospective comparative data, there is little evidence to support one threshold over another [31] therefore the IQ-DILI best practice recommendations have been adopted for this protocol. The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ

Consortium), a science-focused, not-for-profit organization launched the IQ-DILI Initiative in 2016, reached consensus, and proposed the following best practices related to DILI with respect to patients with elevated ALT at baseline:

- If ALT ≥ 3 x baseline and there is no change in TB or liver-related symptoms, repeat measures and initiate close observation [32]
- If ALT ≥ 3 x baseline, TB is normal or elevated and liver-related symptoms (i.e., severe fatigue, nausea, vomiting, right upper quadrant pain), interrupt study drug and initiate close observation [32]

In addition to management guidelines, the criteria used for reporting a potential DILI for adjudication are given below and correspond to the criteria leading to permanent study drug discontinuation.

For any suspicion of DILI or for any other liver related event, it is left to the discretion of the investigator to request a liver biopsy in accordance with the local clinical standards, in order to further assess the case.

6.3.2.1. Treatment discontinuation rule for elevated Aminotransferase (AT) values regardless of baseline values

In all cases, whether baseline Aminotransferase (AT) values are normal or elevated, an increase of AT >10 x ULN will lead to permanent discontinuation of the patient from study drug, and scheduling of EOT DB/EOT LTE visit.

6.3.2.2. Treatment discontinuation rules for elevated Aminotransferase (AT) values according to baseline values

6.3.2.2.1. Monitoring of patients with normal baseline AT values

For patients with normal baseline AT values at V1 who at any visit from V2 onwards during the treatment periods exhibit:

- Increase in AT to ≤ 3 x ULN: no additional action required, schedule next visit as per assessment schedule.
- Increase in AT to >3 x ULN but ≤5 x ULN: retest after 48 to 72 hours.
  If during the following retest:
  - AT remains >3 x ULN but ≤5 x ULN: continue the drug with close serial monitoring (twice a week). Frequency of repeated testing can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic
  - AT increases to >5 x ULN: permanently discontinue patient from study drug and schedule EOT DB/EOT LTE Visit (see Section 5.2.1 and Section 3.5.4).
- Increase in AT >5 x ULN: retest after 48 to 72 hours.
  If during the following retest:
  - AT remains >5 x ULN: permanently discontinue patient from study drug and schedule EOT DB/EOT LTE Visit (see Section 5.2.1 and Section 3.5.4)
  - AT reduces to ≤5 x ULN: continue the drug with close serial monitoring (twice a week). Frequency of repeated testing can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.
- Increase in AT >3 x ULN and increase in TB > 2 ULN: permanently discontinue patient from study drug and schedule EOT DB /EOT LTE Visit (see Section 5.2.1 and Section 3.5.4).
- Increase in AT >3 x ULN and increase in INR>1.5 (in the absence of anti-coagulant therapy): permanently discontinue patient from study drug and schedule EOT Visit (see Section 5.2.1 and Section 3.5.4).

- Increase in AT >3 x ULN and fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash: permanently discontinue patient from study drug and schedule EOT DB/EOT LTE Visit (see Section 5.2.1 and Section 3.5.4).
- Increase in AT >3 x ULN and eosinophilia (> 5%) with total count > ULN: permanently discontinue patient from study drug and schedule EOT DB/EOT LTE Visit (see Section 5.2.1 and Section 3.5.4).

6.3.2.2.2. Monitoring of patients with abnormal baseline AT values

For patients with abnormal AT baseline values at V1 who at any visit post V1 onwards during the treatment periods exhibit:

- Increase in AT to ≤ 3 x baseline value: no additional action required, schedule next visit as per assessment schedule.
- Increase in AT to >3 x baseline value but ≤10 x ULN: retest after 48 to 72 hours:
    - If baseline value < 2 x ULN:
        - AT increase ≤ 5 x baseline: continue the drug with close serial monitoring (twice a week)
        - AT increase > 5 x baseline: permanently discontinue patient from study drug and schedule EOT DB/EOT LTE visit (see Section 5.2.1 and Section 3.5.4)
    - If baseline value > or equal 2 x ULN but < 5 x ULN:
        - AT increase ≤ 3 x baseline: no additional action required, schedule next visit as per assessment schedule
        - AT increase remains > 3 x baseline: permanently discontinue patient from study drug and schedule EOT DB/EOT LTE visit (see Section 5.2.1 and Section 3.5.4)
- Increase in AT >3 x baseline value and increase in TB > 2 x baseline: permanently discontinue patient from study drug and schedule EOT DB/EOT LTE Visit (see Section 5.2.1 and Section 3.5.4).
- Increase in AT > 3 x baseline value and increase in INR by above > 0.2 compared to baseline INR (in the absence of anti-coagulant therapy): permanently discontinue patient from study drug and schedule EOT DB/EOT LTE Visit (see Section 5.2.1 and Section 3.5.4).
- Increase in AT > 3 x baseline value and fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash: permanently discontinue patient from study drug and schedule EOT/EOS Visit (see Section 5.2.1 and Section 3.5.4).
- Increase in AT > 3 x baseline and eosinophilia (> 5%) with total count > ULN: permanently discontinue patient from study drug and schedule EOT DB/EOT LTE Visit (see Section 5.2.1 and Section 3.5.4).

6.3.2.2.3. Monitoring of patients with abnormal TB baseline values

For patients with abnormal TB values at V1 who at any visit post V1 onwards during the treatment periods exhibit:

- Increase in TB to > 1.5 x baseline value: retest after 48 to 72 hours
    - TB remains >1.5 x baseline value: continue study drug and implementation of close observation (testing and physical examination 2-3 times per week). Discontinuation of study should be considered.

6.3.3. Auto-immune hepatitis monitoring

For patients who at any visit post V1 onwards during the treatment periods, exhibits ALT>5 X ULN, IgG serum or smooth muscle autoantibody should be tested (these tests are to be done locally);

if IgG is >2XULN or smooth muscle autoantibody positive, a liver biopsy should be performed at an unscheduled visit; if moderate or severe interface hepatitis is detected on histology, AIH will be confirmed and patient should be discontinued from study drug (if not already discontinued according to discontinuation rules described in Section 6.3.2).

6.3.4. Acute Pancreatitis Monitoring

6.3.4.1. Treatment discontinuation rule for suspected acute pancreatitis

If at any visit during the treatment period, a patient experiences serum amylase and lipase ≥ 3 x ULN, associated with abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back), an ultrasound exam or CT scan will be performed for the diagnosis of pancreatitis. If confirmed, the patient must be discontinued from the study drug immediately and followed up as described in Section 5.2.1.

6.3.5. Monitoring of hepatocellular and bladder cancer

6.3.5.1. Liver monitoring

Ultrasonography of liver and analysis of AFP will be performed at baseline, & then every year (V6, V8, LT3, LT5 , LT7, and LT9 if applicable), AFP will be performed at LVDB, if applicable, as described in Table 1 and Table 2.

6.3.5.2. Bladder & urinary tract monitoring

Ultrasonography of bladder and urinary tract will be performed at baseline, & then every year (V6, V8, LT3, LT5 , LT7, and LT9 if applicable) as described in Table 1.

6.3.6. Safety Review

Safety oversight will be implemented under the direction of a DSMB composed of at least five experienced physicians (an endocrinologist, cardiologist, oncologist, hepatologist and nephrologist) and one independent statistician, all independent from the conduct of the study. Members of the DSMB should be free of conflicts of interest. The members of DSMB will review the progress of the study and perform a safety data review (including review of the adjudication reports issued from the CEC) on a regular basis (at least every six months) to ensure patient safety and preserve study integrity.

A DSMB charter will define the membership, roles, responsibilities, rules and tasks of the DSMB.

6.3.7. Clinical event committee

The CEC will conduct adjudication of the clinical outcomes and DILI events. The CEC assessment and adjudication will occur in a blinded (during DB period) and consistent and unbiased manner throughout the course of the study to determine whether the endpoint meets the protocol specified criteria.

The CEC will be comprised of 3 hepatologists, all of them will be independent from the conduct of the study.

6.4. GUIDANCE FOR INVESTIGATORS

6.4.1. Summary of safety data

The safety and tolerability of elafibranor were confirmed in Phase 1 to Phase 3 studies.

A Phase 1 program has been conducted to assess the safety and tolerability, as well as the PK profile, of elafibranor. Elafibranor daily doses ranged between 5 mg and 360 mg, with a treatment duration up to 18 days. Importantly a PK study in hepatic impaired subjects was recently conducted and concluded that no dose adjustment is required in cirrhotic patients, unless there is a safety concern.

A Phase 2 program has been conducted to assess the safety and efficacy profile of elafibranor in patients suffering from cardiometabolic disorders and NASH.

A Phase 2 study (GFT505B-216-1) in PBC was also completed and included forty five (45) patients with PBC and inadequate response to UCDA. This study evaluated the efficacy and safety of elafibranor at daily doses of 80 mg and 120 mg after 12 weeks of treatment. In the Phase 2 program, the elafibranor daily doses ranged between 30 mg and 120 mg, with a maximum treatment duration of 12 months.

2157 patients with NASH and fibrosis have been randomized in a Phase 3 study (Study GFT505-315-1). In this study, the subjects were receiving 120 mg/day elafibranor or placebo for up to 72 weeks during the first treatment period, followed by a long-term treatment period to assess efficacy on progression to cirrhosis, all-cause mortality and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events of portal hypertension/cirrhosis related events. Given the failure to meet the predefined primary surrogate efficacy endpoint (i.e. NASH resolution without worsening of fibrosis) and following further in-depth review of the efficacy dataset, despite absence of safety issue, it was decided to prematurely terminate the study in October 2020 following sponsor decision.

Based on the cumulative experience gathered to date, gastro-intestinal disorders (abdominal pain, nausea , vomiting, diarrhoea, constipation) are considered common non-serious adverse reactions reasonably associated with elafibranor; most of them are of mild to moderate severity. In addition, these AEs are to be monitored as AESIs (see Section 8.1.2) as well as other AESIs which could be considered as class effect AEs.

Additional details are provided in IB.

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

Other known effects of PPARα agonists include the increase of creatinine, which was observed in our clinical studies, in a range of 1-10%. This increase was reversible at EOT. This should also be monitored in clinical studies.

Liver enzymes will also be monitored in clinical studies, with specific attention paid to DILI. In the elafibranor clinical development program to date, there has been no imbalance in DILI events in individuals who received elafibranor compared to individuals who received placebo.

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 studies [33].

As such, all clinical studies with elafibranor including WOCBP request a negative pregnancy test before Randomization, effective contraceptive measures throughout the study and mandatory study discontinuation upon becoming pregnant. Contraception should be maintained up to 1 month after the last drug intake. Pregnancy tests should be repeated as stated in the Table 2.

For further details, refer to the IB.

6.4.2. Benefit/risk assessment

Clinical studies completed to date have not raised any major safety concerns associated with elafibranor treatment, thus providing a favorable efficacy/safety profile for the drug candidate.

A Phase 2 study in PBC subjects who had an inadequate response to UDCA demonstrated improvement in GGT, lipid and inflammatory markers. Moreover, a significant decrease of ALP levels was observed, resulting in significant treatment effects versus placebo on the primary endpoint, whilst also meeting the composite endpoint used for drug registration (i.e. serum ALP <1 .67 x ULN, an ALP decrease > 15%, and TB < ULN).

Plasma concentrations and PK parameters measured for GFT505 and GFT1007 in subjects with PBC were similar with that measured in healthy volunteers in previous studies with comparable dose regimen. The results obtained in this study suggest that the PK of GFT505 and its active metabolite (GFT1007) are not modified in subjects with PBC.

Despite this favorable benefit-risk profile, an independent DSMB will be established in order to review the safety of the treatment during the study in an unblinded manner, to protect patient welfare and preserve study integrity (Section 6.3.6).

In conclusion, the safety data collected so far and the current knowledge on GFT505 confirm the favorable balance between risks and anticipated efficacy/benefits.

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 white to off-white round coated tablets with no printed inscription. The tablet contains elafibranor and inactive ingredients (microcrystalline cellulose, povidone, croscarmellose, anhydrous colloidal silica, magnesium stearate, Opadry II HP 85F18422).

Placebo tablets to match elafibranor 80 mg will be provided as a white to off-white round coated tablet with no printed inscription. Of note, in the placebo tablet formulation, lactose monohydrate is used for replacing the active substance.

Additional information can be found in the IB.

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, containing 7 tablets each, will be packed in child proof wallets.

Each childproof wallet will contain 5 blisters (covering approximately one month of treatment). Three wallets (covering the period between each visit) will be packaged inside a period box.

7.2.2. Labeling

All labels for study drugs will meet all applicable requirements of the US 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 study 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."

7.3. DOSAGE AND ADMINISTRATION OF ELAFIBRANOR AND PLACEBO

Patients will be informed to take 1 tablet per day of elafibranor 80 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 DB treatment period, the Investigator will register the patient in the IXRS system to randomize him/her.

The Investigator will log into the system using his identification number and access code. The IXRS will then allocate the patient to a treatment group (placebo or elafibranor 80 mg) through a treatment number.

A specific IXRS manual will be provided to the pharmacy and investigator site.

The randomization list will be generated by the Clinical Research Organization (CRO) for data management & statistics, and will be kept under blinded condition to the study patients, investigator site, sponsor and sponsor representative until the database lock and the Sponsor authorization to unblind the study.

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 confirm each study drug dispensation in the IXRS.

At every visit from V1 up to visit V6 (apart from visit V2), every randomized patient will be delivered with one period box.

From visit V6, two period boxes will be delivered at each site visit.

7.7. TREATMENT REPLACEMENT

Treatment replacement, if needed, will be explained in a specific IXRS procedure manual.

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 SV. The number will also be reported in the eCRF. Upon completion of the SV, eligible patients will be randomly assigned to elafibranor 80 mg or placebo at the 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 IXRS. The Investigator will be able to unblind any treatment period box that was dispensed to the patient by connecting to the IXRS (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 IXRS will verify the authorization to unblind the entered treatment period box number and the screen will then display the treatment group. When completed, a blinded confirmatory email will be sent to the Investigator and the Sponsor. The reason for unblinding should be clearly and fully documented by the Investigator.

Unblinding of treatment arm will occur after the database lock of the DB period and the Sponsor authorization.

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 period box/wallets. Compliance will be checked by the Investigator during those visits and recorded in the eCRF.

The compliance will be collected within the 16 days prior the Visit V2 for further PK assessment.

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

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

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

- Treatment carton (kit) number
- Quantity destroyed
- Method of destruction
- Person who disposed of the study drug

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 Non-permitted medication and condition, Appendix 16.2). 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

Some medications are not allowed within the timeframe given in Appendix 16.2.

If it is identified after Randomization that these non-permitted drugs have been administered to a patient within the excluded timeframes, the decision to permanently discontinue the patient will be discussed with the medical monitor (see Section 5.2).

7.12.3. Permitted Medication Under Conditions

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

- UDCA if taken for at least 12 months (and stable dose for ≥ 3 months) prior to screening (SV1)
- Statins and ezetimibe provided the dosage is kept stable for at least 2 months prior to screening
- Colchicine provided the dosage is kept stable for at least 3 months prior to screening.
- Medications for management of pruritus (e.g., cholestyramine, rifampin, naltrexone or sertraline) must be on a stable dose for ≥ 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 bias.

In the event that additional concomitant therapy becomes necessary during the study, 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 (AEs)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical (investigational) product and which does not necessarily 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 FDA.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or, 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 and breastfeeding.

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 study 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 SV that do not worsen
- 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.

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. Adverse events of special interest (AESIs)

AESIs are treatment emergent AEs corresponding to the conceptual definition of:

- CPK elevations of severe intensity or leading to permanent study drug discontinuation
- Muscle injury symptoms of severe intensity corresponding to:
  - Muscle pain or Myalgia
  - Muscle spasms or Tremor
  - Muscle weakness
- Transaminases elevations from baseline of severe intensity or leading to permanent study drug discontinuation
- Autoimmune hepatitis
- Liver injury events of severe intensity corresponding to:
  - Hepatic injury
  - Hepatic impairment
  - Hepatic failure
- Gastrointestinal symptoms of severe intensity corresponding to:
  - Abdominal pain
  - Constipation
  - Diarrhea
  - Nausea
  - Decreased appetite
  - Vomiting
  - Acute cholecystis
  - Acute pancreatitis
- Fatigue and Asthenia of severe intensity
- Serum creatinine elevations of severe intensity or leading to permanent study drug discontinuation
- Renal injury events of moderate or severe intensity corresponding to:
  - Renal injury
  - Renal failure
  - Renal impairment
  - Renal colic
- Neurological abnormalities of moderate to severe intensity corresponding to:
  - Tremor
  - Ataxia
  - Fasciculations
- Parkinson's Disease
- Peripheral edema of moderate to severe intensity
- Weight gain of more than 5% from baseline
- Major Adverse Cardiovascular Events corresponding to:
  - Non-fatal myocardial infarction/unstable angina
  - Non-fatal stroke
  - Unstable Angina
  - Hospitalization for Heart Failure
  - Coronary Revascularization (bypass or percutaneous coronary intervention)

Treatment emergent Pregnancy and outcomes of Pregnancy will be considered as AESIs, and are described in the Section 8.6.1.

8.1.3. Serious Adverse Event

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

- Results in death
- Is life-threatening

- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

or

- Is a congenital anomaly/birth defect.

8.1.4. Clarification on Serious Adverse Events

- Death is an outcome of an AE, not an AE in itself.
- A SAE may occur even if the patient was not being treated with the study drug at the occurrence of the event.
- Life-threatening means that patient is at immediate risk of death.
- 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. Of note, 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.
- Only a persistent or significant or incapacitating disability is implied. 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.
- Congenital anomaly/birth defect includes foetal malformations associated with spontaneous abortions or elective abortions.
- 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 also usually be considered serious.
- 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. wash-out period, laboratory testing procedure, etc…) must be reported as SAE.

8.1.5. Adverse Drug Reaction

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

8.1.6. 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 IB 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 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 AE have occurred at each visit from the date of consent. 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 subject 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 subject'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 CRF.

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

- **Related:** the AE or laboratory test abnormality 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 or other drugs. 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 study drug 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 study drug

- Drug withdrawn – in case a patient is permanently withdrawn from the study drug
- Drug interrupted – 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 AE

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 last study visit of the patient. 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.

AE reporting begins from signature of the patient ICF at the first SV and ends at the last study visit.

8.3.2. Reporting a SAE or an AESI

SAE reporting begins from signature of the patient ICF and ends at the last study visit.

AESI reporting starts from first study drug intake and ends at study end for each patient.

Investigators must notify by email, or fax the Sponsor of all SAEs or AESIs **IMMEDIATELY (within 24 hours of the Investigator becoming aware of the event)** regardless of the causality. The Investigator will be requested to supply as much detailed information regarding the event that is available at the time of the initial contact (such as examinations carried out and laboratory results).

The Investigator is also required to submit follow-up reports to Sponsor or its representative **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. Copies of additional laboratory tests, consultation reports, post mortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable.

In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the Sponsor with the SAE/AESI form, retaining a copy on site with the CRF. If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and sent to the Sponsor as soon as available, retaining a copy on site with the CRF.

Initial and follow-up report will be completed by the Investigator using appropriate template provided to him by the Sponsor.

The expected / unexpected status of the serious and related AE will be judged by the Sponsor or its designated Representative with regards to the reference documents (IB).

The Sponsor or its designated Representative will report all the relevant safety information to the concerned IRB/IEC concerned according to the country specific requirements.

The Investigator must also fulfill his/her obligation regarding AE reporting according to the law in force in his/her country.

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 consolidation of the patient condition.

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, notably for the potential related AEs, 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 AES OR SAES

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.

Reporting timelines for AEs and SAEs/AESIs are described respectively in Section 8.3.1 and Section 8.3.2

8.6. SPECIAL SITUATION REPORTS

8.6.1. Pregnancy

In case of pregnancy a communication will be sent by the Investigator to the Sponsor by emailing a completed pregnancy form within 24 hours of his/her knowledge of the pregnancy.

Pregnancies of females partners of male patients exposed to study drug should also be reported to the Sponsor using the corresponding pregnancy form, provided that females partners sign the corresponding and separate ICF.

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 study drug 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/AESIs as detailed in Section 8.3.2.

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.

8.6.3. Misuse

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

Additional information can be found in the IB.

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. Clinical judgment should always be applied.

Additional information can be found in the IB.

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.

Additional information can be found in the IB.

9 STATISTICAL METHODS AND DATA ANALYSIS

This section is an overview of the key elements of the statistical analysis for this study. 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. The first approved version of the SAP should be available within 3 months of first patient randomized and before the first DSMB data review meeting.

Descriptive summary statistics for continuous variables will include the number of patients, mean, 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.

9.1. ESTIMANDS CONSIDERATIONS

The primary objective of the study is to evaluate the effect of elafibranor (80 mg/day) on cholestasis over 52 weeks of treatment compared to placebo.

The cholestasis is predominantly characterized by elevation of serum ALP. In the Phase 2 study, a significant effect of elafibranor on ALP serum levels was observed from the first visit following baseline and was reinforced up to the end of the active treatment period. Thus, a rapid decrease of the ALP serum levels in elafibranor group and no change in placebo group can be expected.

To limit the occurrence of intercurrent events (ICEs) such as study treatment discontinuations due to lack of efficacy and/or use of rescue medication such as OCA, the patients and the investigators will remain blinded of the ALP, GGT and 5' NT results until the dabase lock and the Sponsor authorization to unblind the study. Thus, no between group imbalance in the occurrence of these events that might bias the treatment effect estimate in favor of elafibranor is expected.

As detailed below, in line with ICH E9 (R1) addendum; five attributes (treatment condition ,population, endpoint, ICEs and population level summary) have been specified to translate the primary objective into treatment effect that is to be estimated (estimands):

- Primary estimand

The composite strategy imputing non response for patients who experienced ICEs prior to week 52 will be applied.

- *A. Treatment condition:* Administration of Elafibranor or Placebo on top of UDCA or in subjects intolerant to UDCA,
- *B. Population:* Randomized patients with PBC and Inadequate Response or Intolerance to UCDA
- *C. Endpoint:* Response to treatment (binary variable) indicating a successful response at week 52 for a subject with ALP <1.67 x ULN, TB ≤ ULN and ALP decrease ≥ 15%, and who does not stop prematurely the study treatment nor use any rescue therapy,
- *D. Intercurrent events:* To be considered as non response irrespective of data after the study treatment discontinuation or use of rescue therapy being missing or not,
- *E. Population-level summary:* Between treatment group difference in response proportions.

The primary estimand can be defined as the between treatment group difference in proportions of patients, from all randomized patients, achieving response at week 52, defined as ALP < 1.67 x ULN,

TB ≤ ULN and ALP decrease ≥ 15%, and not stopping prematurely the study treatment nor using rescue therapy.

In addition, two strategies will be explored as supplementary analysis:

- The hypothetical strategy will be investigated comparing the potential outcomes that would have been observed at week 52 between the treatment arms as if:
  - The patients who experienced an ICE would follow their initial randomized treatment
  - The patients who experienced an ICE from both arms would continue on placebo

In addition, a tipping point analysis will explore various scenarios among the hypothetical strategy where missing outcomes experienced after an ICE vary independently from Elafibranor and placebo groups

- The treatment policy strategy will be investigated where patients are classified as responders based on their outcome value at week 52 regardless of treatment discontinuation or use of rescue therapy.

- Key secondary estimands

Key-secondary endpoint: Response to treatment based on ALP normalization at week 52.

The composite strategy imputing non response for patients who experienced ICEs prior to week 52 will be applied.

- *A. Treatment condition*: Administration of Elafibranor or Placebo on top of UDCA or in subjects intolerant to UDCA,
- *B. Population:* Randomized patients with PBC and Inadequate Response or Intolerance to UCDA,
- *C. Endpoint:* Response to treatment (binary variable) indicating a successful normalization of ALP at week 52 without stopping prematurely the study treatment not using any rescue therapy,
- *D. Intercurrent events:* To be considered as non response irrespective of data after the study treatment discontinuation or use of rescue therapy being missing or not,
- *E. Population-level summary:* Between treatment group difference in response proportions.

The key secondary estimand can be defined as the between treatment groups difference in proportions of patients, from all randomized patients, who successfully normalized their ALP at week 52 and who do not prematurely stop the study treatment nor use any rescue therapy.

The same hypothetical and treatment policy strategies as for the primary estimand will be applied as supplementary and sensitivity analyses.

Key-secondary endpoint: Change in pruritus from baseline through week 52 based on PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4.

The hypothetical strategy assuming that patients who experienced an ICE would have continued within their treatment arm will be applied.

- *A. Treatment condition*: Administration of Elafibranor or Placebo on top of UDCA or in subjects intolerant to UDCA,
- *B. Population:* Randomized patients with PBC and Inadequate Response or Intolerance to UCDA,
- *C. Endpoint:* Change from baseline through week 52 in PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4,
- *D. Intercurrent events:* Any outcome value collected after a treatment discontinuation or use of rescue therapy will be considered as missing,
- *E. Population-level summary:* Between treatment group difference in mean changes from baseline.

The key secondary estimand can be defined as the between treatment groups difference in PBC Worst Itch NRS mean change from baseline from randomized patients with baseline PBC Worst Itch NRS score ≥4 through week 52 or week 24 assuming they continued the assigned treatment after they experienced an ICE.

As for the key binary endpoints, a tipping point analysis point analysis will be performed to explore several scenarios where missing outcomes experienced after an ICE vary independently from Elafibranor and placebo groups.

In addition, the treatment policy strategy will be investigated where all outcome values until week 52 will be used regardless of treatment discontinuation or use of rescue therapy.

Key-secondary endpoint: Change in pruritus from baseline through week 24 based on PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4.

The estimand approach for the change in pruritus from baseline through week 24 based on PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4 will be the same as defined for week 52.

9.2. RANDOMIZATION AND TREATMENT ASSIGNMENT

Random allocation will be made to the 2 treatment groups (elafibranor and placebo) in a 2:1 ratio basis and stratified by the following factors:

1) ALP > 3 x ULN or TB > ULN: Yes/No
2) PBC Worst Itch NRS score (averaged over the 14 days preceding randomization) ≥ 4: Yes/No

During the LTE period, all patients will receive elafibranor 80 mg.

9.3. ENDPOINTS

9.3.1. Primary Endpoint

Response to treatment at week 52 defined as ALP < 1.67 x ULN and TB ≤ ULN and ALP decrease ≥ 15%.

9.3.2. Secondary Endpoints

Key Secondary Endpoints

1-Response to treatment based on ALP normalization at week 52.

2-Change in pruritus from baseline through week 52 on PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4.

3-Change in pruritus from baseline through week 24 based on PBC Worst Itch NRS in patients with baseline PBC Worst Itch NRS score ≥4

Other Secondary Endpoints

1) Change from baseline in ALP at 4, 13, 26, 39 and 52 weeks
2) ALP response defined as 10%, 20% and 40% ALP reduction from baseline at week 52

3) Response to treatment at week 52 according to:
   a) ALP < 1.5 x ULN, ALP decrease ≥ 40% and TB ≤ ULN
   b) ALP < 3 x ULN, AST <2 x ULN and TB < 1 mg/dL (Paris I)
   c) ALP ≤ 1.5 x ULN, AST ≤ 1.5 x ULN and TB ≤ ULN (Paris II)
   d) TB response rate of 15% change
   e) Normalization of abnormal TB and/or albumin (Rotterdam)
   f) TB ≤ 0.6 x ULN
   g) ALP ≤ 1.67 x ULN and TB ≤ 1 mg/dL [1]
   h) No worsening of TB defined as level of TB at week 52 < ULN or no increase from baseline of more than 0.1XULN at week 52
   i) Complete biochemical response defined as normal ALP, TB, AST, ALT, albumin and INR
4) PBC risk scores at week 52: UK PBC score and GLOBE score
5) Response based on the normalization of bilirubin at week 52
6) Response based on the normalization of albumin at week 52
7) Change from baseline to week 52 in hepatobiliary injury and liver function as measured by AST, ALT, GGT, 5' NT, total and conjugated bilirubin, albumin, INR and ALP fractionated (hepatic)
8) Change from baseline to week 52 in biomarkers of inflammation as measured by hsCRP, fibrinogen, haptoglobin and TNF-α
9) Change from baseline to week 52 in immune response as measured by IgG and IgM
10) Change from baseline to week 52 in biomarkers, and non-invasive measures of hepatic fibrosis as measured by ELF (HA, PIINP, TIMP-1), PAI-1, TGF-β, CK-18 (M65 and M30), Pro-C3 and liver stiffness measured by TE (continuous)
11) Change from baseline to week 52 in lipid parameters as measured by TC, LDL-C, HDL-C, calculated VLDL-C and TG
12) Change from baseline to week 52 in FPG
13) Change from baseline to week 52 in bile acids and biomarkers of bile acid synthesis as measured by bile acids, C4 and FGF-19
14) Proportion of responders in PBC Worst Itch NRS according to clinically meaningful change; at least 30% reduction; and one point, two points or three points decrease in score from baseline through week 52 and through week 24 in patients with a baseline NRS score ≥ 4
15) Proportion of patients with no worsening of pruritus from baseline through week 52 and through week 24 measured by the PBC Worst Itch NRS
16) Change from baseline to week 52 in 5D-Itch
17) Change from baseline to week 52 in PROMIS Fatigue Short Form 7a
18) Change from baseline to week 52 in ESS
19) Change from baseline to week 52 in PBC-40
20) Change from baseline to week 52 in health utility as measured by EQ-5D-5L
21) Change from baseline to week 52 in serum markers of bone turnover and in bone mineral density (hip and lumbar) assessed by DEXA scanning
22) Onset of clinical outcomes described as a composite endpoint composed of:
   a) MELD-Na > 14 for patients with baseline MED-Na <12

b) Liver transplant
c) Uncontrolled ascites requiring treatment
d) Hospitalization for new onset or recurrence of any of the following:
    i) variceal bleed
    ii) hepatic encephalopathy defined as West-Haven/Conn of 2 or more
    iii) spontaneous bacterial peritonitis
e) Death

23) Safety and tolerability as assessed by:
a) SAE, AE, AESI, physical examination, vital signs, medical history, ECG
b) Chemistry and hematology
c) Liver markers
d) Renal biomarkers (including urinalysis)
e) Other biochemical safety markers

24) PK assessed by GFT505 and GFT2007 concentrations measurement in plasma

Additionally, the same endpoints as for the DB period (except histology – if applicable - and PK assessment) will be collected over the LTE period to assess the maintenance of efficacy and safety of the treatment.

9.3.3. Exploratory Endpoints (related to histological assessments)

1) Change from baseline in the histological scores:
a) Fibrosis stage according to Nakanuma scoring
b) Bile duct loss score
c) Cholangitis activity
d) Interface Hepatitis activity
e) Stage of disease (Sum of Fibrosis stage by Nakanuma and Bile duct loss score)
f) Other exploratory scores (Fibrosis according to Ishak scoring, portal inflammation, ductular reaction, cholestasis and concentric periductal fibrosis)
2) Correlation between histological fibrosis scores (Nakanuma and Ishak scores) and non invasive markers of fibrosis (liver stiffness, ELF test and ProC3)

9.4. ANALYSIS SETS

The following analysis sets will be used in this study:

- Screened set: all patients who signed ICF. This set will be used to summarize disposition.
- ITT set: all randomized subjects. This set will be used to summarize efficacy.
- PP set: all subjects from the ITT set without any major protocol deviation affecting the primary efficacy endpoint.
- SS: all subjects who were administered at least one dose of study drug. This set will be used to summarize safety.
- PKS: All patients who were administered at least one dose of study drug and have at least one post-dose PK sample. Moreover, patients of the PK set must have data for time of dosing, time of sampling and amount of study drug administered. Whereas all patients are sampled

in order to maintain the blind, the pharmacokinetics set applies only to patients under elafibranor.

- Exploratory (Histological) set: All subjects from the ITT set who consent to have liver biopsy samples collected at baseline and/or week 52

Patients in the ITT and PP sets will be analyzed based on randomized treatment. Patients in the SS will be analyzed based on actual treatment received.

9.5. ANALYSIS OF PRIMARY ENDPOINT

The null hypothesis for response to treatment based on the primary endpoint is that there is no difference in response rates between elafibranor and placebo groups. The alternative hypothesis is that there is a difference in response rates between both groups. The null hypothesis will be tested at a two-sided alpha of 0.05 (see Section 9.6). The efficacy analysis will be performed at the end of the common DB period (week 52) only, but descriptive statistics will be provided over the entire DB period (up to week 104).

The number and percentage of patients with favorable response to treatment will be summarized by treatment group at the end of the 52 weeks of the common DB treatment period as well as at the end of the overall DB period (either V6/V8/LVDB). The response rates (ALP < 1.67 x ULN and TB ≤ ULN and ALP decrease ≥ 15%) at week 52 will be compared between the treatment groups using the exact Cochran-Mantel-Haentzel test stratified by the randomization strata. The estimate of the odds ratio, its 95% CI and the corresponding p-value will be provided. The main analysis will be based on the ITT. To assess the robustness of the results, the same analysis will be replicated on the PP set.

A sensitivity analysis to the statistical model will be performed on both ITT and PP sets, using an exact logistic regression model with treatment group and randomization strata as factors.

Subjects who stopped prematurely the study treatment will be considered as non-responders.

Three supplementary/sensitivity analyses imputing outcome experienced after an ICE at Week 52 will be applied using relevant multiple imputation methods. The imputations will be based on patients completing the week 52 treatment period and relevant baseline covariates:

1) Outcomes will be imputed assuming that patients would follow their initial treatment (rather than switching to placebo after discontinuation). Therefore, the treatment arm will be included in the imputation model as a covariate or separate models will be fitted by treatment arm.

2) Outcomes will be imputed for both placebo and treatment dropouts as if they would continue on placebo (using placebo-based multiple imputation (PBI)).

3) A tipping point analysis will be performed where outcomes will be imputed assuming that the missing outcomes on the two arms vary independently.

A last supplementary analysis will use outcome value at week 52 regardless of treatment discontinuation or use of rescue therapy.

Further details will be provided in the SAP.

9.6. OTHER STATISTICAL ANALYSIS

9.6.1. Key secondary endpoints

The number and percentage of patients with favorable response to treatment (according to ALP normalization) will be described at the end of the common DB treatment period and at the end of the overall DB period (either V6/V8/LVDB), and the same statistical methods as for the primary endpoint will be applied to evaluate the treatment effect at week 52.

The change from baseline in PBC Worst Itch NRS score through week 52 or through Week 24, in patients with baseline PBC Worst Itch NRS score ≥4, will be summarized by treatment group using monthly scores computed every 28 days and will be compared using a MMRM with stratification factors as fixed factors. The statistical model will be used to calculate the mean treatment difference (elafibranor - placebo), 95% CI and the corresponding p-value. The main analysis assumes that patients who experienced an ICE would have continued within their treatment arm. A tipping point sensitivity analysis will evaluate the impact on imputing outcomes in both treatment arms independently. A supplementary analysis based on treatment policy will use outcome values at week 52 regardless of treatment discontinuation or use of rescue therapy. Additionally, the PBC Worst Itch NRS-Past week score obtained during the variable DB period will be described.

The same analyses as described above for the change from baseline in PBC Worst NRS score through week 52 will be repeated for the change from baseline in PBC Worst NRS score through week 24.

All key secondary endpoints will be analysed on ITT and PP sets.

9.6.2. Other secondary endpoints

During the DB period

The continuous endpoints will be described all along the DB period. At week 52, they will be compared between treatment groups using the MMRM with stratification factors as fixed factors. The statistical model will be used to estimate the mean treatment difference and its 95% CI. As for the key secondary endpoint, patients who will experience an ICE will be analyzed as if they would have continued within their treatment arm.

The categorical endpoints will be described at week 52 and at the end of the DB period, and will be analyzed using the exact Cochran-Mantel-Haentzel test stratified by the randomization strata. The statistical model will be used to estimate the odds ratios and its 95% CI. As for the primary endpoint, subjects with missing data will be considered as non-responders.

All the analyses of other secondary endpoints will be performed based on the ITT and additionally, on the PP.

Further details will be provided in the SAP.

PK assessment are described in Section 6.1.4. The statistical considerations applicable to the popPK modeling will be fully described in a dedicated Analysis Plan (popPK SAP).

During the LTE period

All the endpoints defined as primary or secondary endpoints (apart from histology – if applicable - and PK endpoints) will be assessed during the LTE period at the appropriate timepoint to assess the

maintenance of efficacy of the treatment. The endpoints will be summarized by treatment group using descriptive statistics based on both ITT and PP.

9.6.3. Subgroup analyses

Exploratory analyses of the primary and key secondary endpoints will be done for the following subgroups:

- Age (< or ≥ 65 years)
- Gender
- Race
- UDCA treatment at baseline (Yes/No)
- Prior OCA treatment (Yes/No)
- ALP level at baseline (≤ or > 3 x ULN)
- TB at baseline (≤ or > 1 x ULN)
- TB at baseline > ULN or albumin at baseline < LLN (Yes/No)
- TB > 0.6 x ULN (Yes/No)
- Geographic region
- PBC Worst Itch NRS score ≥ 4 (Yes/No)
- ALP > 3 x ULN or TB > ULN (Yes/No)
- Cirrhotic defined by Liver stiffness at baseline ≥ 16.9KPa at Fibroscan exam (Yes/No) and/or cirrhosis on histology
- Advanced disease stage defined as liver stiffness at baseline >10 kPa at Fibroscan exam and/or bridging fibrosis or cirrhosis on histology

Forest plots will be generated for each endpoint for patients in the ITT population. Further details will be provided in the SAP.

9.7. STRATEGIES TO CONTROL TYPE I ERROR

The overall type I error for the primary and key secondary endpoints is two-sided α=0.05.

The fixed-sequence testing approach will be used to control the overall type I error rate at a two-sided 0.05 level. If the primary endpoint is statistically significant at a two-sided 0.05 level, the first key secondary endpoint (ALP normalization) will be tested at the same level. If the first key secondary endpoint is statistically significant at a two-sided 0.05 level, the second key secondary endpoint (change in pruritus through week 24) will be tested at the same level. If the second key secondary endpoint is statistically significant at a two-sided 0.05 level, the third key secondary endpoint (change in pruritus through week 24) will be tested at the same level.

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

9.8. SAMPLE SIZE CALCULATION

All sample size calculations were done in East® 6.5.

9.8.1. Reduction in ALP and TB

The assumptions used for the determination of the sample size are:

- An expected response rate in the placebo group slightly higher than that in the phase 3 pivotal study supporting the regulatory approval of OCA (10%) [4]
- An expected response rates in the Elafibranor group at least similar to OCA (47%)

The response rates from phase 3 pivotal study supporting the regulatory approval of OCA has been estimated after imputation of missing or non reliable data as non response.

One hundred and fifty patients (100 elafibranor and 50 placebo) allow to achieve at least 90% power to demonstrate a statistically significant between group difference of 35% (47% in elafibranor group vs 12% in placebo group) in the response rate at week 52 of the primary efficacy endpoint with a two-sided alpha of 0.05 and using an exact Fisher test.

9.8.2. Normalization in ALP

Assuming 1/50 (2.0%) patient in the placebo arm with ALP normalization at week 52 (key secondary endpoint), 150 patients (100 elafibranor vs 50 placebo) provide at least 80% power to detect a statistically significant between group difference of 20.0% at a two-sided 0.05 alpha level.

9.8.3. Change in pruritus

Assuming a pooled SD of 2.3 points, 60 patients (40 elafibranor vs 20 placebo) with baseline PBC Worst Itch NRS score ≥4 provide at approximately 80% power to detect a statistically significant between group difference of 1.8 points in mean change from baseline in PBC Worst Itch NRS at a two-sided 0.05 alpha level. It is assumed that the same assumptions would apply to the two key secondary endpoints for pruritus (through week 52 and through week 24).

9.9. SAFETY ANALYSIS

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

AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Descriptive statistics will be presented giving the number and percentage of patients reporting at least one AE, the number of events and the EAIR. In addition, comparison of treatment arms will be performed giving EAIR estimates and their CIs. An overall summary of AEs will be provided. 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. SAEs, AESIs, and AEs leading to discontinuation will also be summarized. Narratives will be written for all SAEs, AESIs, and AEs leading to discontinuation.

Clinical laboratory values (hematology, chemistry, and urinalysis) recorded at each timepoint and change from baseline will be summarized by treatment group and overall 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 52 weeks treatment period and end of DB 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 and overall.

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

9.10. EXPLORATORY ANALYSIS (RELATED TO HISTOLOGICAL ASSESSEMENTS)

Descriptive statistics on the histological scores and the non invasive markers of fibrosis (liver stiffness, ELF test and ProC3) will be provided by DB treatment groups and overall in the Exploratory (Histological) set.

Change over time on the histological scores will be described using shift tables. In addition, the value at each visit as well as the change from baseline will be described on the non invasive markers of fibrosis.

For assessing the correlation between the histological fibrosis endpoints (Nakanuma and Ishak scores) and the non invasive markers of fibrosis, the correlation coefficients and their CIs will be estimated depending on the nature and distribution of the endpoints considered.

10 DATA HANDLING AND RECORD KEEPING

10.1. DATA PROTECTION

The contract between the sponsor and their vendors, and study sites specifies the responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

In the event of a potential data security breach concerning personal data processed on behalf of the sponsor, the data protection officer must be informed without undue delay and no later than 24 hours from the discovery of the event. The data protection officer will evaluate the event and notify the Data Protection Authorities within 72 hours, if required. Corrective actions and preventive actions will be implemented to mitigate the possible adverse effects. Affected study participants will be informed accordingly. Ipsen Data Protection Officer can be contacted by email: dataprivacy@ipsen.com.

10.2. CASE REPORT FORM AND SOURCE DOCUMENTS

An eCRF 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 ICH Good Clinical Practice (GCP) guidance requirements.

All study required patient data generated during the study will be recorded in the eCRF, with the exception of SAE forms which will be collected in paper. PRO data and central lab data will be transferred from electronic (source data) in the SDTM datasets. 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 unique 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 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 drug, 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.

10.3. 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 IB, protocol/amendments, drug accountability records, sample informed consent, staff curriculum vitae, and 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 study drug. 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 study. The study 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, GCP (ICH topic E6 R2), applicable regulatory requirements, and the current Declaration of Helsinki 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 attributable, legible, and contemporaneously recorded, original or a true copy, accurate (ALCOA), well-organized, and easily retrievable data.

Before screening any patients in this study, the Study Monitor will review the protocol, the IB, the eCRFs and instructions for their completion and return, the procedure for obtaining informed consent, and all other study procedures (e.g. the laboratory manual, electronic patient-reported outcomes [ePRO] manual, IXRS manual, etc) including the reporting AEs, AESIs 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 study. 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, in accordance with relevant SOPs and GCP (ICH topic E6 R2) 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.

In cases of emergency (e.g., pandemic, political strife, natural disasters), to continue to ensure data monitoring, according to national regulations and under the responsibility of the Investigator, remote access to source documents can be provided to the Study Monitor to perfom remote Source Data Verification (SDV).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 subjects) 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 and the GCP guidelines.

This study 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 auditors/inspectors 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 to this inspection if permitted by the Authorities.

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

The clinical study protocol, each step of the data capture procedure, and the handling of the data, including the final clinical study report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

12 ETHICS AND REGULATORY

12.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The GCP guidelines and the US Code of Federal Regulations (CFR) Title 21 Section 56 (21 CFR 56) require that approval must be obtained from an 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 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/IEC'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 study.

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 suspected unexpected serious adverse reactions (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 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 ICF 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.

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 study drug. 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 local regulations, ICH guidelines, privacy and data protection requirements, where applicable, 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 and by the person who conducted the informed consent discussion prior to protocol-specific procedures being performed.

A separate consent form will be obtained for optional biomarker samples to be collected and to be stored in the blood bank.

Participants to the optional research biobanking programme have the right to withdraw their consent at any time and for any reason during the study or during the period of sample storage (i.e. the entire 15 years during which samples are kept).

If a participant wishes to withdraw their consent for optional biobanking and the samples are still at the investigator site or at the central laboratory at the time, the investigator must inform the study monitor in writing of the participant's decision and destroy the samples.

If the samples are at the sponsor's repository (biobanking vendor), the investigator must inform the sponsor directly using the e-mail address: IpsenBiobanking@ipsen.com, mentioning only the participant ID in this e-mail. The sponsor will ensure destruction of the samples and all corresponding aliquots and issue confirmation of the destruction, which will be forwarded to the investigator. Analyses conducted before the withdrawal will not be affected.

In addition separate consent forms will be obtained for optional liver biopsy sample collection, as well as for pregnant partner data collection.

The Investigator must maintain the original, dated and signed ICFs. A copy of the signed ICFs 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 Clinical Trial Agreement (CTA).

12.5. DEFINITION OF THE END OF THE RESEARCH

The end of the study is defined as completion of the last visit or procedure of the last patient participating in the study globally (last EOT DB/EOT LTE visit).

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.

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

13.2. INSURANCE AND PATIENT INJURY

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

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 study 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 study.

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 Sponsor will prepare an integrated Clinical Study Report (CSR). Prior to issuing the final CSR, the CRO will prepare a draft report for approval by the Sponsor and by the study Steering Committee. The draft report will be submitted for Quality Control, the findings of which will be incorporated into the final version.

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 IB, 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 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 CSR. 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.

Protocol information and (final/interim) study results will be made publicly available on the US website (www.clinicaltrials.gov) and on the EU Clinical Trials Register (www.clinicaltrialsregister.eu) or EU Clinical Trials Portal (https://euclinicaltrials.eu/home). The sponsor also provides clinical trial information to other national clinical trial registries or databases according to local requirements/legislation. A lay summary of the study will be made available on the EU Clinical Trials Portal (https://euclinicaltrials.eu/home) and/or Sponsor website.

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 study results may be published or presented at scientific meetings after agreement between the Sponsor and the Investigators.

If this is foreseen, the investigator should discuss specific publication concepts, including data to be covered, target congress/journal and proposed authors, with the Sponsor for agreement before initiation. 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. The investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

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16 APPENDICES:

16.1. APPENDIX 1: ALCOHOL COMPARISON TABLE

Alcohol type	Alcohol by volume (ABV)	Volume		Amount of alcohol	
		Fluid ounce	mL	Units	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	40%	1.5	45	1	14
Wine	12%	5	150	1	14

Footnote:

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)

16.2. APPENDIX 2: PERMITTED/NON-PERMITTED MEDICATION

A. NON-PERMITTED MEDICATION AND CONDITION

Medications	When
Same pharmacological class (PPAR agonists)	
Thiazoledinediones (glitazones [pioglitazone and rosiglitazone])	From 2 months prior to screening and throughout the study
Fibrates	
Other Medications	
Obeticholic acid (OCA)	From 3 months prior to screening and throughout the study
Seladelpar	
Budesonide and other systemic Corticosteroids (parenteral & oral chronic administration only)	From 3 months prior to screening and throughout the study
Azathioprine	
Cyclosporine	
Methotrexate	
Mycophenolate	
Pentoxyfilline	
Alpha-methyl-dopa	
Sodium valproic acid	
Isoniazide	
Nitrofurantoin	
Amiodarone	
Tamoxifen	
Antibodies or immunotherapy directed against ILs or other cytokines or chemokines	From 12 months prior to screening and throughout the study

B. PERMITTED MEDICATION AND CONDITION

Medications	**When**
Therapies for treatment of PBC	
UCDA	Taken for at least 12 months prior to screening with Dose stability required from at least 3 months prior to screening and throughout the study.
Therapies for treatment of pruritus	
Cholestyramine	Dose stability required for at least 3 months prior to screening and up to the end of the Double Blind period.
Rifampin	
Naltrexone	
Sertraline	
Other Medications	
Colchicine	
Lipid lowering therapy	
Statins	Dose stability required from at least 2 months prior to screening
Ezetimibe	

16.3. APPENDIX 3: SAMPLE PATIENT REPORTED OUTCOME QUESTIONNAIRES:

16.3.1. PBC-40

Patient ID	Date:

For each statement, please circle the response that comes closest to how you feel. If any of the statements do not apply to you please circle 'does not apply'.

Can you say how often the following statements about digestion and diet applied to you IN THE LAST FOUR WEEKS?							
1	I was able to eat what I liked	Never	Rarely	Sometimes	Most of the time	Always	
2	I ate or drank only a small amount, and still felt bloated	Never	Rarely	Sometimes	Most of the time	Always	
3	I felt unwell when I drank alcohol	Never	Rarely	Sometimes	Most of the time	Always	Did not apply /never drink alcohol
And IN THE LAST FOUR WEEKS, how often did you experience any of the following?							
4	I had discomfort in my right side	Never	Rarely	Sometimes	Most of the time	Always	
5	I had dry eyes	Never	Rarely	Sometimes	Most of the time	Always	
6	My mouth was very dry	Never	Rarely	Sometimes	Most of the time	Always	
7	I had aches in the long bones of my arms and legs	Never	Rarely	Sometimes	Most of the time	Always	
Some people with PBC experience itching. How often did you experience itching IN THE LAST FOUR WEEKS? If you did not itch, please circle 'does not apply'							
8	Itching disturbed my sleep	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/ no itch
9	I scratched so much I made my skin raw	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/no itch
10	I felt embarrassed because of the itching	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/no itch

Fatigue can also be a problem for many people with PBC. How often did the following statements apply to you IN THE LAST FOUR WEEKS?

11	I had to force myself to get out of bed	Never	Rarely	Sometimes	Most of the time	Always
12	I had to have a sleep during the day	Never	Rarely	Sometimes	Most of the time	Always
13	Fatigue interfered with my daily routine	Never	Rarely	Sometimes	Most of the time	Always
14	I felt worn out	Never	Rarely	Sometimes	Most of the time	Always
15	I felt so tired, I had to force myself to do the things I needed to do	Never	Rarely	Sometimes	Most of the time	Always
16	I felt so tired, I had to go to bed early	Never	Rarely	Sometimes	Most of the time	Always
17	Fatigue just suddenly hit me	Never	Rarely	Sometimes	Most of the time	Always
18	PBC drained every ounce of energy out of me	Never	Rarely	Sometimes	Most of the time	Always

The next section is about the effort and planning that can be involved in living with PBC. Thinking about THE LAST FOUR WEEKS, how often did the following statements apply to you?

19	Some days it took me a long time to do anything	Never	Rarely	Sometimes	Most of the time	Always
20	If I was busy one day I needed at least another day to recover	Never	Rarely	Sometimes	Most of the time	Always
21	I had to pace myself for day-to-day things	Never	Rarely	Sometimes	Most of the time	Always

The following statements are about the effects that PBC may have on things like memory and concentration. Thinking about THE LAST FOUR WEEKS, how often did the following statements apply to you?

22	Because of PBC I had to make a lot of effort to remember things	Never	Rarely	Sometimes	Most of the time	Always
23	Because of PBC I had difficulty remembering things from one day to the next	Never	Rarely	Sometimes	Most of the time	Always
24	My concentration span was short because of PBC	Never	Rarely	Sometimes	Most of the time	Always

25	Because of PBC, I had difficulty keeping up with conversations	Never	Rarely	Sometimes	Most of the time	Always	
26	Because of PBC, I found it difficult to concentrate on anything	Never	Rarely	Sometimes	Most of the time	Always	
27	Because of PBC, I found it difficult to remember what I wanted to do	Never	Rarely	Sometimes	Most of the time	Always	

Now some more general statements about how PBC may be affecting you as a person. How much do the following statements apply to you?

28	Because of PBC, I get more stressed about things than I used to	Not at all	A little	Somewhat	Quite a bit	Very much	
29	My sex life has been affected because of PBC	Not at all	A little	Somewhat	Quite a bit	Very much	Does not apply
30	Having PBC gets me down	Not at all	A little	Somewhat	Quite a bit	Very much	
31	I feel I neglect my family because of having PBC	Not at all	A little	Somewhat	Quite a bit	Very much	Does not apply
32	I feel guilty that I can't do what I used to do because of having PBC	Not at all	A little	Somewhat	Quite a bit	Very much	
33	I worry about how my PBC will be in the future	Not at all	A little	Somewhat	Quite a bit	Very much	

These statements relate to the possible effects of PBC on your social life. Thinking of your own situation, how much do you agree or disagree with them?

34	I sometimes feel frustrated that I can't go out and enjoy myself	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
35	I tend to keep the fact that I have PBC to myself	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
36	I can't plan holidays because of having PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
37	My social life has almost stopped	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

The next section is about the impact that PBC may be having on your life overall. How much do you agree or disagree with the following statements?

38	Everything in my life is affected by PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
39	PBC has reduced the quality of my life	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
40	I can still lead a normal life, despite having PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

The next few questions are about your general health and well being:

A	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor
B	And how would you have rated it before you had PBC?	Excellent	Very good	Good	Fair	Poor
C	COMPARED TO ONE YEAR AGO, how would you rate your health in general now?	Much better	Somewhat better	About the same	Somewhat worse	Much worse

THANK YOU FOR TAKING THE TIME TO COMPLETE

16.3.2. Epworth Sleepiness Scale (ESS)

Name: _____ Today's date: _____

Your age (yrs): _____ Your gender (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired?

This refers to your usual way of life recently.

Even if you haven't done some of these things recently, try to figure out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = **no chance** of dozing
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each item as best as you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g., a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car or bus, while stopped for a few minutes in traffic	

THANK YOU FOR YOUR COOPERATION

16.3.3. 5-D Itch Scale

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

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

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

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

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

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

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

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

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

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

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

16.3.4. PROMIS Fatigue Short Form 7a

Please respond to each question by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
FATEXP20	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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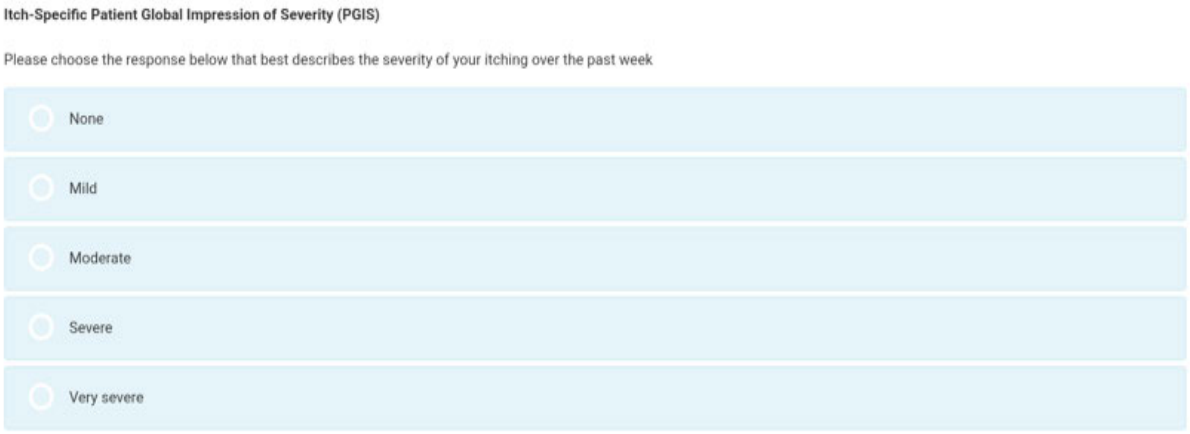
16.3.5. The Patient Global Impression of Change (PGIC)

Itch-Specific Patient Global Impression of Change (PGIC)

Please choose the response below that best describes the overall change in your itching since you started taking the study medication

- Much better
- A little better
- No change
- A little worse
- Much worse

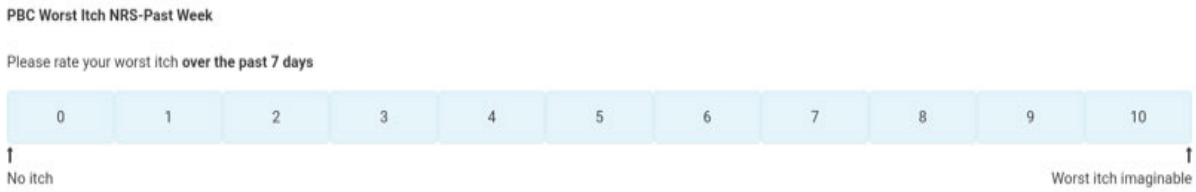
16.3.6. The Patient Global Impression of Severity (PGIS)



16.3.7. PBC Worst Itch NRS

PBC Worst Itch NRS

PBC Worst Itch NRS-Past Week



16.3.8. EuroQoL EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐