Statistical Analysis Plan

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

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Only the final version (and subsequent finalized amendments) requires signatures

I confirm that I have reviewed this document and agree with the content.

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AASLD	American Association for the Study of Liver Diseases
ACR	Albumin/Creatinine Ratio
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	ALkaline Phosphatase
ALT	ALanine aminoTransferase
ANCOVA	ANalysis of COVAriance
AST	Aspartate Aminotransferase
AT	Aminotransferase
ATC	Anatomical Therapeutic Chemical
BCL6	B-Cell Lymphoma 6
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
Bx	Biological assessment visit
C4	serum 7α-hydroxy-4-cholesten-3-one
CA	Competent Authorities
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Confidence Interval
CK-18	cytokeratin-18
CPK	Creatine PhosphoKinase
CRN	Clinical Research Network
CRO	Clinical Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report

CTCAE	Common Terminology Criteria for Adverse Events
CYP	CYtochrome P450
CV	Coefficient of Variation
DCA	DeoxyCholic Acid
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DSMB	Data Safety Monitoring Board
EASL	European Association for the Study of the Liver
ECG	ElectroCardioGram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EOT	End of Study Treatment
FDA	Food and Drug Administration
FGF19	Fibroblast Growth Factor 19
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GPP	Good Pharmacoepidemiology Practice
HBsAg	Hepatitis B surface Antigen
HCC	HepatoCellular Carcinoma
HCV	Hepatitis C Virus
HDL-C	High-Density Lipoprotein Cholesterol
HIV	Human Iimmunodeficiency Virus
hPPAR	human Peroxisome Proliferator-Activated Receptor
HRT	Hormonal Replacement Therapy
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IL-6	Interleukin-6
INR	International Normalized Ratio

IP	Investigational Product
IR	Insulin Resistance
IRB	Institutional Review Board
ITT	Intent-To- Treat
IVRS/IWRS	Integrated Voice/Web Response System
LDL-C	Low-Density Lipoprotein Cholesterol
LPLV	Last Patient Last Visit
LSS	Life Science Services
M2	anti-inflammatory macrophages
Max	Maximum
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model End stage Liver Disease
Min	Minimum
mITT	modified Intent To Treat
N/A	Not Applicable
NASH	NoAalcoholic SteatoHepatitis
NCEP ATP III	National Cholesterol Education Program's Adult Treatment Panel III
NF-κB	Nuclear Factor kappa B
PBC	Primary Biliary Cholangitis
PD	PharmacoDynamics
PK	PharmacoKinetics
PPAR	Peroxisome Proliferator-Activated Receptor
PPS	Per Protocol Set
PRV	Pre-Randomization Visit
PT	Preferred Term
QC	Quality Control
QoL	Quality of Life
QTc	corrected QT
SADR	Serious Adverse Drug Reaction

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV	Screening Visit
TEAE	Treatment-Emergent Adverse Event
TGF-β	Transforming Growth Factor Beta
TLC	Therapeutic Lifestyle Change
TLF	Table, Listing, and Figure
TNFα	Tumor Necrosis Factor-alpha
UDCA	UrsoDeoxyCholic Acid
UK	United Kingdom
ULN	Upper Limit of Normal
UV-LLNA	UV- Local Lymph Node Assay
VAS	Visual Analogue Score
WHO	World Health Organization

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures that will be produced and the statistical methodologies that will be used are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. RESPONSIBILITIES

[redacted] will perform the statistical analyses and will be responsible for the production and quality control of all tables and listings. This SAP only describes efficacy and safety analyses. Pharmacokinetic (PK) analysis is not within the scope of this SAP and will be performed by the sponsor or sponsor-designated third party.

2.2. TIMINGS OF ANALYSES

The primary analysis of safety and efficacy is planned after all subjects complete the final study visit or withdraw early from the study. No interim analyses will be performed, and no DSMB has been set-up for this study. This SAP details these analyses and has been finalized prior to unblinding of the study.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

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

3.2. SECONDARY OBJECTIVE(S)

To assess the following endpoints at Visit 5 (W+eek 12):

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

3.3. SAFETY OBJECTIVES

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

- adverse events (AEs) and serious adverse events (SAEs)
- physical examination
- vital signs
- medical history
- ECG
- hematological parameters
- liver markers
- other biochemical safety parameters

3.4. EXPLORATORY OBJECTIVE

To determine PK parameters of elafibranor (GFT505) 80 and 120 mg and its main active circulating metabolite, GFT1007, in patients with PBC and to explore an exposure-response relationship. PK analysis is not within the scope of this SAP and will be described in a separate document (see Section 2.1).

3.5. BRIEF DESCRIPTION

This is a Phase 2, proof-of-concept, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of elafibranor 80 mg and 120 mg once daily versus placebo in a PBC population. Patients will be randomized to 80-mg elafibranor, 120-mg elafibranor, or placebo in a 1:1:1 ratio.

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

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

3.6. SUBJECT SELECTION

3.6.1. Inclusion Criteria

1. Must have provided written informed consent
2. Males or females 18 to 75 years of age
3. Definite or probable PBC diagnosis as demonstrated by the presence of at least 2 of the following 3 diagnostic factors:
    - History of elevated ALP levels for at least 6 months

- Positive Anti-Mitochondrial Antibodies (AMA) titers (> 1/40 on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay (ELISA) or positive PBC-specific antinuclear antibodies
- Liver biopsy consistent with PBC

4. ALP ≥ 1.67x upper limit of normal (ULN) ('inadequate response to UDCA')
5. Taking UDCA for at least 12 months (stable dose for ≥ 6 months) prior to Screening Visit
6. Contraception: Females participating in this study must be of non-childbearing potential or must be using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:

   a) Cessation of menses for at least 12 months due to ovarian failure
   b) Surgical sterilization such as bilateral oophorectomy, hysterectomy, or medically documented ovarian failure
   c) Using a highly effective non-hormonal method of contraception (bilateral tubal occlusion, vasectomized partner or intrauterine device)
   d) Double contraception with barrier and highly effective hormonal method of contraception (oral, intravaginal, or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation, oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation or intrauterine hormone-releasing system). The hormonal contraception must be started at least 1 month prior to randomization.

7. Must agree to comply with the trial protocol

3.6.2. Exclusion Criteria

1. History or presence of other concomitant liver diseases including:

   - Positive hepatitis B surface antigen (HBsAg) at Screening
   - Positive HCV RNA (tested for in case of known cured HCV infection or positive HCV Ab at Screening)
   - Alcoholic liver disease
   - Primary sclerosing cholangitis (PSC)
   - Definite autoimmune hepatitis (AIH) or 'AIH-PBC overlap syndrome'
   - Biopsy-confirmed non-alcoholic steatohepatitis (NASH)
   - Known history of alpha-1 antitrypsin deficiency, or other metabolic forms of
   - chronic liver disease
   - Gilbert's syndrome (due to interpretability of bilirubin levels)

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

- 3 months prior to screening and throughout the trial (up to last study visit) : azathioprine, colchicine, cyclosporine, methotrexate, mycophenolate mofetil, pentoxifylline; budesonide and other chronic systemic corticosteroids; and potentially hepatotoxic drugs (including *a*-methyl-dopa, sodium valproic acid, isoniazide, or nitrofurantoin)

- 12 months prior to inclusion visit and throughout the trial (up to last study visit): antibodies or immunotherapy directed against interleukins or other cytokines or chemokines

- NOTE: Anti-pruritus treatment, including rifamycin, is allowed if prescribed for at least 6 months prior to screening, patient is on stable dose at least 3 months prior to screening, and patient continues at the same dose throughout the study

12. If female: known pregnancy, has a positive urine pregnancy test (confirmed by a positive serum pregnancy test), or lactating

13. Known history of human immunodeficiency virus (HIV) infection

14. Medical conditions that may cause nonhepatic increases in ALP (eg, Paget's disease)

15. Other clinically significant medical conditions that are not well controlled or for which medication needs are anticipated to change during the study

16. Anticipated changes to current medications (that will be continued) during the course of the study

17. History of alcohol abuse, defined as consumption of more than 30 g pure alcohol per day for men and more than 20 g pure alcohol per day for women, or other substance abuse within 1 year prior to Day 0 (randomization visit)

18. Participation in another study with an investigational drug, biologic, or medical device using active substance within 30 days prior to screening, or within 5 half-lives of the active substance, whichever is longer

19. History of noncompliance with medical regimens or patients who are considered to be potentially unreliable

20. Mental instability or incompetence, such that the validity of informed consent or compliance with the study protocol is uncertain

21. Known hypersensitivity to the investigational product or any of its formulation excipients

22. Evidence of any other unstable or untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease

3.7. DETERMINATION OF SAMPLE SIZE

It is planned to randomize 15 patients per treatment arm (45 in total). All sample size calculations were done using PASS 13 software.

Fifteen patients in each of the elafibranor arms and placebo arm or 45 patients in total would achieve greater than 80% power to detect a percentage decrease of 20% for each dose-placebo comparison. This calculation assumes that the standard deviation (on the percentage relative change from baseline) in each elafibranor arm is 18 and for placebo arm is 15 and were based on the results from the Phase 2b elafibranor trial (Clinical Study Report [CSR] not yet available). The sample size calculation is based on a 2-sided 2-sample unequal-variance t-test with a significance level (alpha) of 0.05.

3.8. TREATMENT ASSIGNMENT AND BLINDING

Eligible patients will be randomized in a 1:1:1 ratio to receive elafibranor 80 mg, elafibranor 120 mg, or placebo using centralized randomization.

Identification numbers will be assigned to each patient at the Screening Visit. The number will also be reported in the eCRF. Upon completion of the Screening Visit, if the patient fulfills all the criteria to enter the study, the Investigator will register the patient in the IVRS/IWRS (integrated voice/web response) system to pre-randomize him/her (at least 1 week before Visit 1).

The IVRS/IWRS will check if the Investigator is authorized to use the system (using identification number and access code). The IVRS/IWRS will then allocate the patient to a treatment arm (placebo, elafibranor 80 mg, or elafibranor 120 mg) through a treatment number and will immediately forward the information to the Drug Distribution Centre, which will be responsible to send to the site the corresponding treatment package allocated to the patient for the 12-week period, within 1 week at most. This labeled package will include 3 period boxes, one for each period [Visit 1-Visit 3], [Visit 3-Visit 4], and [Visit 4-Visit 5]. A confirmatory e-mail will also be sent to the Investigator and to the Sponsor. The pharmacy will acknowledge receipt of the study drug in the IVRS/IWRS.

During the study, the Investigator, patient, and study personnel will be blinded to the treatment allocation. Both elafibranor and placebo tablets and packaging are indistinguishable. The randomization code may be broken by the Investigator when urgent action is required for the clinical management of the patient. For each patient, the list of treatment numbers allocated to the patient will be stored in the IVRS/IWRS. The Investigator will be able to unblind any treatment carton that was dispensed to the patient by connecting to the IVRS/IWRS (**24-hour and 7-day access**) and entering

his/her identification number and access code. A back-up phone Interactive Response Technology (IRT) module will also be available should the site be unable to access the internet. The IVRS/IWRS will verify the authorization to unblind the entered treatment carton number, and the screen will then display the treatment arm. When completed, a blinded confirmatory e-mail will be sent to the Investigator and the Sponsor.

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

3.9. ADMINISTRATION OF STUDY MEDICATION

Both elafibranor and placebo tablets and packaging are indistinguishable. Patients will be informed to take 2 tablets per day of elafibranor 80 mg or 120 mg or placebo orally with a glass of water each morning before breakfast.

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

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

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

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

3.10. STUDY PROCEDURES AND FLOWCHART

This study consists of a Screening Visit up to 4 weeks prior to randomization and 5 study visits over a period of 12 weeks.

Table 1: Study General Assessment Schedule

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

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

[a] All inclusion/exclusion criteria, including biological and histological criteria, assessed at V1
[b] Height is measured only at SV
[c] There are a total of 9 PK sampling time points: 8 each at V1 and V2; the 9th sample is taken at 24 h on the following day (V1(PK) and V2(PK), respectively).

[d] 24 h sampling time point to be done at ambulatory visit (pre-dose, fasting)
[e] At least 1 week before visit V1 and after eligibility confirmation
[f] A pre-randomization confirmation
[g] only in case of premature discontinuation, EOT needs to be performed

Table 2: Study Biological Assessment Schedule

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

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

[a] for Women of Childbearing potential only (WOCBP)
[b] assessment of presence of myoglobin in urine may be done locally at the discretion of the PI, **only** in case of clinically significant CPK elevation
[c] in case of premature discontinuation, end of treatment visit should be performed between 16 and 30 days after last drug intake
[d] Bile acid panel includes the following: **(**cholic acid (CA), glycocholic acid (GCA), taurocholic acid (TCA), chenodeoxycholic acid (CDCA), glycochenodeoxycholic acid (GCDCA), taurochenodeoxycholic acid (TCDCA), deoxycholic acid (DCA), glycodeoxycholic acid (GDCA), taurodeoxycholic acid (TDCA), lithocholic acid (LCA), glycolithocholic acid (GLCA), taurolithocholic acid (TLCA), ursodeoxycholic acid (UDCA), glycoursodeoxycholic acid (GUDCA), tauroursodeoxycholic acid (TUDCA), hyocholic acid (HCA), glycohyocholic acid (GHCA), taurohyocholic acid (THCA), hyodeoxycholic acid (HDCA), glycohyodeoxycholic acid (GHDCA) and taurohyodeoxycholic acid (THDCA).

4. ENDPOINTS

4.1. PRIMARY EFFICACY ENDPOINT

The primary endpoint of the study is relative change from baseline in serum ALP levels comparing each elafibranor dose group to placebo at EndPoint (Visit 5 or EOT value, must be last post baseline value under treatment).

All blood samples for efficacy and/or for safety assessment (as described in Table 2: Study Biological Assessment Schedulewill be returned and analyzed by the central laboratory (BARC: Ghent – Belgium, or New York – USA).

A laboratory manual will be provided to each trial site.

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

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

The option to retest during the study is left to the Investigator's judgment. During Screening, retesting (to be performed at Retesting Screening Visits) is limited to CPK, and HCV RNA (in case of positive HCV Ab at Screening Visit).

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

4.2. SECONDARY EFFICACY ENDPOINTS

The following secondary endpoints will be assessed at EndPoint (Visit 5 or EOT value, must be last post baseline value under treatment):

- Absolute change from baseline in ALP
- Response to treatment based on composite endpoints:
    - ALP < 1.67 × ULN and total bilirubin within normal limit and > 15% decrease in ALP

- ALP < 2 × ULN and total bilirubin within normal limit and > 40% decrease in ALP

- Response according to Paris I, Paris II, Toronto I, Toronto II, UK-PBC risk score
- Response to treatment on normalization of ALP
- Response to treatment on normalization of bilirubin
- Response to treatment on normalization of albumin
- Response on at least 10%, 20%, 40% decrease in ALP
- Absolute and relative change from baseline in ALT, AST, GGT, 5'nucleotidase, total bilirubin, conjugated bilirubin, albumin
- Absolute and relative change from baseline in lipid parameters
- Absolute and relative change from baseline in bile acids
- Absolute and relative change from baseline in C4, FGF19
- Absolute and relative change from baseline in IgM
- Absolute and relative change from baseline in inflammatory and liver fibrosis markers
- Absolute and relative change from baseline in pruritus (through 5D-itch scale & visual analogue score VAS)
- Absolute and relative change from baseline in quality of life (using PBC 40 questionnaire)
- Adverse Events (AEs)
- Cardiovascular parameters (12-lead ECG, heart rate, blood pressure)
- Hematology and safety parameters

4.3. SAFETY ENDPOINTS

The tolerability and safety of once per day oral administration of elafibranor in 80-mg and 120-mg doses in patients with PBC:

- adverse events (AEs) and serious adverse events (SAEs)
- physical examination
- vital signs
- medical history
- ECG
- hematological parameters
- liver markers
- other biochemical safety parameters

5. ANALYSIS SETS

5.1. ENROLLED SET

The Enrolled Set will include all subjects who sign informed consent. This set will be used for subject listings and summaries of subject disposition.

5.2. SAFETY SET

The Safety Set (SS) will include all randomized subjects who were administered at least one dose of study medication. Subjects will be analyzed according to treatment received. The SS will be used for all analyses of safety.

5.3. INTENT-TO-TREAT

The Intent-to-Treat (ITT) population will include all randomized subjects.

Based on the ITT principle, the modified ITT (mITT) will include all randomized patients receiving at least one study drug dose with available baseline value and at least one post baseline value for the primary endpoint Subjects will be analyzed according to randomized treatment. The mITT population will be used for all analyses of primary and secondary efficacy endpoints.

5.4. PER-PROTOCOL SET

The per-protocol Set (PPS) includes all subjects from the mITT population who are compliant with the study protocol without any major protocol deviations. Classification of protocol deviations as major or minor will be agreed on at the Data Review Meeting (DRM) prior to database lock. Analysis based on the PPS will be performed for the primary efficacy endpoint and key secondary endpoints as an additional analysis. Subjects will be analyzed according to randomized treatment.

Criteria for exclusion from the PPS are defined in section 5.5.

5.5. PROTOCOL DEVIATIONS

Protocol deviations are collected and agreed at the DRM to evaluate protocol deviations considered to have major impact on subject safety or the validity of the study data. Subjects with major protocol deviations will be excluded from the PPS under the assumption that the deviation may have an impact on the efficacy analysis. Important protocol deviation categories may include, but are not limited to the following:

- Inclusion/Exclusion Criteria not met
- Informed Consent: Informed Consent Form not signed or signed late

- Informed Consent: Other
- Randomization: Randomized and Not Treated
- Randomization: Treated and not randomized
- Randomization: Multiple Randomizations
- Randomization: Other
- Investigation Product/Dosing: Incorrect IP kit given to Patient
- Investigation Product/Dosing: IP Storage
- Investigation Product/Dosing: IP Dosing
- Investigation Product/Dosing: other
- Prohibited Concomitant Treatment
- Visit Window
- Study Procedure: Major Non-Compliance
- Site Staff Authorization, Delegation, Training

Further major protocol deviations will be defined during the DRM.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

All subjects entered into the database will be included in subject data listings. Summary tables will be provided for all subjects. Unless otherwise specified, all demographic and baseline data will be presented by treatment arm and overall. Efficacy and safety data will be presented by treatment arm.

Quantitative (continuous) data—absolute values and changes from baseline, where appropriate—will be summarized with number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Confidence intervals (CIs; 95%, 2-sided) will be added where applicable.

In the case of similarity between the ITT and mITT, the primary population for efficacy analysis will be the ITT set and otherwise the mITT set. Supportive analyses based on the PPS will be conducted for the primary and key secondary endpoints. The primary population for safety analysis will be the safety population.

Qualitative (categorical) data will be summarized using number of observations (n) and frequency and percentages of subjects. Unless stated otherwise, the calculation of percentages will be based on the total number of subjects with nonmissing data in the set of interest. Confidence intervals (CIs; 95%, 2-sided) will be added, where applicable.

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

All tests of hypotheses will be 2-sided and conducted at the 5% significance level, and all confidence intervals (CIs) will be 2-sided at the 95% level. No adjustment for multiplicity will be made for the primary and secondary efficacy variables.

All statistical analyses will be performed using SAS® (Version 9.3 or higher, SAS Institute Inc., Cary, NC, USA).

6.2. KEY DEFINITIONS

Definition of Baseline

Baseline value is defined as last nonmissing value prior to first study drug dose.

For all secondary and safety endpoints, the same definition will apply. It will be assumed that all assessments on Day 0 occur prior to dosing.

End of Treatment (EOT) Visit

In case of premature discontinuation of the study drug, EOT visit refers to the visit scheduled within 30 days of final study drug administration.

End of Treatment (EOT) Value

Last post-baseline value under treatment.

End of Study (EOS) Visit

For all patients who complete the double-blind treatment period, the EOS visit refers to the visit scheduled at least 16 days but not more than 30 days after Visit 5.

Treatment Period

The Treatment Period covers the duration that a subject is under treatment in the study between the date of first study drug intake and the date of last study drug intake.

Study Duration (in days)

Day of study termination = Date of EOS visit (or EOT visit in case of premature discontinuation) – Date of Visit 1(Day 0) + 1

Definition of Study Completion and Withdrawal

A subject will be defined as "study completed" if s/he completes the follow-up period of the study after having performed all the planned visits. Termination/withdrawal at a different time point will be considered as study discontinuation/withdrawal.

Endpoint Value

Endpoint value is considered the value at Visit 5 (Week 12) or EOT value (last post-baseline value under treatment).

Relative Change from Baseline

Relative change from baseline is defined as percentage change from baseline to Endpoint.

Change from Baseline

Absolute change from baseline:

Absolute change = Post baseline value – Value at baseline

6.3. MISSING DATA

The primary efficacy endpoint is based on the availability of a post baseline measure of ALP.

Incomplete/missing start and stop dates will be handled as follows:

Incomplete AE/concomitant medication or treatment start date will be imputed:

If the AE/concomitant medication or treatment start month = month of the first treatment, the missing start day will be imputed with the day of the first treatment, otherwise Missing start day with '01'.

If the AE/concomitant medication or treatment start year = year of the first treatment then with the date of the first treatment. Missing start year with the date of the first treatment,
otherwise Missing start day and month with the 1st of January.

Incomplete AE/concomitant medication or treatment stop date will be imputed:

Missing stop day with last day (28/29/30/31) of the month.

Missing stop day and month with 31st of December.

Missing stop year with the date of study termination.

For all other data, all available data will be included in the analyses and will be summarized as far as possible. Unless otherwise specified, there will be no substitution of missing data, ie, missing data will not be replaced; missing data will be handled as 'missing' in the statistical evaluation.

6.4. VISIT WINDOWS

The following visit windows are currently proposed for this study. These are protocol defined windows but visits will be included in the TLFs as recorded in the CRF.

Table 3: Visit Windows

Visit	Target Trial Day	Allowable window
Screening (Week -4 to -1)	-28 to -7	N/A
Visit 1 (randomization/ Week 0)	0	0
Visit 2 (Week 2)	14	± 1 day
Visit 3 (Week 4)	28	± 2 days
Visit 4 (Week 8)	56	± 2 days
Visit 5 (Week 12)	84	± 2 days
EOT*	Within 16-30 days post last drug intake	N/A
EOS**	Within 16-30 days post V5	N/A

* *Only in case of premature discontinuation*
** *Only in case of patients completing V5*

6.5. POOLING OF CENTERS

No investigation of center effects is planned; data from all centers will be pooled.

6.6. SUBGROUPS

No subgroup analyses are planned for this study.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

In the case of similarity between the SS, ITT and mITT and consistency between actual and assigned treatments, tables will not be duplicated.

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

Subject disposition will be summarized by presenting the number of subjects enrolled in the study (signed informed consent) and the number and percentage of patients that were:

- Screen Failures (Enrolled Population)
- Randomized (Enrolled Population)
- Received at least 1 dose of study medication (Enrolled population)
- Number of subjects in each analysis set (SS, ITT, mITT, PPS)
- Completed the 12-week treatment period
- Discontinued from the study with primary reason for premature discontinuation

The summaries will be presented by treatment arm (elafibranor 80 mg, elafibranor 120 mg, and placebo) and overall.

Listings including the patient disposition, status with respect to inclusion and exclusion criteria, and population eligibility will be presented.

Major protocol deviations and deviations that may affect the efficacy analysis will be summarized for randomized subjects by treatment arm (elafibranor 80 mg, elafibranor 120 mg, and placebo) and overall. All protocol deviations will be listed, and sorted by patient number and date of deviation (if available). This by-patient listing will identify whether a specific protocol deviation is major or minor, and whether it is considered to potentially affect the analysis of efficacy.

All data will be listed and sorted by patient number.

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics will be based on the information provided at the Screening Visit. The characteristics will be presented by treatment schedule (elafibranor 80 mg, elafibranor 120 mg, and placebo) and overall for each analysis set (SS, ITT, mITT, and PPS). The characteristics to be summarized are given below with details of whether they will be summarized as categorical or continuous:

- Age (years)-continuous
- Gender-categorical
- Race-categorical
- Ethnicity-categorical
- Height (cm)-continuous
- Weight (kg) -continuous
- BMI (kg/m2)- continuous
- SBP (mgHg)
- DBP (mgHg)
- Pulse Rate (Beats/min)
- Childbearing potential status-categorical
- Screening Visit and Baseline Biological labs (including haematology, Biochemistry, Lipids, Inflammatory Markers, Liver Markers...-Continuous

Age at study entry will be calculated as (date the informed consent was signed – date of birth) / 365.25 rounded down to the nearest integer.

All data will be listed.

Viral serology data (HIV, hepatitis B, and hepatitis C) assessed at screening will be listed only.

7.3. MEDICAL HISTORY AND CONCOMITANT DISEASES

The medical history reported on the eCRF will be coded to Medical Dictionary for Regulatory Activities (MedDRA) terminology (latest available version).

Medical history will be defined as any clinically significant past medical conditions that ended before screening. Medical history will be summarized for the SS population with number and percentage of subjects with at least one medical history item, and number and percentage of subjects by system organ class (SOC) and preferred term (PT). The terms will be sorted alphabetically by SOC and PT.

Concomitant diseases will be defined as any clinically significant current medical conditions that were ongoing at screening. Concomitant diseases will be summarized for

the SS, ITT and mITT sets with number and percentage of subjects with at least one concomitant disease, and number and percentage of subjects by system organ class (SOC) and preferred term (PT). The terms will be sorted alphabetically by SOC and PT.

Concomitant diseases will be flagged on the medical history data listing.

7.4. OTHER BASELINE CHARACTERISTICS

Baseline characteristics are defined as all results of the examinations performed prior to the first elafibranor or placebo administration at the randomization visit. These include several safety laboratory tests that will be summarized by treatment arm and overall by means of summary statistics (see Section 9 for more details).

Baseline characteristics for screened failed subjects will be provided.

Administration of standard diet and exercise recommendations at Screening Visit will be listed only.

7.5. MEDICATION

Prior and concomitant medications (during and after treatment) will be coded using the latest available version of the Anatomical-Therapeutic-Chemical (ATC) classification text from the World Health Organization Drug Dictionary (WHO DD) and summarized separately. The number and percentage of patients taking a medication will be displayed by therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term. If a therapeutic subgroup or preferred term is unavailable 'Uncoded' will be used. Patients will only be counted one time in each unique ATC-Level 2, ATC-Level 4 and generic term. Tables will be sorted alphabetically by therapeutic subgroup and preferred drug name.

If it is identified after Randomization that any nonpermitted drugs have been administered to a patient within the excluded timeframes, the patient will be permanently discontinued from the study drug. The number and percentage of subjects taking nonpermitted medication or treatment during the study will be summarized within the protocol deviation summary. Prohibited medications and timeframe for exclusion are listed in Table 4.

All prior and concomitant medications will be listed and will include both the medication name as reported by the Investigator as well as the coded information.

Table 4: Nonpermitted Medications

Medication	Time window for exclusion
Indomethacin	From Randomization up to EOT Visit
Thiazoledinediones (glitazones)	From 2 months prior to Screening Visit up to EOT Visit
Fibrates	From 2 months prior to Screening Visit up to EOT Visit
Obeticholic acid	From 2 months prior to Screening Visit up to EOT Visit
Budesonide and other systemic corticosteroids	From 3 months prior to Screening Visit up to EOT Visit
Azathioprine	From 3 months prior to Screening Visit up to EOT Visit
Colchicine	From 3 months prior to Screening Visit up to EOT Visit
Cyclosporine	From 3 months prior to Screening Visit up to EOT Visit
Methotrexate	From 3 months prior to Screening Visit up to EOT Visit
Mycophenolate	From 3 months prior to Screening Visit up to EOT Visit
Mofetil	From 3 months prior to Screening Visit up to EOT Visit
Pentoxyfilline	From 3 months prior to Screening Visit up to EOT Visit
Alpha-methyl-dopa	From 3 months prior to Screening Visit up to EOT Visit
Sodium valproic acid	From 3 months prior to Screening Visit up to EOT Visit
Isoniazide	From 3 months prior to Screening Visit up to EOT Visit
Nitrofurantoin	From 3 months prior to Screening Visit up to EOT Visit
Antibodies or immunotherapy directed against interleukins or other cytokines or cheomkines	From 12 months prior to Screening Visit up to EOT Visit

7.5.1. Prior Medication

Prior medications are defined as medications taken at any time during the 30 days prior to screening that stop before the administration of the first dose of study drug at randomization visit (Day 0). Any changes to prior medications (dose, regimen, etc.) during the study will be considered a new *Concomitant Medication*.

The number and percentage of subjects with prior medications will be summarized for the SS by therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term.

In addition, prior Duration (years) and Dose (mg) at screening of UDCA will be summarized separately.

Prior duration of UDCA at screening will be calculated as [(date of screening – date of first UDCA dose)+1]/ 365.25 rounded to one decimal precision.

7.5.2. Concomitant Medication

Concomitant medications are those with a start date on or after the first dose of study treatment, or those with a start date before the first dose of study treatment and a stop date on or after the first dose of study treatment or still ongoing at the end of the study.

If a medication cannot be classified as “prior” or “concomitant” after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

The number and percentage of subjects with concomitant medications during the treatment phase will be summarized for the SS by therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term.

8. EFFICACY

In the case of similarity between the ITT and mITT, all efficacy analyses will be conducted on the ITT set and otherwise on the mITT set. Supportive analysis of the primary efficacy endpoint and key secondary endpoints will be conducted using the PPS.

In addition to the statistical analyses described in the sections below, descriptive summaries (as per Section 8) and data listings sorted by unique patient number will be presented for all efficacy variables.

All blood sampling for primary and secondary efficacy endpoints will be performed by trained personnel at each site. Blood samples will be processed and shipped as outlined in the laboratory manual.

8.1. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

The primary efficacy endpoint is defined as relative change from baseline to Endpoint in serum ALP.

Actual values and the relative change from baseline will be summarized with descriptive statistics for continuous variables.

Relative change in ALP will be calculated by:

[(Endpoint value – Baseline Value) / Baseline value)] x 100.

Baseline value will be computed as last nonmissing value prior to first study dose at randomization visit (V1).

Endpoint will be computed as:

- Value at V5 or
- EOT value (must be last postbaseline value under treatment).

ALP relative change from baseline will be summarized as continuous by treatment arm.

The relative change in ALP from baseline will be compared between 120 mg elafibranor and placebo and between 80 mg elafibranor and placebo using a nonparametric randomization-based Analysis of Covariance method (LaVange et al, 2005). This methodology uses weighted least squares on the treatment differences of outcome and covariate means. The resulting model estimates give the treatment effects for the outcomes, adjusting for the covariates added into the model.

The method will be applied using the SAS NParCov4 macro (©Zinc and Koch, 2001), adjusting for baseline ALP level as a covariate. It is important to note that this method

can only be applied to data with a binary treatment variable. Each dose-placebo comparison will be performed independently, not accounting for multiplicity.

The macro will be applied to compare the relative change from baseline in ALP (PCTCHG) between the 2 active treatments (elafibranor 80 mg, 120 mg) and placebo, adjusting for baseline ALP (BASE). If there are baseline imbalances that are deemed to be important in influencing the relative change of ALP due to random chance, the corresponding variables may be added as further explanatory variables in the primary and supportive models.

Assumptions for this model are minimal:

- Randomization to treatment
- Subjects in the trial are a simple random sample

The macro will be applied in the following steps:

1. Create a dataset DATAIN. The dataset should include one observation per subject and include the variables TRTPN (1 denotes placebo, 2 denotes elafibranor 80mg and 3 denotes elafibranor 120mg), BASE (baseline ALP) and PCTCHG (relative change at endpoint in ALP from baseline) calculated as described above. Restrict DATAIN to subjects with TRTPN=1 and TRTPN=2.

2. Apply the macro as shown:
%NPARCOV4(OUTCOMES=PCTCHG,COVARS=BASE,C=0,HYPOTH=NULL,STRATA=NONE,TRTGRPS=TRTP, TRANSFORM=NONE,COMBINE=NONE,DSNIN=DATAIN,DSNOUT=DATAOUT)

3. Dataset _OUTDAT_COVTEST contains the evaluation of the covariate imbalance. P-value > 0.05 indicates random imbalance for the distribution of covariates between the 2 treatments.

4. Extract the relevant data from the output datasets. Dataset _OUTDAT_DEPTEST gives the estimate (beta), standard error (sebeta) and p-value (pvalue) for the treatment difference and dataset _OUTDAT_CI gives a 95% CI for this treatment estimate. The model compares TRTPN 2 vs 1.

5. Repeat steps 1-4 for elafibranor 120 mg vs. placebo (TRTPN = 1 and TRTPN=3).

A supportive analysis of elafibranor's effect on ALP changes will be conducted based on an analysis of covariance (ANCOVA) model, with relative change in ALP from baseline as the response variable and with the treatment arm and baseline ALP level as explanatory variables.

This will be applied in the following steps:

1. Take the full dataset DATAIN, described above with all 3 treatment arms retained in the dataset.

2. In order to assess the equality of slopes assumption, the model is run including the interaction effect between TRTPN and BASE.

```
PROC GLM DATA=DATAIN;
        CLASS TRTPN (ref='1');
        model PCTCHG=TRTPN BASE TRTPN|BASE/solution;
        lsmeans TRTPN/CL PDIFF ;
run;
```

If p-value for interaction is <0.05, equal slopes cannot be assumed and we cannot run the model without the interaction effect. A significant interaction indicates that the covariate influences the response variable and that it needs to be taken into account.

If p-value for the interaction is >0.05 then the equality of slopes assumption is met and the model is assessed by:

```
PROC GLM DATA=DATAIN;
        CLASS TRTPN (ref='1');
        model PCTCHG=TRTPN BASE /solution;
        lsmeans TRTPN/CL PDIFF ;
run;
```

If there are baseline imbalances, determined above, that are deemed to be clinically important in influencing the relative change of ALP due to random chance, the corresponding variables may be added as further explanatory variables in the supportive model as in the primary model. The SAS code above will be repeated, including these covariates.

8.2. SECONDARY EFFICACY ENDPOINTS AND ANALYSES

All secondary endpoints will be calculated at EndPoint (Visit 5 (Week 12) or EOT value, must be last post baseline value under treatment.

For all secondary endpoints involving binary outcomes (response to composite endpoints, response rate according to PBC risk scores, normalization of bilirubin and albumin), the differences in proportions will be assessed independently for each dose-placebo comparison using the Fisher exact test. Number of responders for each endpoint will summarized with descriptive statistics for categorical variables. These outcomes are detailed in 8.2.1 to 8.2.4 below.

For calculation of response, the following ULN and reference ranges will be used:

- ALP ULN 105 U/L for females, 129 U/L for males
- BIL ULN <1.20 mg/dL
- ALB reference range: 3.5-5.2 g/dL for patients aged 18y-60y. 3.2-4.6 g/dL for patients aged 61y-91y
- ALT ULN<33 U/L for females, <41 U/L for Males
- PLT reference range: 170-390 for females, 165-310 for males.

Example SAS code is shown below for the first dose-placebo comparison where DATAIN is the dataset defined above with one row per subject including the response and treatment variables:

```
PROC FREQ DATA=DATAIN;
where TRTPN = 1 and TRTPN = 2;
TABLES RESPONSE*TRTPN/FISHER;
run;
```

If important baseline imbalances occur by chance, determined above, confounding variables may be added into a binomial regression model.

Continuous secondary endpoints will be summarized with descriptive statistics for continuous variables. These outcomes are detailed in 8.2.2 for PBC risk score (calculated based on the UK-PBC score) and in 8.2.5 below.

For all secondary endpoints involving continuous outcomes, the differences in each dose-placebo comparison will be assessed:

- For relative change from baseline, using a nonparametric randomization-based Analysis of Covariance method similar to that used as the primary efficacy analysis for the primary efficacy endpoint (see section 8.1).
- For absolute change from baseline, using an ANCOVA model, similar to that used as the supportive analysis for the primary efficacy endpoint (see section 8.1).

Certain endpoints such as absolute and relative change from baseline in QOL (PBC40), Pruritus scoring (5D itch scale) and VAS will be summarized descriptively only.

8.2.1. Response Rate Based on 2 Composite Endpoints

Response will be defined using 2 separate composite endpoints:

- ALP less than 1.67 X ULN and total bilirubin within normal limit and >15% reduction in ALP from baseline
- ALP < 2 × ULN and total bilirubin within normal limit and > 40% reduction in ALP from baseline

8.2.2. Response Rate according to PBC Risk Scores

Response rates will be defined according to each following definition:

- Paris I: ALP ≤3x ULN, AST ≤2x ULN and normal bilirubin
- Paris II: ALP and AST ≤1.5x ULN with normal bilirubin
- Toronto I: ALP ≤1.67x ULN
- Toronto II: ALP ≤1.76

In addition, continuous PBC risk score will be calculated at EndPoint (Visit 5 or EOT value) based on the UK-PBC score. This will be calculated at each of the 3 survivor functions, detailed below.

> UK-PBC: 1-baseline survival function^exp(0.0287854*(alpEPxuln-1.722136304) - 0.0422873*(((altastEPxuln/10)^-1) - 8.675729006) + 1.4199 * (LN(bilEPxuln /10)+2.709607778) -1.960303*(albxlln -1.17673001)-0.4161954*(pltxlln - 1.873564875))
>
> Where:
> Baseline survivor function=0. 982 (at 5 years); 0. 941 (at 10 years); 0.893 (at 15 years).
> alpEPxuln=ALP at EndPoint/Upper Level Normal ALP
> altastEPxuln=(ALT, AST or TA) at EndPoint/upper level normal of the value
> bilEPxuln=bilirubin at EndPoint/upper level normal bilirubin
> albxlln=alb at baseline/alb lower level normal
> pltxlln=plt at baseline/ plt lower level normal

Only descriptive statistics at EndPoint will be provided on the continuous PBC risk score.

8.2.3. Response Rate According to Normalized Laboratory Values

Response defined as percent of patients with a normalized level of each of the following laboratory parameters and endpoint:

- ALP
- ALB

- BIL

8.2.4. Response Rate According to Reduction in ALP Levels

Response is calculated by a reduction in ALP from baseline of at least:

- 10%
- 20%
- 40%

8.2.5. Change from Baseline

All laboratory parameters will be analyzed using international units.

Absolute and relative change at EndPoint (Visit 5/ EOT value) from baseline will be calculated for the following parameters:

- gamma-glutamyl transferase (GGT)
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- 5'nucleotidase
- bilirubin (total and conjugated)
- albumin
- total cholesterol, LDL-chol, HDL-Chol, Triglycerides
- Bile acids : Total Free, Total Conjugated and Total where:
    - Total Free = sum(CA, CDCA, DCA, LCA, UDCA, HCA, HDCA)
    - Total conjugated = sum(GCA, GCDCA, GDCA, GLCA, GUDCA, GHCA, GHDCA, TCA, TCDCA, TDCA, TLCA, TUDCA, THCA, THDCA)
    - Total = sum(Total free, Total conjugated)
- C4, FG19
- IgM

- Biomarkers of inflammation and liver fibrosis: TNF-α, TGF-β, IL-6, cytokeratin-18 (CK-18), and autotaxin
- Quality of life: PBC 40 QOL-Descriptive Only
- Pruritus: 5-D Pruritus Questionnaire and Visual Analogue Score (VAS)-Descriptive Only

The PBC40 QOL questionnaire is scored by domain by summing all of the values from the corresponding question. Values are assigned to the response in each question as detailed below:

Domain/ Question Number	Response/ Score
Digestion and Diet	**Total Score=15**
1	Never=5, Rarely=4, Sometimes=3, Most of the time=2, Always=1
2	Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
3	Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5, Did not apply=0
Experience any of the Following	**Total Score=20**
4-7	Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
Itching	**Total Score=15**
8-10	Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5, Did not apply=0
Fatigue	**Total Score=40**
11-18	Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
Effort and Planning	**Total Score=15**
19-21	Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
Memory and Concentration	**Total Score=30**
22-27	Never=1, Rarely=2, Sometimes=3, Most of the time=4, Always=5
Affects you as a person	**Total Score=30**
28,30, 32-33	Not at all=1, A little=2, Somewhat=3, Quite a bit=4, Very Much=5
29,31	Not at all=1, A little=2, Somewhat=3, Quite a bit=4, Very Much=5, Does not apply=0
Effects your social life	**Total Score=20**
34-37	Strongly Agree=5, Agree=4, Neither Agree nor Disagree=3, Disagree=2, Strongly Disagree=1
Overall Impact on your life	**Total Score=15**
38-39	Strongly Agree=5, Agree=4, Neither Agree nor Disagree=3, Disagree=2, Strongly Disagree=1
40	Strongly Agree=1, Agree=2, Neither Agree nor Disagree=3, Disagree=4, Strongly Disagree=5

The total Pruritus scoring (5D itch scale) score is generated by summing across all questions.

9. SAFETY

All analyses described in this section will be performed on the SS and will be presented by treatment arm. The results will be descriptive in nature. All data will be summarized and listed.

Safety will be assessed on the basis of exposure, compliance, AEs, laboratory parameters, vital signs and physical examination.

9.1. EXTENT OF EXPOSURE

The duration of exposure will be expressed as the time in days from the first treatment through to last treatment day (inclusive). Duration of exposure will be summarized for the SS using summary statistics for continuous variables.

9.2. TREATMENT COMPLIANCE

From Visit 1 and at subsequent visits while the patient is being treated with the study drug, the patient will be directed to bring back all used and unused cartons and blisters. Compliance will be checked with the Investigator during those visits and recorded on the electronic case report form (eCRF). The total number of days treatment was interrupted during the treatment period will be summarized using summary statistics for continuous variables for estimation of drug compliance, treatment interruptions will be recorded on the eCRF and percentage compliance will be calculated as: 100 * actual tablets taken/expected tablets taken where tablets actual taken is defined as the sum of the tablets taken and tablets expected to be taken is defined as (date of last dose – date of first dose) + 1.

The number and percentage of compliant patients will be presented for the SS, where compliant is defined as percentage compliance between 80.0% and 120.0% inclusive. The following percentage compliance categories will be presented :<80.0%; ≥80.0% to <120.0%; ≥120.0%

9.3. ADVERSE EVENTS / ADVERSE DRUG REACTIONS

Adverse events (AEs) will be coded using MedDRA to give a preferred term and a SOC term for each event.

All reported AEs (whether treatment emergent or not) will be included in by-subject AE listings. A separate listing will be created with all the distinct levels of SOC, Preferred Terms and the verbatim Investigator description reported in the study. Sorting will be alphabetically by SOC, Preferred Term and then verbatim description.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical (investigational) product and which does not necessarily have to have a causal relationship with this treatment. The term

AE is synonymous with the term “adverse experience” as used by the Food and Drug Administration (FDA).

- treatment emergent AE (TAEs) are events with start date on or after the date of first dose of study treatment and up to 28 days after date of last dose of study treatment or events with start date prior to the date of first dose of study treatment whose severity worsens on or after the date of first dose of study treatment. A SAE is any untoward medical occurrence that at any dose:

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

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

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

Summary tables will be based on treatment-emergent adverse events (TEAEs). Relationship to study drug is categorized as “related”, “possibly related”, “unlikely related”, “not related” and “not assessable. Relationship to trial medication is not expected to be missing after data cleaning, however, if relationship is confirmed as missing, the AE will be considered as treatment related.

The incidence of TEAEs will be presented using counts and percentages of patients with AEs and tabulated by SOC and PT. SOC will be sorted alphabetically and PT within SOC will be sorted by descending frequency based on the incidence across subjects overall. If a patient has multiple occurrences (start and stop) of an event associated with a specific SOC or PT within a SOC, a patient will only be counted once in the incidence count for the SOC or PT within SOC respectively.

The incidence of all AEs by SOC and PT will be presented for the following categories:

- Any AE
- Any TEAEs
- Any TEAEs related to study medication
- Any Serious TEAEs
- Related Serious TEAEs
- Any TEAEs leading to permanent withdrawal of study drug
- Any TEAEs by maximum intensity

Deaths, other SAEs, and AEs leading to permanent or temporary withdrawal of study drug will be listed including the treatment arm, start and stop dates/times of the AE, and days on study relative to the day of first dose of study drug.

The following listings will be provided:

- Listing of subjects who died
- Listing of subjects with Serious TEAEs
- Listing of subjects with non-treatment-emergent SAEs
- Listing of subjects with TEAEs leading to withdrawal or temporary withdrawal of study drug

9.4. LABORATORY EVALUATIONS

All laboratory analyses will be analyzed by the central laboratory (BARC: Ghent – Belgium, or New York – USA).

As a general rule of thumb, each value below/above the limit of quantification will be imputed numerically to the nearest value below/above the limit, respecting the same number of digits than numerical values (e.g. if the number of digit=0, substract/add 1 to the limit of quantification; if the number of digit=1, substract/add 0.1 to the LOQ, etc).

Clinical laboratory evaluations include hematology, chemistry and urinalysis. The parameters to be assessed along with the time-points for measurement are given in Table 5 below.

Table 5: Clinical laboratory parameters

Laboratory Parameter	Time Points Assessed
Hematology	
haemoglobin	V1 to V5 or EOT value
haematocrit	V1 to V5 or EOT value
RBC	V1 to V5 or EOT value
WBC	V1 to V5 or EOT value
differential count	V1 to V5 or EOT value
platelet count	V1 to V5 or EOT value
prothrombin time	V1 to V5 or EOT value
reticulocytes count	V1 to V5 or EOT value
Biochemistry	
alkaline phosphatase	V1 to V5 or EOT value
ALT	V1 to V5 or EOT value
AST	V1 to V5 or EOT value
GGT	V1 to V5 or EOT value
CPK	V1 to V5 or EOT value
5 nucleotidase	V1 to V5 or EOT value
total and conjugated bilirubin	V1 to V5 or EOT value
creatinine	V1 to V5 or EOT value
eGFR*	V1 to V5 or EOT value
total proteins	V1 to V5 or EOT value
albumin	V1 to V5 or EOT value
electrolytes (sodium, potassium, chloride, calcium)	V1 to V5 or EOT value
hsCRP	V1 to V5 or EOT value
fibrinogen	V1 to V5 or EOT value
haptoglobin	V1 to V5 or EOT value
lipase	V1 to V5 or EOT value
amylase	V1 to V5 or EOT value
Total Cholesterol	V1 to V5 or EOT value
HDL C	V1 to V5 or EOT value
TG	V1 to V5 or EOT value
LDL-C	V1 to V5 or EOT value
Serum Cystatin C	V1 to V5 or EOT value
Urinalysis	
Specific gravity	V1 to V5 or EOT value
pH	V1 to V5 or EOT value
Protein*	V1 to V5 or EOT value
Glucose*	V1 to V5 or EOT value
Ketones*	V1 to V5 or EOT value
bilirubin	V1 to V5 or EOT value
Urobilinogen*	V1 to V5 or EOT value
Blood*	V1 to V5 or EOT value
Nitrite*	V1 to V5 or EOT value
-	
Urinary albumin	V1 to V5 or EOT value
urinary creatinine	V1 to V5 or EOT value
urinary ACR*	V1 to V5 or EOT value

For each parameter not marked with an asterisk in the above table, laboratory tests and change from baseline will be summarized by treatment arm at each scheduled visit

using descriptive statistics for continuous variables. Clinical laboratory assessments will be classified with respect to laboratory reference ranges.

Each parameter marked with an asterisk will be described at each visit as follows:

- eGFR: "≤60", ">60" ml/min/1.73m^2
- urinary ACR: "<30", [30 – 300],]300-1000], ">1000" mg/g
- Urinary parameters such as protein, glucose, ketones, urobilinogen, blood, and nitrite: "negative", "positive"

Furthermore, for these parameters changes in these categories over time will be described by means of "shift tables" comparing the value at Visit 5 (Week 12) or EOT value to baseline value.

For the laboratory parameters of significance (ALT, AST, GGT, 5-nucleotidase, CPK, and total and conjugated bilirubin), the value for each parameter will be assigned a classification according to whether the value is lower than, within, or higher than the corresponding reference range. Changes in these categories over time will be described by means of "shift tables" comparing the value at Visit 5 (Week 12) or EOT value to baseline value.

For the laboratory parameters of clinical interest (ALT, AST, GGT, 5-nucleotidase, CPK, total and conjugated bilirubin) the number and percentage of patients reporting markedly abnormal laboratory values (<3xULN, between 3xULN and <5xULN, x>=5 ULN) will also be summarized by treatment arm. For these calculations, each subject may be counted once in the given laboratory parameter, as applicable.

A by-patient listing, sorted by patient identifier, will present all laboratory results (scheduled or unscheduled) and will include flags to identify whether a result is outside of the normal range and whether it is markedly abnormal.

9.5. VITAL SIGNS

The following vital signs will be assessed at all visits:

- SBP (mmHg)
- DBP (mmHg)
- Pulse Rate (beats/min)
- Weight (Kg)

For all parameters, absolute values and change from baseline will be presented for scheduled visits using descriptive statistics for continuous variables.

A by-patient listing, sorted by patient identifier, will be presented including all vital sign results (scheduled or unscheduled).

9.6. ECG

A 12-Lead ECG will be performed at each scheduled study visit. The following ECG parameters will be assessed at each scheduled study visit visits:

- Overall ECG Evaluation
- Heart Rate (bpm)
- PR Interval (msec)
- QRS Duration (msec)
- QT Duration (msec)
- RR Duration (msec)
- QTcB - Bazett's Correction Formula (msec)
- QTcF - Fridericia's Correction Formula (msec)

For all parameters, absolute values and change from baseline will be presented for scheduled visits using descriptive statistics for continuous variables.

A by-patient listing, sorted by patient identifier, will be presented including all ECG results. A separate by-patient listing will also be presented, including patients with an abnormal Investigator interpretation of ECG results.

9.7. PHYSICAL EXAMINATION

A by-patient listing, sorted by patient identifier, will be presented including all physical examination results (scheduled or unscheduled) and will include flags to identify whether there were any new clinically significant findings.

9.8. STANDARD DIET AND EXERCISE RECOMMENDATIONS

A by-patient listing, sorted by patient identifier, will be presented including compliance to standard diet and exercise recommendations.

10. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The Per-Protocol Population has been amended to analyze based on randomized treatment rather than actual treatment.

A modified Intent-to-Treat population was added as in addition to a baseline measure, a post baseline measure is needed to assess the treatment effect. Thus, in the case of non similarity between ITT set and mITT set, all efficacy analyses will performed on the mITT set rather than on the ITT set.

Definition of baseline has been clarified for all endpoints to be the last non missing value taken prior to first dose of study drug.

Bile acids CDCA, Cholic Acid, Litocholic Acid and DCA will be analysed as total conjugated bile acids, total free bile acids and total bile acids. These are defined within the SAP.

Definition of EndPoint value has been clarified to be Visit 5 or the last post baseline measure under treatment regardless of premature withdrawal.

Due to better stability, the measurement of lysophosphatidic acid has been replaced by autotaxin measurement.

11. REFERENCE LIST

LaVange LM, Durham TA, Koch GG. Randomization-based nonparametric methods for the analysis of multicentre trials. *Stat Methods Med Res.* 2005;14(3):281-301.

Zink R, Koch G. NParCov3: A SAS/IML Macro for nonparametric randomization-based analysis of covariance. *J Stat Softw.* 2012:50(3).

Analysis of Clinical Trials Using SAS: a Practical Guide Dmitrienko A, Moleberghs G, Chuang-Stein C, Offen W (2005) ISBN 1590475046.

12. PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.3 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

12.1. GENERAL CONSIDERATIONS

The following items need to be clarified upfront with the sponsor and Medical Writing and modified as per study requirements.

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TFLs will follow ICH E3 guidance.

12.2. TABLE, LISTING, AND FIGURE FORMAT

12.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8
- The data displays for all TLFs will have a minimum 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as nonprintable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (eg, μ). Certain subscripts and superscripts (eg, cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

12.2.2. Headers

- All output should have the following header at the top left of each page:

<Sponsor Name> Protocol XXX [redacted]study number xxx)
Draft/Final Run <date>

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (ie, the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

12.2.3. Display Titles

- Each TLF should be identified by the designation and a numeral. (ie, Table 14.1.1).
- ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C "Table of Contents for Tables Listings and Figures in Statistical Analysis Plan"). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents.
- The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced.
- A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set

12.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment arm columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment arm in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of patients in the analysis set.

- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

12.2.5. Body of the Data Display

12.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- whole numbers (eg, counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

12.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment arms in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (eg, Medical History, Reasons for Discontinuation from the Study), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (eg, 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment arm who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC alphabetically, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed alphabetically. If incidence for more than 1 term is identical, they should then be sorted by highest incidence. Missing descriptive statistics or p-values which cannot be estimated should be reported as “-”.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than 1 page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

12.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of patient number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen (“-”) with a corresponding footnote (“- = unknown or not evaluated”), or as “N/A”, with the footnote “N/A = not applicable”, whichever is appropriate.

- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (eg, 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

12.2.5.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (eg, treatment mean change from Baseline) values will be displayed on the Y-axis.

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes should be avoided, where possible.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than 6 lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (ie, 'Program : myprogram.sas Listing source: 16.x.y.z').

13. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. [redacted] SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

[redacted] SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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Intent to treat Set (ITT) / Modified Intent to treat Set (mITT)

Listing 16.2.4.5
Medical History (Prior and Concomitant)
Intent to treat Set (ITT) / Modified Intent to treat Set (mITT)

Listing 16.2.4.7
Standard Diet and Exercise recommendations
Intent to treat Set (ITT) / Modified Intent to treat Set (mITT)

Listing 16.2.4.8
Prior and concomitant medications
Intent to treat Set (ITT) / Modified Intent to treat Set (mITT)

Listing 16.2.5.1
Randomization and treatment administration
Safety Set (SS)

Listing 16.2.5.2
Drug accountability
Safety Set (SS)

Listing 16.2.5.3
IP Compliance
Safety Set (SS)

Listing 16.2.6.1
Primary Efficacy Endpoint: Serum Alkaline Phosphotase
Intent to treat Set (ITT) / Modified Intent to treat Set (mITT)

Listing 16.2.6.2
Secondary Efficacy Endpoints: Response Rates
Intent to treat Set (ITT) / Modified Intent to treat Set (mITT)

Listing 16.2.6.3
Secondary Efficacy Endpoints: Absolute and relative change From Baseline
Intent to treat Set (ITT) / Modified Intent to treat Set (mITT)

Listing 16.2.6.4
Secondary Efficacy Endpoints: Absolute and relative change From Baseline Priuritus Scoring (5D Itch Scale)
Intent to treat Set (ITT) / Modified Intent to treat Set (mITT)

Listing 16.2.6.5
Secondary Efficacy Endpoints: Absolute and relative change From Baseline PBC40 QOL questionaire
Intent to treat Set (ITT) / Modified Intent to treat Set (mITT)

Listing 16.2.7.1
Listing of All Adverse Events (AE)
Safety Set (SS)

Listing 16.2.8.1.1
Listing of Hematology Laboratory Parameters
Safety Set (SS)

Listing 16.2.8.1.2
Listing of Biochemistry Laboratory Parameters
Safety Set (SS)

Listing 16.2.8.1.3
Listing of Urinalysis Laboratory Parameters
Safety Set (SS)

Listing 16.2.8.1.4
Listing of Liver Markers Laboratory Parameters
Safety Set (SS)

Listing 16.2.8.1.5
Listing of Inflammatory marker Laboratory Parameters
Safety Set (SS)

Listing 16.2.8.1.6
Listing of Other Laboratory Parameters
Safety Set (SS)

Listing 16.2.8.2.1
Listing of Vital Signs
Safety Set (SS)

Listing 16.2.8.2.2
Listing of Electrocardiogram (ECG) parameters
Safety Set (SS)

Listing 16.2.8.2.3
Listing of Physical Examination
Safety Set (SS)

Listing 16.2.8.2.4
Listing of Standard Diet and Exercise Recommendations
Safety Set (SS)

17. APPENDICES

List all appendices as needed.