STATISTICAL ANALYSIS PLAN

INVENTIVA

Study IVA_01_337_HNAS_16_002

EudraCT 2016-001979-70

A randomized, double-blind, placebo-controlled, multicenter, dose-range, proof-of-concept, 24-week treatment study of IVA337 in adult subjects with nonalcoholic steatohepatitis (NASH)

Version 1
May, 13th 2020

Sponsor	CRO
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1 List of abbreviations and definition of terms

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
CAP	Controlled Attenuation Parameter
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel
CPK	Creatine PhosphoKinase
CRF	Case Report Form
CRN-B	CRN Hepatocyte Ballooning score
CRN-F	CRN Fibrosis score
CRN-I	CRN Lobular Inflammation score
CRN-S	CRN Steatosis score
CS	Clinically Significant
DBL	Data Base Lock
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End Of Study
EPOS	Elucidating Pathways of Steatohepatitis
EPP	Evaluable patient population
FAS	Full Analysis Set
FFA	Free fatty acids
FFS	Flinders Fatigue Scale
GGT	Gamma GT
HDL	High Density Lipoproteins
HLR	Head Line Results
HR	Heart rate
IMP	Investigational Medicinal Product (i.e. treatment)
LDL	Low Density Lipoproteins
MCHC	Mean Corpuscular Haemoglobin Concentration
MCMC	Markov chain Monte Carlo
MCV	Erythrocytes Mean Corpuscular Volume
MH	Medical History
MMRM	Mixed Model for Repeated Measures
NAFLD	Non Alcoholic Fatty Liver Disease

Abbreviation	Definition
NAS	NAFLD Activity Score
NASH	Non Alcoholic SteatoHepatitis
NCS	Non Clinically Significant
NFS	NAFLD Fibrosis Score
NNT	Number Needed to Treat
OC	Observed Cases
OCUT	Observed Cases Under Treatment
OR	Odds Ratio
PD	Protocol Deviation
PP	Per Protocol
PT	Preferred Term
PTAE	Post Treatment Adverse Events
QC	Quality Control
RBC	Red Blood Cells
RR	Risk Ratio
SAE	Serious Adverse Event
SAF	Steatosis Activity Fibrosis
SAF-A	SAF Activity score
SAF-F	SAF Fibrosis score
SAF-I	SAF Lobular Inflammation score
SAF-S	SAF Steatosis score
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SF-36	Short Form Health Survey 36 items
SH	Surgical History
SOC	System Organ Class
TE	Transient Elastrography
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures, Listings
USA	United States of America
WBC	White Blood Cells

2 Introduction

This document describes the frame of the statistical analysis that will be conducted for the study *"A randomized, double-blind, placebo-controlled, multicenter, dose-range, proof-of-concept, 24-week treatment study of IVA337 in adult subjects with nonalcoholic steatohepatitis (NASH)"*.

This Statistical Analysis Plan has been written in agreement with:
- The Clinical Study Protocol version 5.1 dated March 25th, 2020
- The blank electronic Case Report Form (eCRF) version 13.0 dated January, 14th 2020
- The annotated eCRF version 13.0 dated January, 14th 2020

This document will be reviewed, approved and signed by the sponsor of the study (Biostatistician and the Clinical Research Physician), before the database lock [DBL].

This document is the reference document for all the statistical analyses of this study, except the analyses presented during DSMB (Data Safety Monitoring Board) meetings and pharmacokinetics/pharmacodynamics analyses that will be analysed separately, with specific statistical analysis plans developed.

The purpose of this document is to describe:
- The characteristics of the study as defined in the protocol: objectives, design and conduct of the study
- The criteria/variables analysed and the derived variables to be created
- The planned statistical analysis and the methodology used.

3 Study description

3.1 Study objective

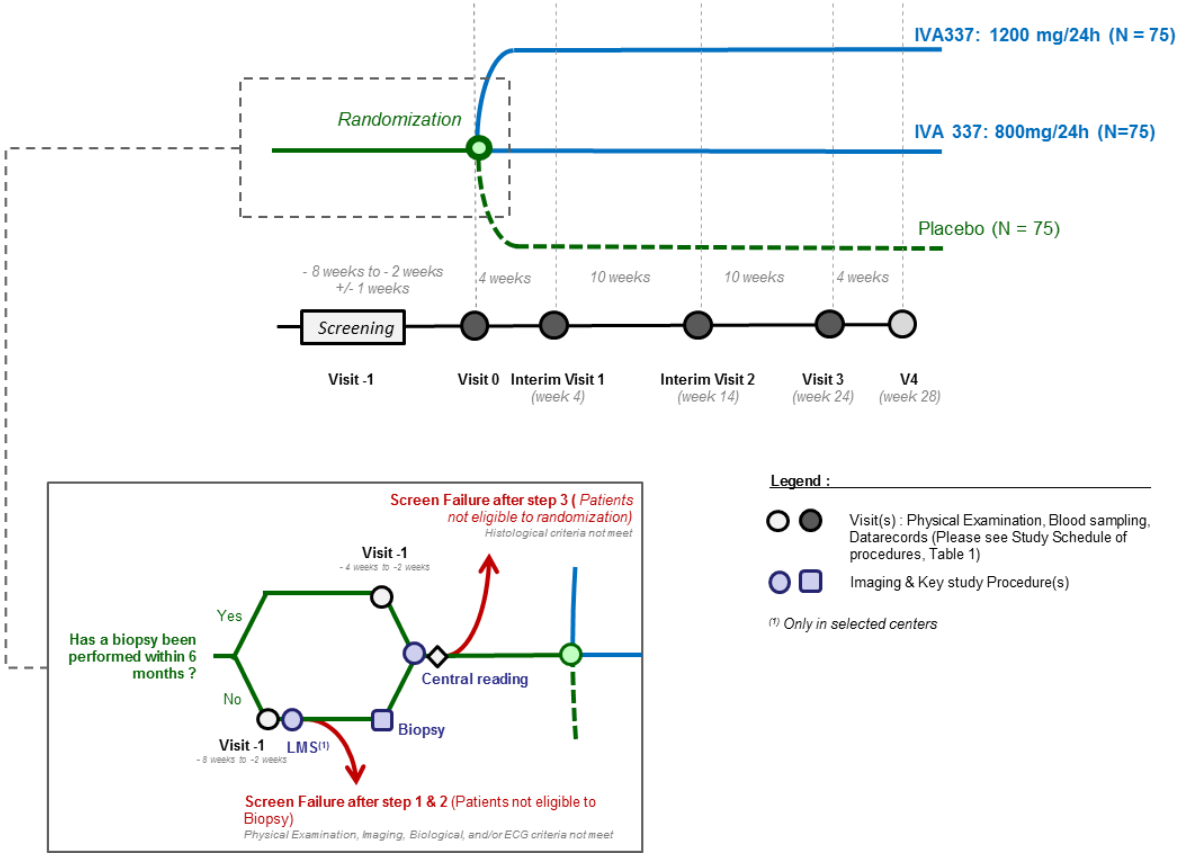
The main objective of this IIb, Proof of Concept study is to assess the safety and the efficacy on the activity part of the Steatosis Activity Fibrosis (SAF) histological score (inflammation and ballooning) of a 24-week treatment with two doses of lanifibranor (IVA337) (800, 1200 mg/24h) versus placebo in NASH adult patients.

3.2 Study design

This is a
- Three arm (placebo, lanifibranor (IVA337) 800 and 1200 mg/day),
- Randomised (1:1:1, stratified on diabetes),
- Placebo-controlled,
- Double-blind,
- Parallel-assignment,
- Dose-range,
- Multicenter: at least 60 sites across 13 European countries (i.e., Belgium, France, Italy, Spain, United-Kingdom, Poland, Czech Republic, Germany, The Netherlands, Switzerland, Austria, Portugal, Slovenia), Canada, Australia, Mauritius and the United States of America (USA) will participate,
- 24-week treatment study.

The study will require at least 30 months of enrolment period, to randomise 225 patients (i.e. at least 300 screened patients), for a total study duration of up to 38 months.

The overall study design is shown in Figure below.



3.3 Study plan

Patients will undergo 6 visits:

- Screening visit (V-1, -8 weeks to -2 weeks)
- Randomisation (V0),
- Interim visit 1 (V1, 4 weeks after V0),
- Interim visit 2 (V2, 14 weeks after V0),
- End of treatment visit (V3, 24 weeks after V0)
- And a follow-up visit (28 weeks after V0).

A detailed list of procedures performed at each visit is presented in Table 1 and Table 2 Table 1below, depending on whether a liver biopsy of less than 6 months is available before screening or not.

Table 1: Study Schedule of procedures (if a liver biopsy of less than 6 months is available before screening)

Study Period		Screening	Treatment				Follow up
Visit		V-1	V0	V1	V2	V3	V4
Weeks (target+/-3days, referred to V0)		-4 to -2	0	4	14	24	28
Informed consent		X					
Inclusion/exclusion criteria		X	X				
Demographics, Medical history		X					
Alcohol consumption		X	X	X	X	X	X
Physical examination/ vital signs:	*height (inclusion only), weight, waist circumference, SBP, DBP, HR*	X	X	X	X	X	X
12-lead Electrocardiogram		X		X		X	
Pregnancy test *((a): Blood test, βHCG; (b): Urine Test)*		X(a)	X(b)				
HIV serology		X					
Concomitant medications		X	X	X	X	X	X
Quality of life questionnaires			X			X	
Urine Samples			X		X	X	X
Blood Samples		X	X	X	X	X	X
FibroScan™ (if available)		X				X	
Central Reading of liver biopsy to confirm NASH diagnosis		X					
Liver biopsy at end of treatment						X	
Primary efficacy evaluation: Inflammation and ballooning SAF		X(c)				X	
Secondary efficacy evaluation							
NAS score and other liver histology indices		X				X	
Inflammatory markers	*fibrinogen, hs-CRP, alpha2-macroglobulin, haptoglobin levels*		X			X	
Glucose metabolism	*fasting glucose and in subjects with T2DM: HbA1c*	X	X	X	X	X	X
	Insulin, HOMA, Peptide C, Fructosamine		X			X	
Lipids	*Lipids: TC, HDL-C, calculated LDL-C and TG*	X	X	X	X	X	X
	FFA, adiponectin, Leptin and apoA1		X			X	
Chemistry	*Plasma Iron, Transferrin, Ferritin*	X				X	
Fibrosis markers	*TIMP-1, TIMP-2, Cytokeratin K18, hyaluronic acid, P3NP, FGF 21*		X			X	
Exploratory criteria Biobank							
Other biomarkers	*IL-6, IL-13, IL-17A, IL1B, TNF-α, INFg, APO B, APO C3, MMP2, MMP9, ProC3 (non-exhaustive list)*		X			X	
Genotype	*PNPLA3, TM6FS2*		X(d)				
Safety assessments							
Hematology	*WBC (+diff. Count), RBC, hemoglobin, MCV, hematocrit, Platelets, reticulocytes, CCMH, Hematocrit*	X	X	X	X	X	X
Inflammatory markers	*Nt-ProBNP*		X			X	
Chemistry	*creatinine, urea, albumin, CPK*	X	X	X	X	X	X
Liver tests	*AST, ALT, ALP, GGT, total bilirubin*	X	X	X	X	X	X
Bone	*B-Crosslaps, Osteocalcin*		X			X	
Coagulation factors	*INR*	X	X	X	X	X	X
Urine dipstick	*Hematuria*		X		X	X	X
Pharmacokinetics: IVA337 (+ metabolites) trough sampling				X		X	
Adverse events			X	X	X	X	X
Dispense study treatment			X	X	X		
Compliance check				X	X	X	

(c) Central reading on biopsy within the 6 months prior to screening to confirm NASH diagnosis;
(d) Only for patients having consent for genetic testing;

Table 2: Study Schedule of procedures (if a liver biopsy is NOT available before screening)

Study Period		Screening			Treatment				Follow up
Visit		V-1			V0	V1	V2	V3	V4
Weeks (target +/- 3 days, referred to V0)		-8 to -4			0	4	14	24	28
Screening Step		1	2	3					
Informed consent		X							
Inclusion/exclusion criteria		X			X				
Demographics, Medical history		X							
Alcohol consumption		X			X	X	X	X	X
Physical examination/ vital signs:	*height (inclusion only), weight, waist circumference, SBP, DBP, HR*	X			X	X	X	X	X
12-lead Electrocardiogram		X				X		X	
Pregnancy test *(Blood test, βHCG)*		X		X(a)					
Pregnancy test *(Urine Test)*					X				
HIV serology		X							
Concomitant medications		X			X	X	X	X	X
Quality of life questionnaires					X			X	
Urine Samples					X		X	X	X
Blood Samples		X		X(a)	X	X	X	X	X
LiverMultiScan/ Magnetic Resonance (in selected sites)			X(b)						
FibroScan™		X						X	
Liver biopsy				X(c)				X	
Primary efficacy evaluation: Inflammation and ballooning SAF				X				X	
Secondary efficacy evaluation									
NAS score and other liver histology indices				X				X	
Inflammatory markers	*fibrinogen, hs-CRP, alpha2-macroglobulin, haptoglobin levels*				X			X	
Glucose metabolism	*fasting glucose and in subjects with T2DM: HbA1c*	X		X(a)	X	X	X	X	X
	Insulin, HOMA, Peptide C, Fructosamine				X			X	
Lipids	*Lipids: TC, HDL-C, calculated LDL-C and TG*	X		X(a)	X	X	X	X	X
	FFA, adiponectin, Leptin and apoA1				X			X	
Chemistry	*Plasma Iron, Transferrin, Ferritin*	M			X			X	
Fibrosis markers	*TIMP-1, TIMP-2, Cytokeratin K18, hyaluronic acid, P3NP, FGF 21 (non-exhaustive list)*				X			X	
Exploratory criteria Biobank									
Other biomarkers	*IL-6, IL-13, IL-17A, IL1B, TNF-a, INFg, APO B, APO C3, MMP2, MMP9, ProC3 (non-exhaustive list)*				X			X	
Genotype	*PNPLA3, TM6F52*				X(d)				
Safety assessments									
Hematology	*WBC (+diff. Count), RBC, hemoglobin, MCV, hematocrit, Platelets, reticulocytes, CCMH, Hematocrit*	X		X(a)	X	X	X	X	X
Inflammatory markers	*Nt-ProBNP*				X			X	
Chemistry	*creatinine, urea, albumin, CPK*	X		X(a)	X	X	X	X	X
Liver tests	*AST, ALT, ALP, GGT, total bilirubin*	X		X(a)	X	X	X	X	X
Bone	*B-Crosslaps, Osteocalcin*				X			X	
Coagulation factors	*INR*	X		X(a)	X	X	X	X	X
Urine dipstick	*Hematuria*				X		X	X	X
Pharmacokinetics: lanifibranor (+ metabolites) trough sampling						X		X	
Adverse events					X	X	X	X	X
Dispense study treatment					X	X	X		
Compliance check						X	X	X	

(a) to be done only if there are more than 4 weeks between V-1 and V0;
(b) to be done after checking inclusion / exclusion criteria, incl. lab tests , ECG and Fibroscan;
(c) to be done after checking the results of the Fibroscan and/or the Liver MultiScan/ Magnetic Resonance (in selected centers);
(d) Only for patients having consent for genetic testing;

3.4 Study Population

3.4.1 Inclusion Criteria

Inclusion criteria	**Corresponding protocol versions**										
	V1.0	**V1.1**	**V1.2** FRANCE	**V1.2** GERMANY	**V1.2** SWITZERLAND	**V1.3** SWITZERLAND	**V2.0**	**V3.0**	**V4.0**	**V4.2**	**V5.0** **V5.1**
1. Adult subjects, age ≥18 years	X	X	X	X	X	X	X	X	X	X	X
2. NASH histological diagnosis according to the currently accepted definition of both EASL 2.and AASLD (56,60,61), requiring the combined presence of steatosis (any degree ≥ 5%) + lobular inflammation of any degree + liver cell ballooning of any amount, on a liver biopsy performed ≤ 6 months before screening in the study and confirmed by centralized reading during the screening period *and* a. SAF Activity score of 3 or 4 (>2) b. SAF Steatosis score ≥ 1 c. SAF Fibrosis score < 4	X	X	X	X	X	X	X	X	X (Addition of possibility of biopsy done at screening)	X (Addition of possibility of biopsy done at screening)	X (Addition of possibility of biopsy done at screening)
3. Subject agrees to have a liver biopsy performed after 24 weeks of treatment	X	X	X	X	X	X	X	X	X	X	X
4. Compensated liver disease with the following hematologic and biochemical criteria on entry into protocol: − ALT < 10xULN − Hemoglobin > 11 g/dL for females and > 12 g/dL for males − White blood cell (WBC) > 2.5 K/µL − Neutrophil count > 1.5 K/µL − Platelets > 100 K/µL − Total bilirubin < 35µmol/L. Patients with bilirubin ≥ 35µmol/L can be included if non-conjugated bilirubin in the setting of a Gilbert's syndrome − Albumin > 36 g/L − TP > 80% or INR < 1.4	X	X	X	X	X	X	X	X	X (TP > 80%) removed	X (Change of unit to adapt protocol units to the ones of the central lab reports)	X (Change : before randomization instead of on entry into protocol + Hemoglobin ≥ 110 g/L (11 g/dL) for females and ≥ 120

Inclusion criteria	Corresponding protocol versions										
	V1.0	**V1.1**	**V1.2** FRANCE	**V1.2** GERMANY	**V1.2** SWITZERLAND	**V1.3** SWITZERLAND	**V2.0**	**V3.0**	**V4.0**	**V4.2**	**V5.0 V5.1**
– Serum creatinin < 1.3 mg/dL (men) or < 1.1 mg/dL (women) or estimated glomerular filtration rate ≥ 60 mL/min/1.73m^2											g/L (12 g/dL) for males + Precision of range in another unit
5. No other cause of chronic liver disease (autoimmune, primary biliary cholangitis, HBV, HCV, Wilson's, α-1-antitrypsin deficiency, hemochromatosis, etc…).	X	X	X	X	X	X	X	X	X	X	X (adding "considered to have an impact on the patient's safety or on the efficacy evaluation ")
6. If applicable, have a stable type 2 diabetes, defined as HgbA1c < 8.5% and fasting glycemia <10 mmol/L, no changes in medication in the previous 6 months, and no new symptoms associated with decompensated diabetes in the previous 3 months	X ("decompensated") not mentioned	X	X	X	X	X	X	X	X	X	X Correcting typo + Précision of fasting glycemia in mg/dL + Change "no change in medication" by "no introduction of new medication"

Inclusion criteria	Corresponding protocol versions										
	V1.0	**V1.1**	**V1.2** FRANCE	**V1.2** GERMANY	**V1.2** SWITZERLAND	**V1.3** SWITZERLAND	**V2.0**	**V3.0**	**V4.0**	**V4.2**	**V5.0 V5.1**
											+ Adding "Minor modifications of anti-diabetic treatments or dosages are allowed if done in a context of stable type 2 diabetes, i.e. HbA1c ≤ 8.5% in the previous 6 months"
7. Have a stable weight since the liver biopsy was performed defined by no more than a 5 % loss of initial body weight	X	X	X	X	X	X	X	X	X	X	X
8. Negative pregnancy test or post-menopausal. Women with childbearing potential (i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile) must be using a highly effective method of contraception (i.e. combined (estrogen and progestogen containing) hormonal/ progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner). The contraceptive method will have to be followed for at least one menstruation cycle after the end of the study.	X No details	X Details on definition of women with childbearing potential and highly effective method of contraception, including "sexual abstinence"	X Same as previous with mention of follow-up "The contraceptive method will have to be followed for at	X Details on definition of women with childbearing potential and highly effective method of contraception, including "sexual abstinence"	X Same as previous without mention of "sexual abstinence"	X Same as previous without mention of "sexual abstinence"	X	X	X	X	X

Inclusion criteria	**Corresponding protocol versions**										
	V1.0	**V1.1**	**V1.2** FRANCE	**V1.2** GERMANY	**V1.2** SWITZERLAND	**V1.3** SWITZERLAND	**V2.0**	**V3.0**	**V4.0**	**V4.2**	**V5.0 V5.1**
		. No mention of follow-up after the end of the study	least one menstruation cycle after the end of the study"	. No mention of follow-up after the end of the study							
9. Subjects having given her/his written informed consent	X (“Subjects must be willing to give written informed consent”)	X (“Subjects must be willing to give written informed consent”)	X (“Subjects must be willing to give written informed consent”)	X	X (“Subjects must be willing to give written informed consent”)	X (“Subjects must be willing to give written informed consent”)	X	X	X	X	X

3.4.2 Non-Inclusion Criteria

Non-Inclusion criteria	**Corresponding protocol versions**										
	V1.0	**V1.1**	**V1.2** FRANCE	**V1.2** GERMANY	**V1.2** SWITZERLAND	**V1.3** SWITZERLAND	**V2.0**	**V3.0**	**V4.0**	**V4.2**	**V5.0** **V5.1**
1. Evidence of another form of liver disease	X	X	X	X	X	X	X	X	X	X	X Adding "considered to have an impact on the patient's safety or on the efficacy evaluation."
2. History of sustained excess alcohol ingestion: daily alcohol consumption > 30 g/day (3 drinks per day) for males and > 20 g/day (2 drinks/day) for females	X	X	X	X	X	X	X	X	X	X	X Adding "History of sustained excess alcohol ingestion **in the year before the pre-study treatment biopsy**"
3. Unstable metabolic condition: Weight change > 5kg in the last three months, diabetes with poor glycemic control (HgbA1c > 8.5%), introduction of an antidiabetic or of an anti-obesity drug/malabsorptive or restrictive bariatric (weight loss) surgery in the past 6 months prior to screening	X	X	X	X	X	X	X	X	X	X (Addition of "> 11 lbs" for the weight change)	X Change : "Weight change > 5%" + Delete "/malabsorptive"
4. History of gastrointestinal malabsorptive bariatric surgery within less than 5 years or ingestion of drugs known to produce hepatic steatosis including corticosteroids, high-dose estrogens, methotrexate, tetracycline or amiodarone in the previous 6 months	X	X	X	X	X	X	X	X	X	X	X Adding "**oral** corticosteroids" + replace "high dose" by '(dose >5mg/day prednisone equivalent) + adding tamoxifen + adding "Corticosteroids administered by routes other than oral are allowed. One short (<2 weeks) course of

Non-Inclusion criteria	Corresponding protocol versions										
	V1.0	**V1.1**	**V1.2** FRANCE	**V1.2** GERMANY	**V1.2** SWITZERLAND	**V1.3** SWITZERLAND	**V2.0**	**V3.0**	**V4.0**	**V4.2**	**V5.0** **V5.1**
											oral corticosteroids, more than 3 months before the pre-study treatment biopsy is also allowed.”
5. Significant systemic or major illnesses other than liver disease, including congestive heart failure (class C and D of the AHA), unstable coronary artery disease, cerebrovascular disease, pulmonary disease, renal failure, organ transplantation, serious psychiatric disease, malignancy that, in the opinion of the investigator, would preclude treatment with IVA337and/or adequate follow up	X	X	X	X	**X**	X	X	X	X (IVA337 replaced by lanifibranor)	X (IVA337 replaced by lanifibranor)	X
6. HBs antigen >0, HCV PCR >0 (patients with a history of HCV infection can be included if HCV PCR is negative since more than 3 years), HIV infection	X	X	X	X	X	X	X	X	X	X	X
7. Pregnancy/lactation or inability to adhere to adequate contraception in women of child-bearing potential	X	X	X	X	X	X	X	X	X	X	X Replace “Pregnancy/lactation” by “Pregnancy or lactation”
8. Active malignancy except cutaneous basocellular carcinoma.	X	X	X	X	X	X	X	X	X	X	X
9. Any other condition which, in the opinion of the investigator would impede competence or compliance or possibly hinder completion of the study	X	X	X	X	X	X	X	X	X	X	X

Non-Inclusion criteria	Corresponding protocol versions										
	V1.0	**V1.1**	**V1.2** FRANCE	**V1.2** GERMANY	**V1.2** SWITZERLAND	**V1.3** SWITZERLAND	**V2.0**	**V3.0**	**V4.0**	**V4.2**	**V5.0** **V5.1**
10. Body mass index (BMI) >45 kg/m^2	X	X	X	X	X	X	X	X	X	X	X
11. Type 1 diabetes and type 2 diabetic patient on insulin	X (Type 2 diabetic patient on insulin) not mentioned	X (Type 2 diabetic patient on insulin) not mentioned	X (Type 2 diabetic patient on insulin) not mentioned	X (Type 2 diabetic patient on insulin) not mentioned	X (Type 2 diabetic patient on insulin) not mentioned	X (Type 2 diabetic patient on insulin) not mentioned	X	X	X	X	X
12. Diabetic ketoacidosis		X	X	X	X	X	X	X	X	X	X
13. Fasting Triglycerides > 300 mg/dL	X	X	X	X	X	X	X	X	X	X	X Adding “(3.39 mmol/L)”.
14. Hemostasis disorders or current treatment with anticoagulants	X	X	X	X	X	X	X	X	X	X	X
15. Contra-indication to liver biopsy	X	X	X	X	X	X	X	X	X	X	X
16. History of, or current cardiac dysrhythmias and/or a history of cardiovascular disease event, including myocardial infarction, except patients with only well controlled hypertension. Any clinically significant ECG abnormality reported by central ECG reading	X (Any clinically significant ECG abnormality reported by central ECG reading) not mentioned	X (Any clinically significant ECG abnormality reported by central ECG reading) not mentioned	X (Any clinically significant ECG abnormality reported by central ECG reading) not mentioned	X (Any clinically significant ECG abnormality reported by central ECG reading) not mentioned	X (Any clinically significant ECG abnormality reported by central ECG reading) not mentioned	X (Any clinically significant ECG abnormality reported by central ECG reading) not mentioned	X	X	X	X	X Adding “confirmed by the Investigator to be Clinically Significant”

Non-Inclusion criteria	Corresponding protocol versions										
	V1.0	**V1.1**	**V1.2** FRANCE	**V1.2** GERMANY	**V1.2** SWITZERLAND	**V1.3** SWITZERLAND	**V2.0**	**V3.0**	**V4.0**	**V4.2**	**V5.0** **V5.1**
17. Participation in any other investigational drug study within the previous 3 months	X	X	X	X	X	X	X	X	X	X	X
18. Have a known hypersensitivity to any of the ingredients or excipients of the IMP including: Lactose monohydrate, Hypromellose, Sodium laurilsulfate, Sodium starch glycolate (type A), Magnesium stearate, Opadry™ II 85F18422		X Ingredients and excipients not detailed	X	X Ingredients and excipients not detailed	X Ingredients and excipients not detailed	X Ingredients and excipients not detailed	X	X	X	X	X
19. Be possibly dependent on the Investigator or the sponsor (e.g., including, but not limited to, affiliated employee).	X	X	X	X	X	X	X	X	X	X	X
20. Creatine phosphokinase (CPK) >5 x ULN			X (ULN) not mentioned				X	X	X	X	X
21. Osteopenia or any other well documented Bone disease. Patient without well documented osteopenia treated with vitamin D and/or Calcium based supplements for preventive reasons can be included			X				X	X	X	X	X Rewording : "Patient whitoutwith history of well documented osteopenia. Patient treated with vitamin D and/or Calcium based supplements for preventive reasons can be included."

Non-Inclusion criteria	**Corresponding protocol versions**										
	V1.0	**V1.1**	**V1.2** FRANCE	**V1.2** GERMANY	**V1.2** SWITZERLAND	**V1.3** SWITZERLAND	**V2.0**	**V3.0**	**V4.0**	**V4.2**	**V5.0** **V5.1**
(The criteria below are applicable only for patients who will undergo a MRI/LMS in selected centers) 22. Claustrophobia to a degree that prevents tolerance of MRI scanning procedure. Sedation is permitted at discretion of investigator. 23. Metallic implant of any sort that prevents MRI examination including, but not limited to: aneurysm clips, metallic foreign body, vascular grafts or cardiac implants, neural stimulator, metallic contraceptive device, tattoo, body piercing that cannot be removed, cochlear implant; or any other contraindication to MRI examination.									X	X	X

3.4.3 Prohibited concomitant medications

Prohibited concomitant medications	**Corresponding protocol versions**										
	V1.0	**V1.1**	**V1.2** FRANCE	**V1.2** GERMANY	**V1.2** SWITZERLAND	**V1.3** SWITZERLAND	**V2.0**	**V3.0**	**V4.0**	**V4.2**	**V5.0 V5.1**
PPAR Gamma agonist, fibrates, ezetimibe, bile salts chelators, phytosterols, fish oils	X	X	X	X	X	X	X	X	X Specification of " PPAR Alpha agonists (fibrates)	X Specification of " PPAR Alpha agonists (fibrates)	X Specification of " PPAR Alpha agonists (fibrates)
Glucagon like peptide-1 receptor agonists (liraglutide, exenatide),	X	X	X	X	X	X	X	X	X Adding "incl" before liraglutide,exenatide	X Adding "incl" before liraglutide,exenatide	X Adding "incl" before liraglutide,exenatide
Insulin							X	X	X	X	X
Vitamins E (alpha-tocopherol)	X Antioxidants such as vitamins E (alpha-tocopherol)	X Antioxidants such as vitamins E (alpha-tocopherol)	X Antioxidants such as vitamins E (alpha-tocopherol)	X Antioxidants such as vitamins E (alpha-tocopherol)	X Antioxidants such as vitamins E (alpha-tocopherol)	X Antioxidants such as vitamins E (alpha-tocopherol)	X Antioxidants such as vitamins E (alpha-tocopherol)	X Antioxidants such as vitamins E (alpha-tocopherol)	X	X	X
Anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban)	X Anticoagulants without specification	X Anticoagulants without specification	X Anticoagulants without specification	X Anticoagulants without specification	X Anticoagulants without specification	X Anticoagulants without specification	X	X	X Adding "incl" before warfarin, dabigatran, rivaroxaban, apixaban	X Adding "incl" before warfarin, dabigatran, rivaroxaban, apixaban	X Adding "incl" before warfarin, dabigatran, rivaroxaban, apixaban
Steroids	X	X	X	X	X	X	X	X	X	X	X
Oral corticosteroids											X

3.4.4 Allowable medications for standard care or precautions

- **Obesity**

Stable weight since the liver biopsy was performed, defined by no more than a 5 % loss of initial body weight

- **Treatment used for the underlying medical condition**

  Treatments are allowed within certain restrictions (described above and below) and provided they have been kept at ***stable doses for at least 6 months before the pre-treatment biopsy.***

  - *Type 2 diabetes*: Metformin is allowed as well as dipeptidyl peptidase-4 inhibitors and sodium-glucose transport protein 2 inhibitors: canagliflozin, dapagliflozin and empagliflozin. Glucagon like peptide-1 receptor agonists (liraglutide, exenatide) or glitazones are not allowed
  - *Hyperlipidemia*: only statins at stable doses will be allowed
  - *Antiplatelets agents*: The antiplatelets agents (aspirin, ticlopidine, clopidogrel, prasugrel, ticagrelor) are allowed
  - *Herbal supplements and Others Supplementation*: Herbal preparations or vitamin supplements should not be taken as it is difficult to know exactly what they contain and could be liver toxic

- **Other Medications**

Medications other than the Investigational Medicinal Product (IMP) and those mentioned above must only be taken exceptionally and with the agreement of the investigator in order to avoid interference with study assessments. The need for other medication may lead to exclusion of the patient from the study.

If symptomatic medication is needed to treat adverse events related to IMP, the investigator will inform the sponsor about the concomitant medication given.

3.5 Changes in the conduct of the study

The last version of the protocol is version 5.1, dated March, 25th 2020. The original protocol was amended 7 times. The list of exhaustive changes is described in the summary of changes from each protocol amendment.

Additionally:

- It was initially planned to consider ‘at least 60’ sites, and finally 92 sites were involved in the study
- It was initially planned to consider ‘at least 300 patients screened’, and finally 868 patients were screened
- It was initially planned to randomise ‘225 patients’, and finally 247 were randomised in the study, mainly due to the multicentric nature of the study.
- As per initial sample size, it was estimated that 100 patients per group were needed to be screened to randomise 75 patients, meaning a screening failure rate of 25%. Based on collected data, the actual observed screening failure rate is of 72%.

The table below list the application date of each protocol version by country and site:

Country	Site	PI	V 1.0	V 1.1	V 1.2	V 1.3	V 2.0	V 3.0	V4.0	V4.2
			Version 28/AUG/2016	Version 19/AUG/2016	Version 10/FEB/2017 CH	Version 19/NOV/2017 CH	Version 10/MAR/2017	Version 02/AUG/2017	Version 02/NOV/2017	Version 12/DEC/2018
Australia	1201	HODGE	NA	NA	NA	NA	NA	19/01/2018	11/04/2018	25/03/2019
Australia	1202	CHINNARATHA	NA	NA	NA	NA	NA	22/12/2017	23/08/2018	29/04/2019
Australia	1203	SKOIEN	NA	NA	NA	NA	NA	22/12/2017	12/06/2018	04/04/2019
Australia	1204	MULLER	NA	NA	NA	NA	NA	22/12/2017	24/05/2018	25/03/2019
Australia	1205	AYONRINDE	NA	NA	NA	NA	NA	29/06/2018	22/08/2018	12/04/2019
Austria	1001	TRAUNER	NA	28/02/2017	NA	NA	27/06/2017	10/11/2017	15/11/2018	11/01/2019
Austria	1002	STAUBER	NA	28/02/2017	NA	NA	27/06/2017	15/11/2017	15/11/2018	11/01/2019
Belgium	1	FRANCQUE	NA	23/01/2017	NA	NA	15/05/2017	16/10/2017	23/05/2018	11/01/2019
Belgium	2	LANTHIER	NA	23/01/2017	NA	NA	15/05/2017	16/10/2017	23/05/2018	11/01/2019
Belgium	3	MORENO	NA	23/01/2017	NA	NA	15/05/2017	16/10/2017	23/05/2018	11/01/2019
Belgium	4	GEERTS	NA	NA	NA	NA	NA	09/02/2018	19/06/2018	11/01/2019
Belgium	5	ROBAEYS	NA	NA	NA	NA	NA	09/02/2018	23/05/2018	11/01/2019
Canada	1301	SEBASTIANI	NA	NA	NA	NA	NA	15/12/2017	30/07/2018	27/02/2019
Canada	1302	STINTON	NA	NA	NA	NA	31/07/2017	12/10/2017	18/04/2018	16/01/2019
Canada	1303	BAILEY	NA	NA	NA	NA	16/08/2017	04/10/2017	11/07/2018	12/02/2019
Canada	1304	MAROTTA	NA	NA	NA	NA	11/10/2017	31/10/2017	09/07/2018	05/03/2019
Canada	1305	TAM	NA	NA	NA	NA	16/06/2017	13/10/2017	31/05/2018	26/02/2019
Canada	1306	DESILET	NA	NA	NA	NA	NA	15/12/2017	21/11/2018	01/03/2019
Canada	1307	HAMET	NA	NA	NA	NA	NA	01/02/2018	31/05/2018	26/02/2019
Czech Republic	901	URBANEK	NA	09/11/2016	NA	NA	24/05/2017	02/11/2017	20/06/2018	11/01/2019
Czech Republic	902	SPERL	NA	02/03/2017	NA	NA	14/06/2017	02/11/2017	18/07/2018	11/01/2019
Czech Republic	903	HEJDA	NA	03/11/2016	NA	NA	01/06/2017	02/11/2017	20/06/2018	11/01/2019
France	201	RATZIU	NA	NA	NA	NA	22/05/2017	03/10/2017	28/02/2018	11/01/2019
France	203	LE CLEACH	NA	NA	NA	NA	NA	NA	28/02/2018	11/01/2019
France	204	BOURSIER	NA	NA	NA	NA	22/05/2017	03/10/2017	28/02/2018	11/01/2019
France	205	ANTY	NA	NA	NA	NA	22/05/2017	03/10/2017	28/02/2018	11/01/2019

Country	Site	PI	V 1.0	V 1.1	V 1.2	V 1.3	V 2.0	V 3.0	V4.0	V4.2
			Version 28/AUG/2016	Version 19/AUG/2016	Version 10/FEB/2017 CH	Version 19/NOV/2017 CH	Version 10/MAR/2017	Version 02/AUG/2017	Version 02/NOV/2017	Version 12/DEC/2018
France	206	NGUYEN-KHAC	NA	NA	NA	NA	22/05/2017	03/10/2017	28/02/2018	11/01/2019
France	207	DI MARTINO	NA	NA	NA	NA	22/05/2017	03/10/2017	28/02/2018	11/01/2019
France	209	GUILLAUME	NA	NA	NA	NA	NA	03/10/2017	28/02/2018	11/01/2019
France	210	DE LEDINGHEN	NA	NA	NA	NA	NA	03/10/2017	28/02/2018	11/01/2019
France	211	LARREY	NA	NA	NA	NA	NA	03/10/2017	28/02/2018	11/01/2019
France	212	GUYADER	NA	NA	NA	NA	NA	03/10/2017	28/02/2018	11/01/2019
France	213	LEVRERO	NA	NA	NA	NA	NA	10/01/2018	28/02/2018	11/01/2019
France	214	LEROY	NA	NA	NA	NA	NA	10/01/2018	28/02/2018	11/01/2019
France	215	CASTERA	NA	NA	NA	NA	NA	10/01/2018	28/02/2018	11/01/2019
France	216	HEZODE	NA	NA	NA	NA	NA	10/01/2018	28/02/2018	11/01/2019
France	217	SERFATY	NA	NA	NA	NA	NA	10/01/2018	28/02/2018	11/01/2019
Germany	801	SCHATTENBERG	NA	NA	NA	NA	21/06/2017	06/11/2017	22/11/2018	11/01/2019
Germany	802	GEIER	NA	NA	NA	NA	21/06/2017	06/11/2017	22/11/2018	11/01/2019
Germany	803	MERLE	NA	NA	NA	NA	21/06/2017	06/11/2017	22/11/2018	11/01/2019
Germany	804	MANNS	NA	NA	NA	NA	21/06/2017	06/11/2017	22/11/2018	11/01/2019
Germany	805	TRAUTWEIN	NA	NA	NA	NA	21/06/2017	06/11/2017	22/11/2018	11/01/2019
Germany	806	GOESER	NA	NA	NA	NA	NA	19/01/2018	22/11/2018	11/01/2019
Germany	807	BOETTLER	NA	NA	NA	NA	NA	08/02/2018	22/11/2018	11/01/2019
Germany	808	HEINZOW	NA	NA	NA	NA	NA	04/04/2018	22/11/2018	11/01/2019
Italy	101	BUGIANESI	NA	10/07/2017	NA	NA	06/02/2018	NA	NA	12/04/2019
Italy	102	SVEGLIATI BARONI	NA	NA	NA	NA	07/06/2018	NA	NA	NA
Italy	103	MIELE	NA	14/02/2018	NA	NA	NA	NA	NA	NA
Italy	104	VALENTI	NA	NA	NA	NA	01/10/2018	NA	NA	NA
Italy	105	CRAXI	NA	18/09/2017	NA	NA	NA	NA	NA	NA
Italy	106	ANDREONE	NA	NA	NA	NA	NA	NA	NA	NA
Italy	107	LAMPERTICO	NA	NA	NA	NA	01/10/2018	NA	NA	NA

Country	Site	PI	V 1.0	V 1.1	V 1.2	V 1.3	V 2.0	V 3.0	V4.0	V4.2
			Version 28/AUG/2016	Version 19/AUG/2016	Version 10/FEB/2017 CH	Version 19/NOV/2017 CH	Version 10/MAR/2017	Version 02/AUG/2017	Version 02/NOV/2017	Version 12/DEC/2018
Italy	108	MANGIA	NA	NA	NA	NA	11/07/2018	NA	NA	NA
Italy	109	NASCIMBENI	NA	NA	NA	NA	NA	NA	NA	NA
Netherlands	1101	TUSHUIZEN	NA	NA	NA	NA	NA	NA	NA	NA
Poland	701	FLISIAK	NA	26/01/2017	NA	NA	26/06/2017	30/11/2017	23/05/2018	02/04/2019
Poland	702	PIEKARSKA	NA	NA	NA	NA	26/06/2017	30/11/2017	23/05/2018	02/04/2019
Poland	703	TOMASIEWICZ	NA	NA	NA	NA	26/06/2017	30/11/2017	23/05/2018	02/04/2019
Portugal	601	CARVALHO	NA	03/01/2018	NA	NA	NA	NA	14/05/2018	11/01/2019
Spain	501	ROMERO GOMEZ	NA	23/12/2016	NA	NA	19/06/2017	06/11/2017	07/03/2018	11/01/2019
Spain	502	CRESPO	NA	23/12/2016	NA	NA	19/06/2017	06/11/2017	07/03/2018	11/01/2019
Spain	503	CALLEJA	NA	23/12/2016	NA	NA	19/06/2017	06/11/2017	07/03/2018	11/01/2019
Spain	504	ANDRADE	NA	23/12/2016	NA	NA	19/06/2017	06/11/2017	07/03/2018	11/01/2019
Spain	505	AUGUSTIN	NA	NA	NA	NA	NA	06/11/2017	07/03/2018	11/01/2019
Switzerland	401	DUFOUR	NA	NA	17/10/2017	28/11/2017	NA	NA	19/02/2019	23/09/2019
Switzerland	402	GOOSSENS	NA	NA	17/10/2017	28/11/2017	NA	NA	19/02/2019	24/09/2019
Switzerland	403	TERZIROLI	NA	NA	17/10/2017	28/11/2017	NA	NA	19/02/2019	25/09/2019
UK	301	MCPHERSON	NA	13/02/2017	NA	NA	06/07/2017	01/11/2017	22/05/2018	11/01/2019
UK	302	AGARWAL	NA	NA	NA	NA	NA	12/02/2018	22/05/2018	11/01/2019
UK	303	RYDER	NA	NA	NA	NA	NA	12/02/2018	22/05/2018	11/01/2019
Bulgaria	1501	MATEVA	NA	NA	NA	NA	NA	NA	12/03/2018	08/04/2019
Bulgaria	1502	GENOV	NA	NA	NA	NA	NA	NA	12/03/2018	05/04/2019
Bulgaria	1503	BALABANSKA	NA	NA	NA	NA	NA	NA	12/03/2018	05/04/2019
Bulgaria	1504	TOMOV	NA	NA	NA	NA	NA	NA	12/03/2018	15/04/2019
Bulgaria	1505	KATZAROV	NA	NA	NA	NA	NA	NA	12/03/2018	08/04/2019
Bulgaria	1506	STEFANOVA-PETROVA	NA	NA	NA	NA	NA	NA	12/03/2018	08/04/2019
Bulgaria	1507	HANDZHIEV	NA	NA	NA	NA	NA	NA	12/03/2018	05/04/2019
France	218	KWIATEK	NA	NA	NA	NA	NA	NA	NA	31/12/2018

Country	Site	PI	V 1.0	V 1.1	V 1.2	V 1.3	V 2.0	V 3.0	V4.0	V4.2
			Version 28/AUG/2016	Version 19/AUG/2016	Version 10/FEB/2017 CH	Version 19/NOV/2017 CH	Version 10/MAR/2017	Version 02/AUG/2017	Version 02/NOV/2017	Version 12/DEC/2018
Mauritus	1401	ROUZIER	NA	NA	NA	NA	NA	NA	11/04/2018	13/03/2019
Poland	704	NAPORA	NA	NA	NA	NA	NA	NA	NA	02/04/2019
Poland	705	HARTLEB	NA	NA	NA	NA	NA	NA	NA	02/04/2019
Slovenia	1701	SIBLI	NA	NA	NA	NA	NA	NA	NA	11/04/2019
Slovenia	1702	GERIC	NA	NA	NA	NA	NA	NA	NA	25/04/2019
US	1601	NEFF	NA	NA	NA	NA	NA	NA	NA	28/03/2019
US	1602	HARRISON	NA	NA	NA	NA	NA	NA	NA	12/02/2019
US	1603	CALDWELL	NA	NA	NA	NA	NA	NA	NA	16/05/2019
US	1604	REINDOLLAR	NA	NA	NA	NA	NA	NA	NA	14/06/2019
US	1605	LAZAS	NA	NA	NA	NA	NA	NA	NA	15/02/2019
US	1606	SANYAL	NA	NA	NA	NA	NA	NA	NA	29/05/2019
US	1607	ABDELMALEK	NA	NA	NA	NA	NA	NA	NA	09/05/2019
US	1608	TETRI	NA	NA	NA	NA	NA	NA	NA	Cancelled
US	1609	ALKHOURI	NA	NA	NA	NA	NA	NA	NA	20/02/2019
US	1610	DENHAM	NA	NA	NA	NA	NA	NA	NA	Cancelled
US	1611	CASTANEDA	NA	NA	NA	NA	NA	NA	NA	12/02/2019
US	1612	LOOMBA	NA	NA	NA	NA	NA	NA	NA	24/05/2019
US	1613	HALEGOUA-DEMARZIO	NA	NA	NA	NA	NA	NA	NA	29/05/2019
US	1614	SYAL	NA	NA	NA	NA	NA	NA	NA	08/04/2019
US	1615	MYERS	NA	NA	NA	NA	NA	NA	NA	28/03/2019
US	1616	BROWN	NA	NA	NA	NA	NA	NA	NA	10/04/2019

4 Statistical methods

4.1 General statistical considerations

4.1.1 Software used

All statistical analyses will be performed with the SAS® software version 9.4 or higher.

4.1.2 Statistical deliverables

Statistical results will be delivered in several batches:
- the first batch will contain the Head Line Results (HLR)
- the other batches being all other results described in this Statistical Analysis Plan (SAP).

The contents of the HLR and other results are defined in Appendix 2 - Contents of statistical deliverables.

4.1.3 Statistical quality control

Derived datasets

For most important derived datasets an independent double programming will be performed (Quality Control (QC) type 3): for a given derived dataset, 2 programmers independently write a program to produce the dataset; then the 2 datasets obtained by the 2 programmers are compared using the SAS® COMPARE procedure; content as well as structure of the 2 datasets should be 100% similar. For other datasets a simple control will be performed. Appropriate documentation of QC will be developed.

The following deliverables will be provided at time of final analysis:
- Specifications for derived datasets
- Analysis datasets in SAS format
- SAS programs generating the derived datasets

Tables Listing Figures (TFLs)

All SAS programs and TFLs will be programmed and quality controlled by the study SAS programmer (self-inspection of the programs/logs and results).

Additionally a QC will be performed by the study biostatistician:
- Simple programming for all HLR tables (QC type 2): study biostatistician will use some SAS® procedures which allow verifying the statistical results obtained
- Review of the program and the associated statistical output(s) for non HLR TLFs (QC type 1): check of the mean, the standard deviation, the minimum, the maximum for quantitative variables, the frequencies and the percentages for the qualitative variables and the size of the populations

Appropriate documentation of QC will be developed.

The following deliverables will be provided at time of final analysis:

- Two separate documents compiling all TLFs: one for Appendix 14 and another one for Appendix 16.2
- SAS programs generating the outputs: TFLs

The detailed strategy put in place for HLRs QC (from derived datasets to TFLs) is provided in “

See appended document: INVENTIVA_NATIVE_SAP_Mock_Up_TFLs

Appendix 3 – Strategy for analysis QC” of this document.

4.1.4 Descriptive statistics

Continuous variables will be described using: number of non-missing observations (N), number of missing observations (Nmiss), arithmetic mean (Mean), standard deviation (SD), minimum (MIN), quartile 1 (Q1), median (Median), quartile 3 (Q3) and maximum (MAX).
MIN, Q1, Median, Q3 and MAX will be given at the data number of decimal points but limited to 2 decimals. Mean and SD will be given at 1 additional decimal point but limited to 3 decimals.
The 95% two-sided confidence interval (CI) will be calculated when appropriate using the standard method (Standard normal distribution).

Categorical variables will be presented using N, Nmiss and percentages (%). Missing data will not be included in the denominator for the calculation of percentages.
Proportions will be displayed with one decimal.
The 95% two-sided CIs will be calculated when appropriate using the exact (Clopper-Pearson) method.

All descriptive statistics will be done by treatment group (Placebo, lanifibranor 800 mg/day and 1200 mg/day) and overall (for baseline characteristics only).

4.1.5 Treatment groups comparison

For statistical tests, the type I error risk of these will be set at 5% (2-sided) without adjustments for multiplicity testing, unless specified otherwise.

P-values will be presented with 3 decimals. Any p-value less than 0.001 will be presented as <0.001, even if it would normally round up to 0.001.

Hochberg procedure for multiplicity testing

When specified, the ascending Hochberg procedure will be used to adjust for multiplicity testing. This procedure is a powerful tool that decreases the false discovery rate: this is the expected proportion of "discoveries" (significant results) that are actually false positives. Adjusting the rate helps to control for the fact that sometimes small p-values (less than 5%) happen by chance, which could lead to incorrectly reject the true null hypotheses. In other

words, the procedure helps to avoid type I errors (false positives). To run the procedure, the following steps will be followed:

1. Put the individual p-values (without multiplicity adjustment) in ascending order, from smallest to largest.
2. Assign ranks to the p-values. For example, the smallest has a rank of 1, the second smallest has a rank of 2.
3. Calculate each individual p-value's critical value, using the formula (i/m)Q, where:
    - i = the individual p-value's rank,
    - m = total number of tests,
    - Q = the false discovery rate (type I error)
4. Compare original p-values to the critical ones from Step 3; find the largest p value that is smaller than the critical value.

As an example, the following table shows the result of 2 tests *(lanifibranor 800 mg vs. placebo* and *lanifibranor 1200 mg vs. placebo*) with their p-values. The list of p-values are ordered (Step 1) and then ranked (Step 2) in the 3rd column. The last column shows the calculation of the critical value with a false discovery rate of 5% (Step 3). For instance, last column for test 2 (lanifibranor 800 mg vs. placebo) is calculated as (2/2) * 0.05 = 0.050:

Test	**p-value observed**	**Rank (i)**	**(i/m)Q=(i/2)x0.05**
Lanifibranor 1200 mg vs. placebo	0.020	1	0.025
Lanifibranor 800 mg vs. placebo	0.028	2	0.050

As the p-value associated to the test *"lanifibranor 1200 mg vs. placebo"* (p-value = 0.020) is smaller than its associated critical value (critical-value = 0.025), the test is considered as statistically significant after multiplicity adjustment according to the ascending Hochberg procedure. Similarly, the test *"lanifibranor 800 mg vs. placebo"* is considered as statistically significant after multiplicity adjustment according to the ascending Hochberg procedure: p-value = 0.028 < critical-value = 0.050.

Comparison of treatment groups for **quantitative variables** will be performed using:

- an Analysis of Covariance (**ANCOVA**) using the SAS MIXED procedure with the treatment and the diabetic status as covariates when specified

  Or

- a Mixed Model for Repeated Measures (**MMRM**) when specified using the SAS MIXED procedure with:
    a. The absolute change from baseline of the analysis variable as endpoint (MODEL statement of the MIXED procedure)
    b. The time, treatment, the diabetic status, the interaction (treatment * time) and the baseline value as fixed effects (MODEL statement of the MIXED procedure). Time, treatment and diabetic status being considered as categorical variables
    c. A time repeated measure (REPEATED statement of the MIXED procedure) within each subject (SUBJECT = subject as option of the REPEATED

statement). An unstructured (type=UN) variance covariance matrix being used as option of the REPEATED statement

d. The Kenward-Roger approximation to estimate denominator degrees of freedom and adjust standard errors (ddfm=kr option in MODEL statement)

In order to explore the validity of the model (and more accurately the assumption regarding independence, normality and constant variance of residuals), the following graphs will be provided: Q-Q plot of the residuals, distribution of residuals with its corresponding normal density estimate and scatterplot of residuals vs. predicted values.

With such models (ANCOVA, MMRM) different treatment effects will be evaluated:

- **Evaluation of treatment effect (Each dose vs. placebo) at week 24**: In order to evaluate each treatment dose versus placebo at week 24 the following contrasts of interest will be used:
  - 800 mg/day vs. placebo: -1 for Placebo, 1 for 800 mg/day and 0 for 1200 mg/day
  - 1200 mg/day vs. placebo: -1 for Placebo, 0 for 800 mg/day and 1 for 1200 mg/day.

  In order to take into account multiplicity of tests, the ascending Hochberg procedure will be applied (see section 4.1.5).

- **Evaluation of dose effect (800 mg vs. 1200 mg) at week 24:** In order to evaluate the dose of 800 mg/day versus the dose of 1200 mg/day at week 24 the following contrast of interest will be used:
  - 800 mg/day vs. 1200 mg/day: 0 for Placebo, -1 for 800 mg/day and 1 for 1200 mg/day

- **Time course of the response of each treatment group**: In order to evaluate the time course of the response of each dose (separately) at each time-point the following contrasts of interest will be used for each dose:
  - week 4 vs. week 14: -1 for week 4, 1 for week 14, 0 for week 24 and 0 for week 28
  - week 4 vs. week 24: -1 for week 4, 0 for week 14, 1 for week 24 and 0 for week 28
  - week 4 vs. week 28: -1 for week 4, 0 for week 14, 0 for week 24 and 1 for week 28
  - week 14 vs. week 24: 0 for week 4, -1 for week 14, 1 for week 24 and 0 for week 28
  - week 14 vs. week 28: 0 for week 4, -1 for week 14, 0 for week 24 and 1 for week 28
  - week 24 vs. week 28: 0 for week 4, 0 for week 14, -1 for week 24 and 1 for week 28

  In order to take into account multiplicity of tests, the ascending Hochberg procedure will be applied (see section 4.1.5).

Lowest dose will always be considered as reference for treatment effect calculation. As well as earliest visit will always be considered as reference for time course evaluation.

Comparisons of treatment groups for **qualitative variables** will be done using the FREQ procedure with Cochran–Mantel–Haenszel (**CMH**) test option, stratified on the diabetic status at Baseline (yes/no). The primary measure of the effect size will be the CMH odds ratio with an adjustment for diabetic status. Because the odds ratio is not easy to interpret when the rate of responders in the placebo group is not very small the odds ratio (OR) will be converted in

Risk Ratio (RR) using the following formula RR = (P1/P0) = OR/[(1−P0) + (P0×OR)]. The same formula will be applied to OR 95% CI lower and upper bounds to obtain RR 95% CI. The log-binomial model will preferentially be used in the absence of convergence or estimability issue for estimating the effect size with RR. The primary handling of heterogeneity of result across strata will be performed through the Breslow-Day test. If the homogeneity hypothesis is rejected, then the estimate of the difference in percentage points between each dose and placebo along with the 95% C.I. will be provided within each stratum, as well as the p-value of the association test between treatment and qualitative variable (Chi-2 test or Fisher's exact test). If the interaction between stratum and treatment (Breslow Day test) is significant it means that the treatment effect has not the same magnitude in diabetic and non-diabetic patients. In the absence of qualitative interaction there will be no further adjustment of the type one error for multiplicity of testing. Smallest dose will always be considered as reference for OR/RR calculation.

Dose-response relationship for **qualitative variables** will be estimated using the Cochran-Armitage trend test via the LOGISTIC procedure (See Reference 5). Within this model, dose will be considered as a quantitative covariate (0 mg, 800 mg and 1200mg) and diabetic status as a qualitative covariate (Presence, Absence). The p-value assessing the significant dose-response relationship at week 24 will be provided based on this model (Score test).

4.1.6 Missing data

4.1.6.1 General considerations

Unless otherwise specified, missing data will not be replaced. In this case, the descriptive analyses of each variable will be based on the available data, i.e. Observed Cases (OC) analysis, considering missing data as non-informative. The number of missing data will be documented for each analysis.

4.1.6.2 Dates

Imputation rules for missing first dose date / last dose date:

- Missing first dose date / last dose date at intermediate visits will remain missing
- Missing first dose date at time of randomisation will be imputed as the date of randomisation
- Missing end dose date at time of Visit 3 will be imputed as follow:
    - If the patient prematurely withdrew from the study due to AE and if the month/year of EOT date is equal to month/year of start date of AE, then the EOT date will be replaced by the start date of AE
    - If the patient prematurely withdrew from the study due to a reason other than AE, then:
        - If last contact date is missing then the date of last visit performed under treatment (V3 or V2 or V1) will be considered as the EOT date
        - If last contact date is provided, then it will be considered as the EOT date.
    - If the patient completed the treatment period, and if the month/year of EOT date is equal to month/year of date of Visit 3, then the EOT date will be replaced by the date of Visit 3

Imputation rules for partial or missing start dates for AE:

- If month and year are present:
    - If month/year of AE corresponds to month/year of a physical examination with an abnormal value and if verbatim of AE corresponds to the finding of this physical examination, then impute the day by the day of physical examination with an abnormal value
    - Otherwise, if month/year of AE corresponds to month/year of first treatment intake then impute the day with the day of first intake of treatment
    - Otherwise, impute by the first day of the month
- If only the year is present, impute by January 1st of that year. If the year is the same as the year of the date of first dose, impute by the day of first intake of treatment.
- If the start date is entirely missing, impute by the day of first intake of treatment. If after imputation AE start date is posterior to AE end date, then imputed start date should be replaced by AE end date.

Imputation rules for partial or missing start dates for concomitant medications and medical history:

- If the month and year are present, impute the day by the first of that month. If the month and year are the same as those of the date of first dose, impute the day with the day of first intake of treatment.
- If only the year is present, impute by January 1st of that year. If the year is the same as the year of the date of first dose, impute by the day of first intake of treatment.
- If the start date is entirely missing, impute by the day of first intake of treatment. If after imputation concomitant medication or medical history start date is posterior to concomitant medication or medical history end date, then imputed start date should be replaced by concomitant medication or medical history end date.

Imputation rules for partial or missing stop dates for AE, concomitant medication and medical history:

- If the month and year are present, impute the day by the last day of that month.
- If only the year is present, impute by December 31st of that year.
- If the stop date is entirely missing, assume the event or medication is ongoing.

For any partial dates other than start and stop dates, for AE, concomitant medical and medical history:

- If only month and year are present, impute by 15th of that month,
- If only the year is present, impute by July 1st of that year
- If date is fully missing, impute by corresponding visit date.

4.1.6.3 Main criteria

The following method of missing data imputation will be used for main efficacy criteria analysis (qualitative endpoints: Responder vs. Non-responder):

1. Primary imputation method

Patients with a missing data will be considered as Non-responder.

2. Secondary imputation method

Patients with a missing data will be considered as Non-responder in case of premature treatment withdrawals due to: Adverse event or Other: Lack of efficacy. The other reasons will be clearly reviewed during Blind Data Review Meeting (BDRM) to identify 'Lack of efficacy'.
In all other cases, missing data will remain missing.

3. Observed cases (OC)

Missing data will remain missing, only observed cases will be used.

4. Observed cases under treatment (OCUT)

Biopsy:
Only observed cases within 14 days after study treatment last intake will be considered:

- Missing data will remain missing
- Any biopsy data collected more than 8 days after study treatment last intake will not be considered as assessed under treatment, meaning will be considered as missing for the OCUT analysis

Safety (Treatment Emergent Adverse Event):

- Adverse events that started after 28 days will be considered as Post Treatment Adverse Events (PTAE)

All other procedures:
Only observed cases within 3 days after study treatment last intake will be used:

- Missing data will remain missing
- Will also be considered as missing any data collected more than 3 days after study treatment last intake

Note:

- Data collected at Visit 3 being an early treatment discontinuation, should not be taken into account for Week 24 (i.e. actual V3) data descriptions
- For OCUT analysis where data available at Week 28 (i.e. V4) should be described, all Week 28 (i.e. V4) data that are within 4 weeks ± 2 weeks compared with Week 24 (i.e. V3) are to be taken into account.
  Data collected at Visit 4 being the visit following an early treatment discontinuation, should not be taken into account for Week 28 (i.e. actual V4) data descriptions
- For all analysis based on biopsy data, data collected at actual V3 should be taken into account as well as data collected at Visit 3 being an early treatment discontinuation.

4.1.7 Handling centres

In order to explore any potential "center" or geographical effect on primary criteria, centers need to be pooled in order to have enough patients by "group".

Three strategies of center pooling will be used to explore any potential "center" effect:

1. Centers will be distributed in 2 groups: Bulgaria (the main recruiter in the study) and all other countries
2. Centers will be distributed in 3 groups according to the number of randomised and treated patients (i.e. in the FAS, see section 4.3.3):
    - 3 or less patients randomised and treated
    - From 4 to 9 patients randomised and treated
    - 10 or more patients randomised and treated

4.1.8 Visit reallocation

Not Applicable.

4.2 Sample size calculation

The expected rate of responders according to the retained definition was estimated to 10% for the placebo by a group of clinical experts. An excess rate of responders of 20% was accepted as clinically pertinent. It corresponds to a multiplication of chance of success (responders) of 3 and a NNT (Number Needed to Treat) of 5. The sample size required to reach a power of at least 80% is 72 patients per group with a two-sided alpha of 0.025 (adjustment for multiplicity). The sample size is sensitive to the rate of responders in the placebo group. For example, if the rate of responders is 15% instead of 10% then 85 patients are required. If the true rate is lower than 10% then less patients may be sufficient. The sample size is therefore rounded in the conservative side of 75 patients per group.

Based on the experience of previous clinical trials, it is estimated that 100 patients per group will need to be screened to randomise 75 patients after central reading of liver biopsy confirms the NASH diagnosis and activity (screening failure rate of 25%). However, as detailed in section 3.5, the observed screening failure rate was of 72%), consistent with all other clinical trial performed in NASH with such a high screening failure rate.
In case the end of study liver biopsy slides are not available or not interpretable in more than 5% of patients, an amendment will be submitted to increase sample size accordingly.

4.3 Analysis populations

4.3.1 Screened patients

The screened patients will consist of all patients who signed the informed consent (with an informed consent date completed).

4.3.2 Randomized set of patients

The randomized set of patients will consist of all randomized patients.
In case of treatment error, the treatment assigned in the randomization list will prevail over the actual received treatment. Additionally, in case of stratification error at randomization, strata assigned via the randomization will be taken into account for the analysis.
Reminder: Randomisation stratified on diabetes (presence/absence).

4.3.3 Full analysis set (FAS)

The full analysis set will consist of all randomized patients who received at least one dose of the assigned treatment.
In case of error in the assignment of treatment, the actual treatment will be used in the FAS instead of the treatment assigned in the randomization list.
Additionally, in case of stratification error at randomization, actual strata will be taken into account for the analysis.

4.3.4 Safety set of patients

The safety set of patients will consist of the FAS who will have taken at least one dose of treatment, regardless any protocol deviations. 'No adverse event' confirmed by the investigator in the AE form will be considered as a post-baseline assessment of safety.
In case of treatment error, the actual treatment will be used.

4.3.5 Evaluable patient population (EPP)

The evaluable patient population will consist of the FAS after exclusion of all patients without post-randomization efficacy assessment (SAF score at visit 3).

- All patients who prematurely discontinued the study treatment:
  - due to a reason linked to study treatment intake (adverse event) or lack of efficacy (recorded in 'Other') will be included in the EPP. In this case, the patient will be non-responder (see 'Secondary imputation method' in section 4.1.6.3).
  - for a reason not linked to study treatment intake (such as lost to follow-up or consent withdrawal) will be excluded from the EPP.

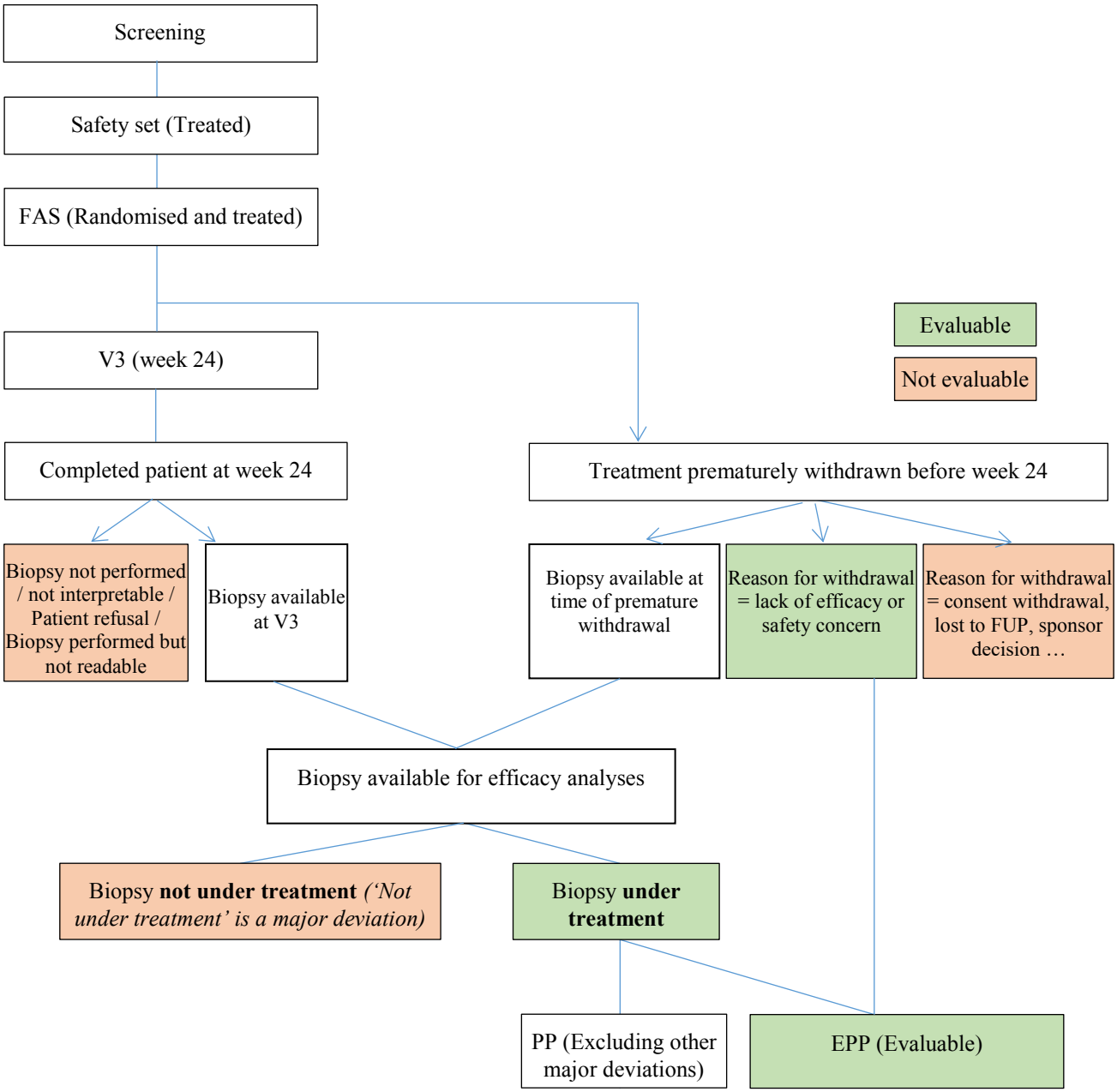
  The reasons of study treatment premature discontinuation will be solely reviewed during BDRM to correctly define the EPP.
- Patients that completed their study treatment up to Visit 3:
  - with an efficacy assessment at Visit 3 (biopsy performed, readable and performed within 14 days following last intake) will be included in the EPP.
  - without efficacy assessment at Visit 3 (biopsy not performed because patient refusal, biopsy not readable, biopsy not performed within 14 days following last intake…) will be excluded from the EPP.

The same rule will be applied for other binary efficacy variables.

4.3.6 Per protocol set of patients

This set will be composed of all patients of the FAS free from major protocol deviation, which can bias the estimate of the treatment effect. Patients with major deviations will be listed during the Blind Data Review Meetings and the reason for exclusion will be provided. Post-treatment biopsy evaluable for efficacy not available will be considered as a major protocol deviation.

The figure below summarizes the patient populations to be considered:



Note:

When considering actual treatment received:

- if a patient received both active and placebo IMPs during the study, active IMP will be considered as actual treatment

- if a patient received active IMP at both doses (800 mg and 1200 mg) during the study due to dispensation error(s), the dose of 1200 mg will be considered as actual treatment

4.4 Protocol deviations (PDs)

The list of PDs has already been developed (see Excel file appended to BDRM minutes named "INVEN_21507_Native_Deviation").

All PDs will be carefully identified through eCRF data before the BDRMs. During the BDRMs held before database lock (DBL), each PD will be classified as leading to exclusion from the PP population ("major") or not leading to exclusion from the PP population ("minor").

All PDs related to study inclusion or non-inclusion criteria, conduct of the trial, patient management or patient assessment will be described, such as:

- Violation of inclusion criteria
- Violation of exclusion criteria
- Intake of non-allowed concomitant medications during the treatment period
- Randomisation error
- Lack of compliance
- Primary endpoint not assessable (missing post-treatment biopsy results)
- Etc.

Additionally, the PDs that could not be identified through eCRF data will also be reviewed during the BDRMs. This listing will be based on the PD forms completed by the study monitors. These PDs will be extracted from the listing and imported in the database.

4.5 Derived variables

4.5.1 Baseline data and change from baseline

Baseline data will be considered as the last available non-missing data before or equal to the treatment start.

Note: For biopsies, multiple reading rules (see section 4.5.4.1.1) should be applied before calculating Baseline values.

Absolute change from baseline will be calculated as follows:
Value at V_i – Value at baseline, where *i* corresponds to a post-baseline value.

Relative change from baseline (in %) will be calculated as follows:
- if Value at baseline is not equal to 0: [(Value at V_i – Value baseline) / Value at baseline] * 100, where *i* corresponds to a post-baseline value.
- if both values at V_i and at baseline are equal to 0, then the relative change from baseline will be equal to 0%.

Regarding laboratory parameters that are sensitive to the fasting status (Fasting Glucose, HOMA, insulin, C-peptid, Fructosamine, Triglycerides, Total cholesterol, HDL cholesterol, LDL cholesterol, Free fatty acids (FFA), Apoprotein A1, Apoprotein B, Apoprotein C3, Adiponectin, Leptin, FGF-21):
- if the value at Baseline is a non-fasting value when the value at Screening is a fasting value, then the Baseline data will be the value at Screening
- if both values at Screening and Baseline are non-fasting values, then the Baseline data will be the value at Baseline.

Regarding laboratory parameters, the following status will be defined:
- Normal-Normal, if the baseline is within laboratory ranges and all values over time remain with laboratory ranges
- Normal-Abnormal, if the baseline is within laboratory ranges but at least one value over time is not within laboratory ranges
- Abnormal-Normal, if the baseline is not within laboratory ranges and all values over time are within laboratory ranges
- Abnormal-Abnormal, if the baseline is not within laboratory ranges and at least one value over time is not within laboratory ranges

4.5.2 Disposition data

- **Visit performed**

A visit will be considered as performed, if a visit date is reported for this visit.

- **Patient still under treatment, if visit performed**

A patient will be considered as “still under treatment” at a given visit if last treatment intake is ≥ visit date - 3.

- **Patient still ongoing, if visit NOT performed**

A patient will be considered as "still ongoing" at a given theoretical visit if another visit has been performed after this missing one.

- **Patient still under treatment, if visit NOT performed**

A patient will be considered as "still under treatment" at a given theoretical visit if last treatment intake is ≥ theoretical visit date - 3.

- **Study duration (months)**

Study duration (in months) is defined as the time between the randomisation date and the date of End of Study: (Date of End of Study – randomisation date + 1) / 30.4375.

- **Study duration (weeks)**

Study duration (in weeks) is defined as the time between the randomisation date and the date of End of Study: (Date of End of Study – randomisation date + 1) * 52 / 365.25.

- **Premature treatment withdrawal**

A patient will be considered as having prematurely discontinued study treatment if the reason for end of treatment is different from "Treatment period terminated as per protocol".

- **Completer patients**

A patient will be considered as a completer if he/she did not prematurely withdrawn treatment.

4.5.3 Baseline characteristics

- **Age**

Age (in years) is the one reported in the eCRF.

Patients could be classified in 2 categories according to their age:
- <65, ≥65 years old

- **Body Mass Index (kg/m²)**

Body Mass Index (BMI) is equal to the ratio between the weight (in kg) and the square of the height (in meter).

Patients will be classified in 6 categories according to their BMI:
- Underweight: BMI < 18.5 kg/m²
- Normal: BMI in [18.5 - 25[kg/m²
- Overweight: BMI in [25 - 30[kg/m²
- Obese class I (moderate): BMI in [30 - 35[kg/m²
- Obese class II (severe): BMI in [35 - 40[kg/m²
- Obese class III (morbid): BMI ≥ 40 kg/m²

They will also be classified in 2 categories according to their BMI:
- Non-obese: BMI < 30 kg/m²
- Obese: BMI ≥ 30 kg/m²

- **Metabolic Syndrome at Baseline**

A patient will be considered as presenting a metabolic syndrome at Baseline when at least 3 of these parameters are verified (see Reference 1):
- Waist circumference ≥ 94 cm/37 inches in men, ≥ 80 cm/31.5 inches in females
- 'Hypertension' reported in Medical History and ticked as 'ongoing'
    - HYPERTENSION (MedDRA PT code=10020772),
    - DIASTOLIC HYPERTENSION (MedDRA PT code=10012758),
    - ESSENTIAL HYPERTENSION (MedDRA PT code=10015488
- Pre-diabetic/diabetic condition: Actual 'Type 2 diabetes mellitus'=Presence or **Fasting** glucose ≥ 100 mg/dl (5.6 mmol/L) if 'Type 2 diabetes mellitus'=Absence
- Serum triglycerides > 150 mg/dL (i.e. 1.7 mmol/L) or corresponding Medical History reported
    - HYPERTRIGLYCERIDEMIA (MedDRA PT code=10020869),
    - FAMILIAL HYPERTRIGLYCERIDEMIA (MedDRA PT code=10059183),
    - HYPERLIPIDAEMIA (MedDRA PT code=10062060),
    - DYSLIPIDAEMIA (MedDRA PT code=10058108)
- HDL cholesterol < 40 mg/dL (i.e. 1.0 mmol/L) in men, < 50 mg/dL (i.e. 1.3 mmol/L) in females

- **Insulin-resistant status**

- Insulin-resistant: Actual 'Type 2 diabetes mellitus'=Presence or **Fasting** glucose ≥ 100 mg/dl (5.6 mmol/L) if 'Type 2 diabetes mellitus'=Absence
- Non insulin-resistant: **Fasting** glucose < 100 mg/dl (5.6 mmol/L) and 'Type 2 diabetes mellitus'=Absence

- **Prior medication**

A prior medication corresponds to any medication reported in the "PREVIOUS AND CONCOMITANT MEDICATIONS" form of the eCRF with an end date < first treatment intake date (after application of missing dates replacement rules, see section 4.1.6.2)

- **Concomitant medication**

A concomitant medication corresponds to any medication reported in the "PREVIOUS AND CONCOMITANT MEDICATIONS" form of the eCRF with a {start date ≤ first treatment intake date and an end date ≥ first treatment intake date or ongoing} or with a {first treatment intake date ≤ start date ≤ last treatment intake date} (after application of missing dates replacement rules, see section 4.1.6.2)

- **Antidiabetic treatment**

Four antidiabetic classes will be defined:

- Metformin
  - CMDECOD in ("METFORMIN HYDROCHLORIDE" "METFORMIN" "METFORMIN EMBONATE" "DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE W/METFORMIN" "EMPAGLIFLOZIN W/METFORMIN HYDROCHLORIDE" "EUCREAS" "JENTADUETO" "KOMBIGLYZE" "RISTFOR")
- Sulphonylurea
  - WHODDrug ATC code = A10BB
- DPP4i
  - WHODDrug ATC code = A10BH or CMDECOD in ("EUCREAS" "JENTADUETO" "KOMBIGLYZE" "RISTFOR")
- SGLT2
  - CMDECOD in ("DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE" "CANAGLIFLOZIN" "DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE W/METFORMIN" "EMPAGLIFLOZIN W/METFORMIN HYDROCHLORIDE" "DAPAGLIFLOZIN")

A patient will be considered as taking at least one antidiabetic treatment if at least one treatment detailed above is received.

- **Statins**

- HMG-CoA reductase inhibitors (WHODDrug ATC code: C10AA)

- HMG-CoA reductase inhibitors in combination with other lipid modifying agents (WHODDrug ATC code: C10BA)

- **Time between screening biopsy and randomisation (months)**

Time between screening biopsy and randomisation (in months) is defined as the time between the date of screening biopsy and the date of randomisation: (Date of randomisation –date of screening biopsy + 1) / 30.4375

4.5.4 Efficacy

4.5.4.1 Liver biopsy

4.5.4.1.1 Multiple reading at Baseline or V3

In case of multiple reading for a given biopsy at Baseline or at V3, the following strategy needs to be applied:

- If unreadable assessment : choose readable one
- If all are unreadable, the biopsy results will be considered as missing
- If more than 1 readable assessment :
    - Choose the worst case scenario based on the SAF-A score
    - If both SAF-A scores are similar:
        - Choose the worst scenario based on the SAF-F score
        - If both SAF-F scores are similar:
            - Choose the last reading based on reading date

4.5.4.1.2 Biopsy not performed as an efficacy endpoint

Some patients have underwent biopsies during the study that cannot be considered as the biopsies to be analysed for efficacy. These biopsies were identified during data cleaning process, and were actually reported as 'unscheduled' biopsies in the clinical database, in order to differentiate them with the biopsies evaluable for efficacy, reported at Visit 3 (week 24).

4.5.4.1.3 Available biopsy at V3 (Week 24)

Biopsy will be considered as available at Week 24 if SAF-A is non-missing for a biopsy reported at V3 (or for a re-test of a biopsy reported at V3). It will be considered as non-available in all other cases.

Reason for non-availability will be considered as:

- "Treatment Prematurely Withdrawn" for all non-completers patients
- "Non-Readable" if biopsy has been performed at V3 and SAF-A is missing for any completer patient
- "Patient Refusal" if reason for not having performed a biopsy at Visit 3 contains ("NOT AGREE" "REFUS" "NOT WANT") for any completer patient

4.5.4.1.4 Terminology

In the biopsy database, several scores are provided including:

- The SAF Steatosis score (SAF-S) and the CRN Steatosis score (CRN-S) that are similar
- The SAF Lobular Inflammation score (SAF-I) and the CRN Lobular Inflammation score (CRN-I) that may slightly differ. Indeed, score of 1 for SAF-I could be grade 2 for CRN-I.

- The Hepatocyte Ballooning score, considered as the CRN Hepatocyte Ballooning score (CRN-B)
- The SAF Activity score (SAF-A) that is already derived in the database, and that corresponds to the sum of SAF-I and CRN-B
- The CRN NAS score (NAS) that will be defined as the NAS score (NAS). This parameter is already derived in the database, and corresponds to the sum of CRN-S, CRN-I and CRN-B
- The SAF Fibrosis score (SAF-F) and the CRN Fibrosis score (CRN-F) that may slightly differ. Indeed values 1a 1b and 1c for the CRN-F are graded as 1 for SAF-F. In the analyses, stages 1a 1b and 1c for CRN-F will be considered as stage 1.

4.5.4.1.5 Biopsy length

Available biopsy length will be classified as ≤ 8 mm or > 8 mm.

4.5.4.1.6 Response according to SAF activity score (Primary endpoint)

Response is defined as a decrease from baseline to Week 24 of at least 2 points of the SAF Activity score (SAF-A) without worsening of the CRN Fibrosis score (CRN-F). No worsening means that score remains stable or decreases.

4.5.4.1.7 NASH improvement

Improvement is defined as a decrease of at least 2 points of the NAS score (NAS) from baseline to Week 24 without worsening of the CRN Fibrosis score (CRN-F).

4.5.4.1.8 Resolution of NASH without worsening of fibrosis

Resolution of NASH at Week 24 without worsening of fibrosis is defined as:

- CRN Lobular inflammation score (CRN-I) equal to {0, 1} at week 24 and
- CRN Hepatocyte ballooning score (CRN-B) equal to 0 at week 24 and
- No worsening of the CRN-F score from baseline to week 24.

4.5.4.1.9 Improvement of liver fibrosis ≥ 1 stage and no worsening of NASH

Improvement of liver fibrosis ≥ 1 stage and no worsening of NASH is defined from baseline to week 24 as:

- Improvement of CRN-F score ≥ 1 stage and
- No increase of CRN-S score and
- No increase of CRN-I score and

- No increase of CRN-B score

4.5.4.1.10 Resolution of NASH and Improvement of liver fibrosis ≥ 1 stage

Resolution of NASH and Improvement of liver fibrosis ≥ 1 stage is defined as:

- CRN Lobular inflammation score (CRN-I) equal to {0, 1} at week 24 and
- CRN Hepatocyte ballooning score (CRN-B) equal to 0 at week 24 and
- Improvement of CRN-F score ≥ 1 stage from baseline to week 24

4.5.4.1.11 Resolution of NASH without worsening of fibrosis and NASH improvement

Resolution of NASH at Week 24 without worsening of fibrosis and NASH improvement are defined as:

- CRN Lobular inflammation score (CRN-I) equal to {0, 1} at week 24 and
- CRN Hepatocyte ballooning score (CRN-B) equal to 0 at week 24 and
- Decrease of at least 2 points of the NAS score (NAS) from baseline to week 24
- No worsening of the CRN-F score from baseline to week 24.

4.5.4.1.12 Improvement of ISHAK liver fibrosis ≥ 2 stages and no worsening of NASH

Improvement of ISHAK liver fibrosis ≥ 2 stages and no worsening of NASH is defined from baseline to week 24 as:

- Improvement of ISHAK-F score ≥ 2 stages and
- No increase of CRN-S score and
- No increase of CRN-I score and
- No increase of CRN-B score

4.5.4.2 Fibrosis markers

4.5.4.2.1 NAFLD Fibrosis Score (NFS)

NAFLD Fibrosis Score is to be calculated using the following formula: *-1.675 + 0.037 * age (years) + 0.094 * BMI (kg/m²) + 1.13 * (Impaired **Fasting** Glucose/diabetes (yes = 1, no = 0)) + 0.99 * (AST/ALT ratio (no unit)) – 0.013*platelets (×10^9/L) – 0.66*albumin (g/dl)*
(See Reference 2)

The variable '*Impaired **Fasting** Glucose/diabetes (yes = 1, no = 0)'* corresponds to the insulin-resistant status (Yes, No).

A variable predicting the fibrosis will be constructed from the NFS:

- Low probability of fibrosis F3/F4 if score is less or equal to -1.455 (included),
- Fibrosis status indeterminate if -1.455 < score < 0.676,

- High probability of fibrosis F3/F4 if score is greater or equal to 0.676 (included).

4.5.4.2.2 FIB-4 score

FIB-4 score is to be calculated using the following formula: *(age (years) * AST (U/L)) / (platelets ($\times 10^9$/L) * √ALT (U/L))*
(See Reference 3)

A variable predicting the fibrosis will be constructed from the FIB-4 score:

- Low probability of fibrosis F3/F4 if score is less to 1.45 (excluded),
- Fibrosis status indeterminate if 1.45 ≤ score ≤ 3.25,
- High probability of fibrosis F3/F4 if score is greater to 3.25 (excluded).

4.5.4.2.3 ELF Score

ELF score is to be calculated using the following formula: *2.494 + 0.846 ln(Hyaluronic acid) + 0.735 ln(PIIINP) + 0.391 ln(TIMP-1)*
(See Reference 4)

A variable predicting the fibrosis will be constructed from the ELF:

- A score less than 7.7 (excluded) indicates no to mild fibrosis
- A score between 7.7 (included) and 9.8 (excluded) indicates moderate fibrosis
- A score between 9.8 (included) and 11.3 (excluded) indicates severe fibrosis
- A score greater or equal to 11.3 (included) indicates cirrhosis.

4.5.4.2.4 MACK-3 Score

MACK-3 score is to be derived using the computation tool available at the website http://forge.info.univ-angers.fr/~gh/wstat/mack3-calculator.php (last access on 16JAN20120).

The score is based on the following parameters: AST (IU/L), Glycaemia (mmol/l), Insulin (µU/ml) and Cytokeratin M30 (IU/L).
(See Reference 6)

A variable predicting the fibrosis will be constructed from the MACK-3 score:

- If Non metabolic syndrome and AST <35 IU/L: No fibrosis
- If Metabolic syndrome and/or AST ≥35 IU/L:
    - Score less or equal than 0.134 (included): No fibrosis
    - Score between 0.135 (included) and 0.549 (included): Fibrosis undefinable (grey zone)
    - Score greater or equal to 0.550 (included): Fibrosis

4.5.4.2.5 FIBC3 Score

FIBC3 score is to be calculated using the following formula: *-5.939 + (0.053*Age in years) + (0.076*BMI in kg/m²) + (1.614*T2DM (yes = 1, no = 0)) – (0.009*platelets in 10^9/L) + (0.071*PRO-C3 in ng/ml)*
(See Reference 8)

4.5.4.2.6 ABC3D Score

The derived "ABC3D" score comprises: A = Age>50 years, B = BMI>30 kg/m², C = platelet Count<200x10^9/L, 3 = PRO-C3>15.5 ng/ml, D = Diabetes = present.
The presence of each factor scores 1 point, except for T2DM that scores 2 points, yielding to a maximum of 6 (See Reference 8)

4.5.4.3 Glucose metabolism

Available HOMA index will be classified as < 3 or ≥ 3.

4.5.5 Questionnaires

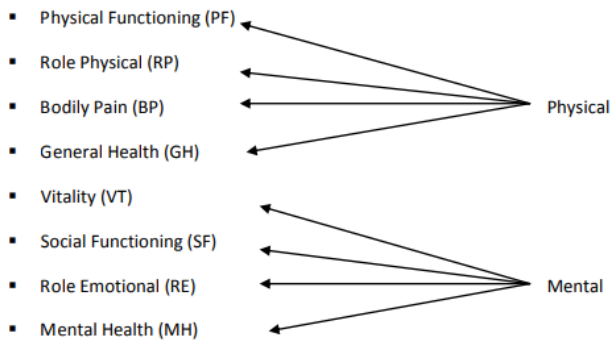
4.5.5.1 Short Form Health Survey (SF-36)

Purpose:

SF-36 is a set of generic, coherent, and easily administered quality-of-life measures. These measures rely upon patient self-reporting and are now widely utilized by managed care organizations and by Medicare for routine monitoring and assessment of care outcomes in adult patients.

Description:

The SF-36 is "a multi-purpose, short-form health survey with only 36 questions". It yields an 8-scale profile including functional health, and mental health.



Derivation:

A specific tool will be provided with the SF-36 questionnaire to calculate the score of the 8 sub-dimensions defined above, as well as the physical component score (PCS) and mental component score (MCS). Each score will be norm-based from 0 to 100.

Interpretation:

All questions are scored on a scale from 0 to 100, the minimum score is 0 (corresponding to a poor health) and maximum is 100 (corresponding to a good health).

Reference:

QualityMetric Health Outcomes Scoring Software User's guide

4.5.5.2 Flinders Fatigue Scale (FFS)

Purpose:

The FSS is a self-report questionnaire, designed to measure daytime fatigue.

Description:

It is a relatively brief measure, containing only 7 items that provide a global measure of fatigue.

Each item ranks from 0 (not at all) to 4 (extremely), except item 5 for which patient need to tick the time(s) of the day where fatigue is experienced (among 7 possible times).

Derivation:

Global score can be calculated by summing scores on all items as 0 (not at all) through 4 (entirely), except for item 5 (for this item, sum each time of day that is ticked).

Interpretation:

Global score ranges from 0 to 31 and higher scores indicate greater fatigue.

Reference:

See Reference 7

4.5.6 Safety

4.5.6.1 Treatment data

- **Date of first study intake**

Minimum of all "date of first intake after previous visit" reported in "Treatment COMPLIANCE" sections of the eCRF.

- **Date of last study intake**

"Date of end of study treatment" reported on the "END OF TREATMENT" form of the eCRF.

- **Treatment duration (months)**

Treatment duration (in months) is defined as the time between the first treatment intake date and the date of last treatment intake: (Date of last intake – date of first intake + 1) / 30.4375.

- **Treatment duration (weeks)**

Treatment duration (in weeks) is defined as the time between the first treatment intake date and the date of last treatment intake: (Date of last intake – date of first intake + 1) * 52 / 365.25.

- **Compliance at Visit(i)**

The compliance (%) at Visit(i) (Vi) corresponds to the ratio between the number of tablets taken and the expected number of tablets to be received between the study first treatment intake and visit Vi.

Tablets taken:

The number of tablets taken between Vi-1 and Vi is equal to the sum of:

- {Real/Estimated number of tablets taken at Vi} on all bottles not returned at visit i (in case of missing returned bottle)
  OR
- {38 - Number of tablets returned at Vi} on all bottles returned at visit i (in case of returned bottle)

[38 is the number of tablets per bottle given to the patient every one month (from V1 to V3)]

The total number of tablets taken between study first treatment intake to Vi corresponds to the sum of the number of tablets taken in each bottle from study first treatment intake to Vi.

[Indeed, patient should take 3 tablets twice a day, i.e. one tablet twice a day from each of the bottles A, B, and C]

If at a given visit the status of at least one bottle (returned / not returned) is not returned or missing, or if a corresponding number of "Real/Estimated number of tablets taken" or "Number of tablets returned" is missing, then the compliance will be considered as being not evaluable.

Tablets to be received at Visit(i):

The total number of tablets to be received at Visit(i) is equal to:

(Visit(i) date – Study first treatment intake date + 1)*3

[Indeed, patient should take 3 tablets, i.e. one tablet from each of the containers A, B, and C each morning]

The compliance (%) for a given visit is defined as:

- ⇨ Total number of tablets taken between study first treatment intake to V_i / Total number of tablets to be received between study first treatment intake to V_i * 100

- **Overall persistence**

The persistence (%) corresponds to the ratio between the actual number of tablets taken and the expected number of tablets to be received between the study first treatment intake and last treatment intake.

Tablets taken:

The total number of tablets taken corresponds to the sum of the number of tablets taken in each bottle at each visit.

See definition above (in section Compliance at Visit(i)).

Tablets to be received:

The total number of tablets to be received is equal to:

(Study last treatment intake date – Study first treatment intake date + 1) *3

- **Overall compliance at time of biopsy at week 24 (when biopsy results at week 24 are available)**

Overall compliance can be calculated as the ratio between actual number of tablets taken between first intake and time of biopsy at week 24, and the theoretical number of tablets to be received up to the time of biopsy at week 24:

Tablets taken:

The total number of tablets taken corresponds to the sum of the number of tablet not returned compared to the number of pills dispensed.

If the date of last intake reported on the EOT form is ≤ date of post-treatment biopsy then tables taken is equal to the number of tables taken up to Visit 3 (see definition above in section compliance at visit(i)).

If the date of last intake reported on the EOT form is > date of post-treatment biopsy then tables taken is equal to the number of tables taken up to Visit 3 (see definition above in section compliance at visit(i)) minus 3*(Date of last intake reported on the EOT form - date of post-treatment biopsy).

Tablets to be received up to the time of biopsy at week 24:

The total number of tablets to be received is equal to:

((Date of biopsy at week 24 – Study first treatment intake date + 1) *3)

- **Overall compliance at time of biopsy at week 24 (when biopsy results at week 24 are available) based on lanifibranor bottles**

The overall compliance based on lanifibranor bottles can be calculated as the actual number of lanifibranor tablets taken and the theoretical number of lanifibranor tablets to be received up to the time of biopsy at week 24:

Lanifibranor tablets taken:

The total number of lanifibranor tablets taken corresponds to the sum of the number of lanifibranor tablets taken in each bottle at each visit.

If the date of last intake reported on the EOT form is ≤ date of post-treatment biopsy then tables taken is equal to the number of tables taken up to Visit 3 (see definition above in section compliance at visit(i)).

If the date of last intake reported on the EOT form is > date of post-treatment biopsy then tables taken is equal to the number of tables taken up to Visit 3 (see definition above in section compliance at visit(i)) minus 3*(Date of last intake reported on the EOT form - date of post-treatment biopsy).

Lanifibranor tablets to be received up to the time of biopsy at week 24:

The total number of lanifibranor tablets to be received is equal to:

- ((Date of biopsy at week 24 – Study first treatment intake date + 1) *3) for patients receiving lanifibranor at the dose of 1200 mg
- ((Date of biopsy at week 24 – Study first treatment intake date + 1) *2) for patients receiving lanifibranor at the dose of 800 mg

4.5.6.2 Adverse Event data

- **Treatment Emergent Adverse Event**

A Treatment Emergent Adverse Event (TEAE) corresponds to an Adverse Event (AE) that occurred on or after first dose of treatment up to 28 days post-last dose.

- **Treatment Emergent Adverse Events related to study treatment**

TEAE related to treatment is defined as a TEAE having a relationship to treatment equals to "Possibly related", "Probably related" or with a missing relationship to study treatment.

Relationship equals to "Unlikely Related" will be considered as not related.

- **Non-Treatment Emergent Adverse Events (non-TEAEs)**

Non-TEAEs are AEs that occurred prior to treatment start.

- **Post-Treatment Adverse Events (PTAEs)**

PTAEs are AEs that occurred more than 28 days after end of treatment.

- **Serious Adverse Events**

By definition, a serious AE (SAE) is an AE that, at any time, fulfils one or more of the following criteria:

- results in death,
- is life threatening (the subject was at immediate risk of death at the time of the event; it does NOT refer to an event which hypothetically might have caused death if it were more severe),
- requires in-subject hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity (substantial disruption of a person's ability to carry out normal life functions),
- is a congenital anomaly/birth defect,
- is any important medical event that may not be immediately life threatening or result in death or hospitalisation but, based upon appropriate medical judgment, may endanger the subject or may require intervention.

The seriousness of the event will be directly assessed by the investigator (specific variable within the AE database); therefore no derivation is needed.

- **Onset day**

Onset day is defined as the time between the first treatment intake date and AE onset date: (AE onset date – date of first intake + 1).

4.5.6.3 Laboratory data

When result is '<x', value to be considered will be 'x-0.01'
When result is '>x', value to be considered will be 'x+0.01'

If after the following replacement a value become < 0 then value is forced to 0.

Baseline will be defined as the last available value before or the same day as first treatment intake.

Before first treatment intake, the last non-missing value before first intake will be selected.

After first treatment intake, in case of retest for a given parameter, the first non-missing value will be selected.

Regarding laboratory parameters that a sensitive to fasting status (Fasting Glucose, HOMA, insulin, C-peptid, Fructosamine, Triglycerides, Total cholesterol, HDL cholesterol, LDL cholesterol, Free fatty acids (FFA), Apoprotein A1, Apoprotein B, Apoprotein C3, Adiponectin, Leptin, FGF-21):

If the status is 'not fasting' and the value remains within laboratory ranges, then this value will be considered as 'fasting' for the analysis. This is applicable for the baseline value (See section 4.5.1) as well as all values collected over time.

4.5.6.4 Electrocardiogram data

In case of retest for a given parameter:

- Before first treatment intake, the last non-missing value will be selected
- After first treatment intake the first non-missing value during a visit will be selected

Available QTcF will be classified in 3 distinct categories:

- > 450 or ≤ 450 ms
- > 480 or ≤ 480 ms
- > 500 or ≤ 500 ms.

QTcF prolongation (Absolute change in QTcF from baseline) will be classified in 2 distinct categories:

- ≥ 60 ms and < 60 ms
- ≥ 30 ms and < 30 ms.

Available HR (Heart Rate) will be classified as:

- < 40 beats/min, ≥ 40 and ≤ 120 beats/min, >120 beats/min

Relative change in HR from baseline will be classified as:

- ≤ 25 % and >25%

4.5.6.5 Vital signs

In case of retest for a given parameter:

- Before first treatment intake, the last non-missing value will be selected
- After first treatment intake the first non-missing value during a visit will be selected

4.6 Modifications from the statistical section of the protocol

4.6.1 Terminology

In the protocol as well as in this SAP, the terminology 'modified ISHAK fibrosis' score is used, that was the terminology used at time of initial protocol development.
Since 2018, both terminologies 'modified ISHAK fibrosis' and 'EPOS' score (Elucidating Pathways of Steatohepatitis') are used for the same scoring system.
No change has been performed in the SAP, but this information is given as a note for the reviewer.

4.6.2 Analysis populations

The following adjustments in analysis populations are to be highlighted:

- Addition of the "screened patients" population to be able to describe the non-randomised patients and the corresponding reasons for non-randomisation
- The "Set of evaluable patient" is called "Evaluable patient population (EPP)" in the current SAP. The definition of this population has been detailed in order to avoid any confusion at time of analysis
- For the "Safety set of patients" the notion "and who have at least one post-baseline assessment of safety" has been suppressed as 'No adverse event' confirmed by the investigator in the AE form will be considered as a post-baseline assessment of safety.
- The following precision has been added for :
    - Randomized set of patients: in case of stratification error at randomization, strata assigned via the randomization will be taken into account for the analysis.
    - Full analysis set (FAS): in case of stratification error at randomization, actual strata will be taken into account for the analysis.

4.6.3 Endpoints

Some additional information have been added in the SAP in order to clearly explain which biopsies should be taken into account for efficacy analysis at week 24 (cases of biopsies with multiple reading, efficacy vs. safety biopsies, definition of available biopsies): see sections 4.5.4.1.1 to 4.5.4.1.3.

The following secondary endpoints have been added:

- NASH improvement (see section 4.5.4.1.7)
- Resolution of NASH and Improvement of liver fibrosis ≥ 1 stage (see section 4.5.4.1.10)
- Resolution of NASH without worsening of fibrosis and NASH improvement (see section 4.5.4.1.11)
- Improvement of ISHAK liver fibrosis ≥ 2 stages and no worsening of NASH (see section 4.5.4.1.12)
- Fibrosis markers: NAFLD Fibrosis Score (NFS), FIB-4 score, ELF Score, MACK-3 Score, FIBC3 Score and ABC3D Score (see section 4.5.4.2)
- No worsening of CRN-F score and modified Fibrosis Ishak score (modified ISHAK-F)

The analysis of the following parameters has been added too:

- Quality of Life: SF-36 and Flinders Fatigue scale (FFS)

- Pharmacokinetic data

4.6.4 Efficacy analysis

The analysis of dose response relationship has been added in the SAP for primary criterion (see section 5.2.2.4) as well as an analysis which explores the evaluation of treatment effect after adjustment on the relative change in weight from baseline (see section 5.2.2.4).

4.6.5 Subgroups analysis

Several subgroups analyses were added (see section 4.7).

4.6.6 Liver Iron Content

In section 6.3.5 Biobank Sample from the protocol, the liver iron content was expected to be collected. However, this parameter was not measured by central laboratory and therefore won't be analysed. The pathologist involved in the central reading of biopsies confirmed that iron overload intensity (collected in the biopsy form) can be used as a rough estimation for liver iron content.
The iron overload intensity will be analysed (see sections 5.1.7 and 5.5.1).

4.7 Analysis of sub-groups/complementary analysis

Subgroup analysis described thereafter, will not be performed if there are not enough patients (i.e. less than 15% in one category).

Main subgroups of interest are:

- Diabetic status at baseline (Yes, No)
- Biopsy length at baseline (≤ 8, >8 mm)
- NAS score at baseline (< 6, ≥ 6)
- SAF-A score at baseline (A2-A3, A4)
- CRN-F score at baseline (F0-F1, F2-F3)
- BMI at baseline (Obese, Non-obese)
- Metabolic syndrome at baseline (Yes, No)
- Insulin-resistance status at baseline (Yes, No)
- By site group No. 1 (Bulgaria, all other countries)
- By site group No. 2 (3 or less patients randomised and treated, from 4 to 9 patients randomised and treated, 10 or more patients randomised and treated)
- Sex (Male, Female)

5 Statistical analyses

5.1 Demographic data and other baseline characteristics

Descriptive analysis will be performed according to the methods detailed in section 4.1.4.

All analysis (except disposition by country) will be provided overall and then according to diabetic status at Baseline.

Analysis performed in the FAS will be repeated in the PP population if the difference between the 2 populations FAS and PP is ≥ 5%.

As the eCRF has changed during the conduct of the study, some sections/variables may not be applicable in some patients.

5.1.1 Patients disposition

The number (%) of patients included in each population will be described overall and then by country: screened patients, non-randomised patients, randomised patients, FAS, EPP, safety patients and PP patients. Percentages will be calculated over the number of randomised patients.

First Patient First Visit, Last Patient First Visit and Last Patient Last Visit will also be described overall and then by country. “First Visit” will be defined as the screening visit (V-1).

The reasons for non-randomisation will also be described among the non-randomised patients, consisting of screening failed patients.

In addition, in order to have an overview of patients’ disposition, the following elements will be described by treatment group and overall in the FAS for each post-randomisation visit:

- Number (%) of patients who performed the visit (Yes/No)
    - If Yes, Number (%) of patients still under treatment (Yes/No)
    - If No:
        - Number (%) of patients still ongoing (Yes/No)
        - Number (%) of patients still under treatment (Yes/No)

Due to the CRF design, Visit 3 was either completed per protocol and performed at week 24, or performed as part of early termination visit. For analysis, visit 3 will be splitted in 2:

- Visit 3 performed as part of early termination visit (i.e. premature EOT)
- Visit 3 performed as part of week 24 visit.

Same strategy will be applied for visit 4:

- Visit 4 performed after a visit 3 performed as part of early termination visit (i.e. follow-up visit following premature EOT)
- Visit 4 performed at week 28 after a visit 3 performed as part of week 24 (i.e. follow-up visit following treatment completed until week 24).

Additionally, for visit 4 performed after a visit 3 as part of week 24, it will be detailed whether visit 4 has been performed within 4 weeks +/- 2 weeks after visit 3 or not.

In order to have an overview of biopsies’ disposition, the following elements will be described at Visit 3 by treatment group and overall in the FAS

- Number (%) of biopsies available (Yes/No)

- If Yes, Number (%) of biopsies still under treatment (Yes/No), i.e. within maximum 14 days after last intake
- If No, Number (%) of biopsies non-available (non-readable, patient refusal, premature permanent treatment discontinuation)

Additionally, patients' treatment status (Treatment completed, Treatment prematurely withdrawn) at time of study end will be described in the FAS overall and by treatment group.

Last visit performed; as well as study duration (weeks) will also be described in the FAS overall and by treatment group.

In case of premature study treatment discontinuation (with or without follow-up visit(s) performed), reason for premature treatment discontinuation will be described: Adverse Event, Lost to follow-up, Treatment stopped upon sponsor request, Consent withdrawn, Withdrawal by patient + Adverse Event, other. Other reasons will also be summarized (Forbidden concomitant treatment, Patient was not available due to personal reasons, IMP issue the patient refused to received it, Withdrawal by patient).

Treatment duration (weeks) will also be described for all patients from the FAS.

5.1.2 Protocol deviations

All PDs for randomised patients will be presented by patient in data listings, with a distinction between PD leading to exclusion from the PP population ("major PD, meaning major impact on efficacy") and not leading to exclusion from the PP population ("minor PD, meaning no or minor impact on efficacy").

Number (%) of patients with at least one PD, with at least one major PD and with at least one minor PD will be summarized overall and by treatment group, and by type. A listing of all PDs recorded will also be provided. The total number of PDs and the total number of "major" and "minor" PDs will be presented in the BDRM document.

All PDs will be reviewed before DBL during the BDRMs.

5.1.3 Demographic characteristics

- Country,
- Sex (Male, Female),
- Age (years),
- Age in class (<65, ≥65 years old),
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other).

5.1.4 Alcohol consumption

- Alcohol consumption at screening (Yes, No)
    - If yes, drinks/day, by sex
- Alcohol consumption between screening and V0 (Yes, No)

- If yes, drinks/day, by sex

A footnote will be provided in the table defining the 'Alcohol consumption'.

5.1.5 Type 2 Diabetes status

- Type 2 diabetes status as reported in the randomisation tool (Yes, No)
- Actual type 2 diabetes status (Yes, No)

5.1.6 Metabolic syndrome

- Presence of metabolic syndrome at Baseline (Yes, No)
  A footnote will be provided in the table defining the 'Presence of metabolic syndrome'.
- Mean number of features involved in the metabolic syndrome definition at Baseline
- Number of features involved in the metabolic syndrome definition at Baseline (0, 1, 2, 3, 4, 5)
- Waist circumference ≥ 94 cm/37 inches in men, ≥ 80 cm/31.5 inches in females (Yes, No)
- Hypertension (Yes, No)
- Type 2 diabetes mellitus = Presence or **Fasting** glucose ≥ 100 mg/dl (5.6 mmol/L) if 'Type 2 diabetes mellitus'=Absence (Yes, No),
- Serum triglycerides > 150 mg/dL (i.e. 1.7 mmol/L) or hypertriglyceridemia / hyperlipidaemia / dyslipidaemia reported as medical history (Yes, No)
- HDL cholesterol < 40 mg/dL (i.e. 1.0 mmol/L) in men, < 50 mg/dL (i.e. 1.3 mmol/L) in females (Yes, No)
- Insulin-resistance status at Baseline (Yes, No)

5.1.7 Liver biopsy

- Timing of the biopsy (At Screening, Within the past 6 months)
- Time between screening biopsy and randomisation (months)
- CRN-S score (S0, S1, S2, S3)
- CRN-S (quantitative)
- CRN-I score (Grades 0, 1, 2)
- CRN-I (quantitative)
- CRN-B score (Grades 0, 1, 2)
- CRN-B (quantitative)
- CRN NAS score (from 0 to 8)
- CRN NAS score (quantitative)
- SAF-I score (Grades 0, 1, 2)
- SAF-I (quantitative)
- SAF-A score (A2, A3, A4)
- SAF-A score (A2-A3, A4)
- SAF-A (quantitative)
- CRN-F score (F0, F1, F2, F3)
- CRN-F score (F0-F1, F2-F3)
- CRN-F score (quantitative)

- Fibrosis Stage (modified Ishak) (Stages 0, 1, 2, 3, 4, 5, 6)
- Fibrosis Stage (modified Ishak) (quantitative)
- Biopsy length (mm)
- Biopsy length (≤ 8, >8 mm)
- Iron overload intensity (Absent, mild, moderate, severe)
- Iron overload location (None, Macrophages, Hepatocytes, Both)

5.1.8 Fibroscan

- Fibroscan performed
- Probe used (M, XL)
- Transient Elastrography (TE) / Stiffness (kPa)
- Controlled Attenuation Parameter (CAP) ($dB.m^{-1}$)

5.1.9 Anthropometric and vital signs

- Weight (kg),
- Height (cm),
- BMI (kg/m^2),
- BMI in class (Underweight, Normal, Overweight, Obese class I (moderate), Obese class II (severe), Obese class III (morbid))
- BMI in class (Non-obese, Obese)
- Waist circumference (cm) (overall and by sex)
- Systolic Blood Pressure (mmHg),
- Diastolic Blood Pressure (mmHg),
- Heart rate (bpm).

5.1.10 Medical/Surgical history

The number (%) of patients with at least one Medical History (MH) or Surgical History (SH) will be presented and corresponding MH/SH will be described by MedDRA System Organ Class (SOC) and Preferred Term (PT) in the FAS, in a decreasing frequency order. This will be done for all Medical History (MH) / Surgical History (SH); then it will be repeated on ongoing ones at baseline only.

5.1.11 Prior medications

The number (%) of patients with at least one prior medication will be presented and corresponding medications will be described by Medication Class (ATC2 levels) and Medication Name in the FAS.

5.1.12 Concomitant medications

The number (%) of patients with at least one concomitant medication will be presented and corresponding medications will be described by Medication Class (ATC2 levels) and Medication Name in the FAS.

The analysis will be done on all concomitant medications in a first time. Then it will be repeated on the following treatments of interest:

- Antidiabetic treatments administered, see section 4.5.3.
- Statin treatments administered, see section 4.5.3.

The number (%) of patients with at least one concomitant medication will be presented overall (all antidiabetic treatments) and for each antidiabetic treatment of interest and for each statin treatment.

5.1.13 Pregnancy test

- Pregnancy test performed (Yes, No)
- If test not performed
    - Reason (Post-menopausal, Other)
- If test performed
    - Test result (Negative, Positive)

5.1.14 Genotype

- Genotype performed (Yes, No)
- If genotype performed
    - PNPLA3 result
    - TM6FS2 result

5.2 Efficacy data

5.2.1 Summary of statistical methods

To summarize, following efficacy analyses will be provided:

- Primary endpoint:

Objectives/Endpoints	Type of analysis	Method of analysis	Population and imputation method
Response according to SAF activity score	Main analysis (Primary analysis of the primary endpoint)	Descriptive Treatment effect: CMH	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH	FAS – Observed Cases under treatment Randomised set – Primary imputation method PP – Observed cases under treatment EPP – Secondary imputation method FAS – Observed Cases
	Subgroups analysis(1)	Descriptive	FAS – Primary imputation method FAS – Observed Cases under treatment
	Secondary analyses	Dose response relationship Dose effect: CMH Site effect: CMH	FAS – Primary imputation method FAS – Observed Cases under treatment PP – Observed cases under treatment
		Treatment effect after adjustment on the relative change in weight from baseline: Logistic	FAS - Observed Cases under treatment

- Secondary endpoints:

Objectives/Endpoints	Type of analysis	Method of analysis	Population and imputation method
NASH improvers	Main analysis	Descriptive Treatment effect: CMH Dose effect: CMH Dose response relationship	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH Dose effect: CMH	FAS – Observed Cases under treatment PP – Observed Cases under treatment EPP – Secondary imputation method
		Dose response relationship	FAS – Observed Cases under treatment PP – Observed Cases under treatment
	Subgroups analysis(2)	Descriptive	FAS – Primary imputation method FAS – Observed Cases under treatment

Objectives/Endpoints	Type of analysis	Method of analysis	Population and imputation method
Resolution of NASH without worsening of fibrosis	Main analysis	Descriptive Treatment effect: CMH Dose effect: CMH Dose response relationship	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH Dose effect: CMH	FAS – Observed Cases under treatment PP – Observed Cases under treatment EPP – Secondary imputation method
		Dose response relationship	FAS – Observed Cases under treatment PP – Observed Cases under treatment
	Subgroups analysis(3)	Descriptive	FAS – Primary imputation method FAS – Observed Cases under treatment

Objectives/Endpoints	Type of analysis	Method of analysis	Population and imputation method
Improvement of fibrosis with no worsening of NASH	Main analysis	Descriptive Treatment effect: CMH Dose effect: CMH Dose response relationship	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH Dose effect: CMH	FAS – Observed Cases under treatment PP – Observed Cases under treatment EPP – Secondary imputation method
		Dose response relationship	FAS – Observed Cases under treatment PP – Observed Cases under treatment
	Subgroups analysis(3)	Descriptive	FAS – Primary imputation method FAS – Observed Cases under treatment

Objectives/Endpoints	Type of analysis	Method of analysis	Population and imputation method
Resolution of NASH and Improvement of fibrosis	Main analysis	Descriptive Treatment effect: CMH Dose effect: CMH Dose response relationship	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH Dose effect: CMH	FAS – Observed Cases under treatment PP – Observed Cases under treatment EPP – Secondary imputation method
		Dose response relationship	FAS – Observed Cases under treatment PP – Observed Cases under treatment
	Subgroups analysis(4)	Descriptive	FAS – Primary imputation method FAS – Observed Cases under treatment

Objectives/Endpoints	Type of analysis	Method of analysis	Population and imputation method
Resolution of NASH without worsening of fibrosis and decrease of 2 points of the NAS score	Main analysis	Descriptive Treatment effect: CMH Dose effect: CMH	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH Dose effect: CMH	FAS – Observed Cases under treatment PP – Observed Cases under treatment
Improvement of ISHAK fibrosis with no worsening of NASH	Main analysis	Descriptive Treatment effect: CMH Dose response relationship	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH	FAS – Observed Cases under treatment PP – Observed Cases under treatment
		Dose response relationship	FAS – Observed Cases under treatment PP – Observed Cases under treatment

Objectives/Endpoints	Type of analysis	Method of analysis	Population and imputation method
Improvement of CRN-S	Main analysis	Descriptive Treatment effect: CMH	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH	FAS – Observed Cases under treatment PP – Observed Cases under treatment
Improvement of CRN-I	Main analysis	Descriptive Treatment effect: CMH	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH	FAS – Observed Cases under treatment PP – Observed Cases under treatment
Improvement of CRN-B	Main analysis	Descriptive Treatment effect: CMH	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH	FAS – Observed Cases under treatment PP – Observed Cases under treatment
Change in CRN-S	Main analysis	Descriptive	FAS – Observed Cases under treatment
	Sensitivity analysis	Descriptive	PP – Observed Cases under treatment
Change in SAF-A	Main analysis	Descriptive	FAS – Observed Cases under treatment
	Sensitivity analysis	Descriptive	PP – Observed Cases under treatment
Change in CRN-I	Main analysis	Descriptive	FAS – Observed Cases under treatment
	Sensitivity analysis	Descriptive	PP – Observed Cases under treatment
Change in CRN-B	Main analysis	Descriptive	FAS – Observed Cases under treatment
	Sensitivity analysis	Descriptive	PP – Observed Cases under treatment

Objectives/Endpoints	Type of analysis	Method of analysis	Population and imputation method
Improvement/No worsening of CRN-F	Main analysis	Descriptive Treatment effect: CMH	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH	FAS – Observed Cases under treatment PP – Primary imputation method
	Subgroups analysis: CRN-F score at baseline (F0-F1, F2-F3)	Descriptive	FAS – Primary imputation method FAS – Observed Cases under treatment
Improvement/No worsening of modified-ISHAK-F	Main analysis	Descriptive Treatment effect: CMH	FAS – Primary imputation method
	Sensitivity analysis	Descriptive Treatment effect: CMH	FAS – Observed Cases under treatment PP – Primary imputation method
	Subgroups analysis: CRN-F score at baseline (F0-F1, F2-F3)	Descriptive	FAS – Primary imputation method FAS – Observed Cases under treatment
Change in CRN-F	Main analysis	Descriptive	FAS – Observed Cases under treatment
	Sensitivity analysis	Descriptive	PP – Observed Cases under treatment
	Subgroups analysis: CRN-F score at baseline (F0-F1, F2-F3)	Descriptive	FAS – Observed Cases under treatment
Change in modified-ISHAK-F	Main analysis	Descriptive	FAS – Observed Cases under treatment
	Sensitivity analysis	Descriptive	PP – Observed Cases under treatment

Objectives/Endpoints	Type of analysis	Method of analysis	Population and imputation method
Glucose metabolism (fasting glucose, insulin, HOMA index, C-peptid, HbA1c and fructosamide)	Main analysis	Descriptive Treatment effect: MMRM or ANCOVA Time course: MMRM *when possible*	FAS – Observed Cases under treatment (considering only fasting values, when specified)
	Subgroups analysis (diabetic status) (HbA1c at for HbA1c)	Descriptive	FAS – Observed Cases under treatment (considering only fasting values, when specified)
Liver enzymes (ALT, AST, GGT, Alkaline Phosphatase, Total Bilirubin)	Main analysis	Descriptive Treatment effect: MMRM Time course: MMRM	FAS – Observed Cases under treatment
	Subgroup analysis (diabetic status)	Descriptive	FAS – Observed Cases under treatment
Plasma lipids levels (TC, HDL-C, LDL-C, TG, apoA1, FFA, Adiponectin, Leptin, APO B, APO C3 and FGF21)	Main analysis	Descriptive Treatment effect: MMRM or ANCOVA *when specified* Time course: MMRM *when possible*	FAS – Observed Cases under treatment considering only fasting values
	Subgroup analysis ; - diabetic status - statins at Baseline	Descriptive	FAS – Observed Cases under treatment considering only fasting values
Efficacy inflammatory markers (fibrinogen, hs-CRP, alpha2 macroglobulin, haptoglobin, IL-13, IL-17a, , IL-6, IL-1b, TNF-a, INFg)	Main analysis	Descriptive Treatment effect: ANCOVA *when specified*	FAS – Observed Cases under treatment

Objectives/Endpoints	Type of analysis	Method of analysis	Population and imputation method
Efficacy fibrosis markers (TIMP-1, TIMP-2, Hyaluronic acid, P3NP, NFS, FIB-4 score, ELF score, MACK-3, FIBC3, ABC3D, Cytokeratin M30, Cytokeratin M65, Liver iron content, MMP2, MMP9, Pro-C3)	Main analysis	Descriptive Treatment effect: ANCOVA *when specified*	FAS – Observed Cases under treatment
	Exploratory analysis	Cross-tabulation with the CRN-F score (F0-F1, F2-F3) *when specified*	FAS – Observed Cases under treatment
Efficacy chemistry markers (Plasma Iron, Transferrin, Ferritin)	Main analysis	Descriptive	FAS – Observed Cases under treatment

Subgroups of interest are :

(1)

- Biopsy length (≤ 8, >8 mm)
- SAF-A at Baseline (A2-A3, A4)
- CRN-F at Baseline (F0-F1, F2-F3)
- NAS score at baseline (<6, ≥6)
- BMI at Baseline (Obese, Non-Obese)Metabolic syndrome at Baseline (Yes, No)
- Insulin-resistance status at Baseline (Yes, No)
- Sex (Male, Female)

(2)

- NAS score at baseline (<6, ≥6)

(3)

- Biopsy length (≤ 8, >8 mm)
- SAF-A at Baseline (A2-A3, A4)
- CRN-F at Baseline (F0-F1, F2-F3)
- NAS score at baseline (<6, ≥6)
- BMI at Baseline (Obese, Non-Obese)Metabolic syndrome at Baseline (Yes, No)
- Insulin-resistance status at Baseline (Yes, No)
- By site group No. 1 (Bulgaria, all other countries)
- By site group No. 2 (3 or less patients randomised and treated, from 4 to 9 patients randomised and treated, 10 or more patients randomised and treated)
- Sex (Male, Female)

(4)

- CRN-F at Baseline (F0-F1, F2-F3)
- NAS score at baseline (<6, ≥6)

5.2.2 Primary efficacy analysis

5.2.2.1 Primary analysis of the primary endpoint

The primary efficacy endpoint is a binary variable (Responder / Non-responder) based on the change from baseline to Week 24 of the A Score (see section 4.5.4.1.6).

The primary population of analysis will be the FAS as described in section 4.3.3. The primary imputation method described in section 4.1.6.3 will be used for missing data replacement.

Descriptive analysis

The number (% with its 95% confidence interval) of responders and non-responders at Week 24 will be summarized in a table using descriptive statistics by treatment group and diabetic status.
The reason for non-response (No decrease of 2 points of SAF-A score, Worsening of CRN-F score, Both, No post-treatment biopsy available) will also be displayed.

Evaluation of treatment effect (each dose versus placebo)

Each treatment dose will be compared to placebo using a CMH test stratified on the diabetic status.

In order to take into account multiplicity of tests, the ascending Hochberg procedure will be applied (see section 4.1.5 for details). The p-values of the 2 tests will be provided and will provide conclusions regarding the primary objective of the study met or not met.

Corresponding CMH Odds ratio (OR) and adjusted-Relative Risk (RR) will be provided with their 95% confidence intervals, in the FAS for the two lanifibranor groups.
The Breslow-Day test will be implemented for homogeneity of the odds ratios between diabetic and non-diabetic patients:

- If the test is significant, then this means that the treatment effect has not the same magnitude in diabetic and non-diabetic patients (significant difference in OR in the 2 populations)
- If the test is not significant, then this means that the treatment effect has the same magnitude in diabetic and non-diabetic patients (no significant difference in OR in the 2 populations).
- Regardless the significance of the test, both OR and RR in diabetic and non-diabetic patients will be provided with their 95% confidence interval

5.2.2.2 Sensitivity analyses

Several sensitivity analyses will be performed on the primary criterion as detailed in table below. Each time, descriptive analysis and evaluation of treatment effect (each dose versus placebo) will be performed as detailed in section 5.2.2.1.

To be confirmed. Indeed qualitative endpoint and not quantitative one => CMH and not MMRM ….

Analysis population	Treatment group	Missing data replacement
FAS	Actual treatment received	Observed cases under treatment*
Randomized set	Randomized treatment assigned	Primary imputation method
PP	Actual treatment received	Observed cases under treatment
EPP	Actual treatment received	Secondary imputation method
FAS	Actual treatment received	Observed cases

** This analysis corresponds to analyses on completers (biopsy at week 24 performed, within maximum 14 days after last intake).*

5.2.2.3 Analysis by subgroups

Descriptive analysis (number, % with its 95% confidence interval) will be performed in the FAS (primary imputation method) and among completers (Observed cases under treatment) as detailed in section 5.2.2.1 for the following subgroups of interest:

- Biopsy length at baseline (≤ 8, >8 mm)
- SAF-A score at baseline (A2-A3, A4)
- CRN-F score at baseline (F0-F1, F2-F3)
- NAS score at baseline (<6, ≥6)
- BMI at baseline (Obese, Non-obese)
- Metabolic syndrome at baseline (Yes, No)
- Insulin-resistance status at baseline (Yes, No)
- Sex (Male, Female)

5.2.2.4 Secondary analyses of the primary endpoint

Dose-response relationship

Moreover, the dose-response relationship will be assessed on the FAS (Primary imputation method and Observed cases under treatment), and on the PP (Observed cases under treatment) according to method detailed in section 4.1.5 (Cochran-Armitage test using PROC LOGISTIC with adjustment on diabetic status).

Evaluation of dose effect (1200 mg vs. 800 mg)

Lanifibranor 1200 mg will be compared to lanifibranor 800 mg using a CMH test stratified on the diabetic status. The same methodology as the one defined in the section 5.2.2.1 (paragraph 'Evaluation of treatment effect (each dose versus placebo)') will be implemented.

Generalizability of the treatment effect: Evaluation of any "site" effect

In order to explore any potential "site" effect on primary criterion, same analysis as those detailed in section 5.2.2.1 will be performed with a stratification on site (after regrouping as defined in section 4.1.7) instead of a stratification on diabetic status. Heterogeneity of results across sites will be tested through the Breslow-Day test (see section 4.1.7).

The two strategies of site regrouping will be used to explore this potential "site" effect as detailed in section 4.1.7.

The population of analysis will be the FAS as described in section 4.3.3. The primary imputation method described in section 4.1.6.3 will be used for missing data replacement.

In a first time, analysis will be done considering all patients. Then it will be repeated on diabetic patients and on non-diabetic patients.

Evaluation of treatment effect after adjustment on the relative change in weight from baseline

In order to evaluate the treatment effect after adjustment on the relative change in weight from baseline, a LOGISTIC model will be run on the FAS - Observed Cases under treatment. For this model, treatment will be considered as a quantitative covariate (placebo, 800 mg and 1200mg), diabetic status as a qualitative covariate (Presence, Absence) and weight variation as a quantitative effect. The p-value assessing the significant dose-response relationship at week 24 will be provided based on this model, as well as the OR for a change of 2% in weight.

5.2.3 Secondary analyses

5.2.3.1 NASH improvement

The endpoint will be a binary variable (Improver / Non-improver) based on the change from baseline to Week 24 of the CRN NAS score (see section 4.5.4.1.7).

Main analysis

The population of analysis will be the FAS as described in section 4.3.3. The primary imputation method described in section 4.1.6.3 will be used for missing data replacement.

- Descriptive analysis

The number (% with its 95% confidence interval) of improvers and non-improvers at Week 24 will be summarized in a table using descriptive statistics by treatment group and diabetic status. The reason for non-improvement (No decrease of 2 points of NAS score, Worsening of CRN-F score, Both, No post-treatment biopsy available) will also be displayed.

- Evaluation of treatment effect (each dose versus placebo)

The same methodology as the one defined in the section 5.2.2.1 (paragraph 'Evaluation of treatment effect (each dose versus placebo)') will be implemented.

- Evaluation of dose effect (1200 mg vs. 800 mg)

Lanifibranor 1200 mg will be compared to lanifibranor 800 mg using a CMH test stratified on the diabetic status. The same methodology as the one defined in the section 5.2.2.4 (paragraph 'Evaluation of dose effect (1200 mg vs. 800 mg)') will be implemented.

- Dose-response relationship

The dose-response relationship will be assessed on the FAS (Primary imputation method and Observed cases under treatment), and on the PP (Observed cases under treatment) according to method detailed in section 4.1.5 (Cochran-Armitage test using PROC LOGISTIC with adjustment on diabetic status).

Sensitivity analyses

Several sensitivity analyses will be performed as detailed in table below. Each time, descriptive analysis, evaluation of treatment effect (each dose versus placebo) and evaluation of dose effect will be performed as detailed above for main analysis.

Analysis population	Treatment group	Missing data replacement
FAS	Actual treatment received	Observed cases under treatment*
PP	Actual treatment received	Observed cases under treatment
EPP	Actual treatment received	Secondary imputation method

** This analysis corresponds to analyses on completers (biopsy at week 24 performed, within maximum 14 days after last intake).*

Analysis by subgroups

Descriptive analysis (number, % with its 95% confidence interval) will be performed in the FAS (primary imputation method) and among completers (Observed cases under treatment) as detailed in section 5.2.2.1 for the following subgroups of interest:

- NAS score at baseline (<6, ≥6)

5.2.3.2 Resolution of NASH without worsening of fibrosis

The endpoint will be a binary variable (responder / non responder) based on the CRN-I and CRN-B scores at Week 24 and the change in CRN-F score from Baseline to Week 24 (see section 4.5.4.1.8).

Main analysis

The population of analysis will be the FAS as described in section 4.3.3. The primary imputation method described in section 4.1.6.3 will be used for missing data replacement.

- Descriptive analysis

The number (% with its 95% confidence interval) of responders and non-responders at Week 24 will be summarized in a table using descriptive statistics by treatment group and diabetic status.
The reason for non-response (CRN-Inflammation > 1, ± CRN-Ballooning > 0, ± Worsening of CRN-F score, No post-treatment biopsy available) will also be displayed.

- Evaluation of treatment effect (each dose versus placebo)

The same methodology as the one defined in the section 5.2.2.1 (paragraph 'Evaluation of treatment effect (each dose versus placebo)') will be implemented.

- Evaluation of dose effect (1200 mg vs. 800 mg)

Lanifibranor 1200 mg will be compared to lanifibranor 800 mg using a CMH test stratified on the diabetic status. The same methodology as the one defined in the section 5.2.2.4 (paragraph 'Evaluation of dose effect (1200 mg vs. 800 mg)') will be implemented.

- Dose-response relationship

Moreover, the dose-response relationship will be assessed on the FAS (Primary imputation method and Observed cases under treatment), and on the PP (Observed cases under treatment) according to method detailed in section 4.1.5 (Cochran-Armitage test using PROC LOGISTIC with adjustment on diabetic status).

Sensitivity analyses

Several sensitivity analyses will be performed as detailed in table below. Each time, descriptive analysis, evaluation of treatment effect (each dose versus placebo), evaluation of dose effect (1200 mg vs. 800 mg) will be performed as detailed above for main analysis.

Analysis population	Treatment group	Missing data replacement
FAS	Actual treatment received	Observed cases under treatment*
PP	Actual treatment received	Observed cases under treatment
EPP	Actual treatment received	Secondary imputation method

** This analysis corresponds to analyses on completers (biopsy at week 24 performed, within maximum 14 days after last intake).*

Analysis by subgroups

Descriptive analysis (number, % with its 95% confidence interval) will be performed in the FAS (primary imputation method) and among completers (Observed cases under treatment) as detailed in section 5.2.2.1 for the following subgroups of interest:

- Biopsy length at baseline (≤ 8, >8 mm)
- SAF-A score at baseline (A2-A3, A4)
- CRN-F score at baseline (F0-F1, F2-F3)
- NAS score at baseline (<6, ≥6)
- BMI at baseline (Obese, Non-obese)
- Metabolic syndrome at baseline (Yes, No)
- Insulin-resistance status at baseline (Yes, No)
- By site group No. 1 (Bulgaria, all other countries)
- By site group No. 2 (3 or less patients randomised and treated, from 4 to 9 patients randomised and treated, 10 or more patients randomised and treated)
- Sex (Male, Female)

5.2.3.3 Improvement of fibrosis by at least 1 stage with no worsening of NASH

The endpoints will be a binary variable (responder / non responder) based on the change from baseline to Week 24 of the CRN-F score and the worsening of NASH (see section 4.5.4.1.9).

Main analysis

The population of analysis will be the FAS as described in section 4.3.3. The primary imputation method described in section 4.1.6.3 will be used for missing data replacement.

- Descriptive analysis

The number (% with its 95% confidence interval) of responders and non-responders at Week 24 will be summarized in a table using descriptive statistics by treatment group and diabetic status.

The reason for non-response (Worsening of CRN-S score, ± Worsening of CRN-I score, ± Worsening of CRN-B score, ± No improvement of CRN-F score, No post-treatment biopsy available) will also be displayed.

- Evaluation of treatment effect (each dose versus placebo)

The same methodology as the one defined in the section 5.2.2.1 (paragraph 'Evaluation of treatment effect (each dose versus placebo)') will be implemented.

- Evaluation of dose effect (1200 mg vs. 800 mg)

Lanifibranor 1200 mg will be compared to lanifibranor 800 mg using a CMH test stratified on the diabetic status. The same methodology as the one defined in the section 5.2.2.4 (paragraph 'Evaluation of dose effect (1200 mg vs. 800 mg)') will be implemented.

- Dose-response relationship

Moreover, the dose-response relationship will be assessed on the FAS (Primary imputation method and Observed cases under treatment), and on the PP (Observed cases under treatment) according to method detailed in section 4.1.5 (Cochran-Armitage test using PROC LOGISTIC with adjustment on diabetic status).

Sensitivity analyses

Several sensitivity analyses will be performed as detailed in table below. Each time, descriptive analysis, evaluation of treatment effect (each dose versus placebo), evaluation of dose effect (1200 mg vs. 800 mg) will be performed as detailed above for main analysis.

Analysis population	Treatment group	Missing data replacement
FAS	Actual treatment received	Observed cases under treatment*
PP	Actual treatment received	Observed cases under treatment
EPP	Actual treatment received	Secondary imputation method

** This analysis corresponds to analyses on completers (biopsy at week 24 performed, within maximum 14 days after last intake).*

Analysis by subgroups

Descriptive analysis (number, % with its 95% confidence interval) will be performed in the FAS (primary imputation method) and among completers (Observed cases under treatment) as detailed in section 5.2.2.1 for the following subgroups of interest:

- Biopsy length at baseline (≤ 8, >8 mm)
- SAF-A score at baseline (A2-A3, A4)
- CRN-F score at baseline (F0-F1, F2-F3)
- NAS score at baseline (<6, ≥6)
- BMI at baseline (Obese, Non-obese)
- Metabolic syndrome at baseline (Yes, No)
- Insulin-resistance status at baseline (Yes, No)
- By site group No. 1 (Bulgaria, all other countries)
- By site group No. 2 (3 or less patients randomised and treated, from 4 to 9 patients randomised and treated, 10 or more patients randomised and treated)
- Sex (Male, Female)

5.2.3.4 Resolution of NASH and Improvement of fibrosis by at least 1 stage

The endpoint will be a binary variable (responder / non responder) based on the CRN-I and CRN-B scores at Week 24 and the change in CRN-F score from Baseline to Week 24 (see section 4.5.4.1.10).

Main analysis

The population of analysis will be the FAS as described in section 4.3.3. The primary imputation method described in section 4.1.6.3 will be used for missing data replacement.

- Descriptive analysis

The number (% with its 95% confidence interval) of responders and non-responders at Week 24 will be summarized in a table using descriptive statistics by treatment group and diabetic status.
The reason for non-response (CRN-I score not equal to {0, 1}, ± CRN-B score not equal to 0, ± No improvement of CRN-F score, No post-treatment biopsy available) will also be displayed.

- Evaluation of treatment effect (each dose versus placebo)

The same methodology as the one defined in the section 5.2.2.1 (paragraph 'Evaluation of treatment effect (each dose versus placebo)') will be implemented.

- Evaluation of dose effect (1200 mg vs. 800 mg)

Lanifibranor 1200 mg will be compared to lanifibranor 800 mg using a CMH test stratified on the diabetic status. The same methodology as the one defined in the section 5.2.2.4 (paragraph 'Evaluation of dose effect (1200 mg vs. 800 mg)') will be implemented.

- Dose-response relationship

Moreover, the dose-response relationship will be assessed on the FAS (Primary imputation method and Observed cases under treatment), and on the PP (Observed cases under treatment) according to method detailed in section 4.1.5 (Cochran-Armitage test using PROC LOGISTIC with adjustment on diabetic status).

Sensitivity analyses

Several sensitivity analyses will be performed as detailed in table below. Each time, descriptive analysis, evaluation of treatment effect treatment effect (each dose versus placebo), evaluation of dose effect (1200 mg vs. 800 mg) will be performed as detailed above for main analysis.

Analysis population	Treatment group	Missing data replacement
FAS	Actual treatment received	Observed cases under treatment*
PP	Actual treatment received	Observed cases under treatment
EPP	Actual treatment received	Secondary imputation method

** This analysis corresponds to analyses on completers (biopsy at week 24 performed, within maximum 14 days after last intake).*

Analysis by subgroups

Descriptive analysis (number, % with its 95% confidence interval) will be performed in the FAS (primary imputation method) and among completers (Observed cases under treatment) as detailed in section 5.2.2.1 for the following subgroups of interest:

- CRN-F score at baseline (F0-F1, F2-F3)
- NAS score at baseline (<6, ≥6)

5.2.3.5 Resolution of NASH without worsening of fibrosis and NASH improvement

The endpoint will be a binary variable (responder / non responder) based on the CRN-I and CRN-B scores at Week 24, the change in CRN-F score and CRN NAS score from Baseline to Week 24 (see section 4.5.4.1.11).

Main analysis

The population of analysis will be the FAS as described in section 4.3.3. The primary imputation method described in section 4.1.6.3 will be used for missing data replacement.

- Descriptive analysis

The number (% with its 95% confidence interval) of responders and non-responders at Week 24 will be summarized in a table using descriptive statistics by treatment group and diabetic status.
The reason for non-response (CRN-I score not equal to {0, 1}, ± CRN-B score not equal to 0, ± Worsening of CRN-F score, ± No decrease of 2 points of NAS score, No post-treatment biopsy available) will also be displayed.

- Evaluation of treatment effect (each dose versus placebo)

The same methodology as the one defined in the section 5.2.2.1 (paragraph 'Evaluation of treatment effect (each dose versus placebo)') will be implemented.

- Evaluation of dose effect (1200 mg vs. 800 mg)

Lanifibranor 1200 mg will be compared to lanifibranor 800 mg using a CMH test stratified on the diabetic status. The same methodology as the one defined in the section 5.2.2.4 (paragraph 'Evaluation of dose effect (1200 mg vs. 800 mg)') will be implemented.

Sensitivity analyses

Several sensitivity analyses will be performed as detailed in table below. Each time, descriptive analysis, evaluation of treatment effect treatment effect (each dose versus placebo), evaluation of dose effect (1200 mg vs. 800 mg) will be performed as detailed above for main analysis.

Analysis population	Treatment group	Missing data replacement
FAS	Actual treatment received	Observed cases under treatment*

PP	Actual treatment received	Observed cases under treatment

** This analysis corresponds to analyses on completers (biopsy at week 24 performed, within maximum 14 days after last intake).*

Analysis by subgroups

None

5.2.3.6 Change in components Steatosis (CRN-S), Activity (SAF-A), Inflammation (CRN-I) and Ballooning (CRN-B)

5.2.3.6.1 Improvement

The endpoints are the following components: CRN-S, CRN-I and CRN-B scores. For each component, the following variable will be considered based on the change from baseline to Week 24:

- Improvement of at least 1 point change of the component (Yes, No)

Descriptive analysis

The population of analysis will be the FAS as described in section 4.3.3. The primary imputation method described in section 4.1.6.3 will be used for missing data replacement.

The number (% with its 95%CI) of improvement (Yes, No) at Week 24 will be summarized in a table using descriptive statistics by treatment group and diabetic status.

Evaluation of treatment effect (each dose versus placebo)

The same methodology as the one defined in the section 5.2.2.1 (paragraph 'Evaluation of treatment effect (each dose versus placebo)') will be implemented.

Sensitivity analyses

Several sensitivity analyses will be performed as detailed in table below. Each time, descriptive analysis will be performed as detailed above for main analysis.

Analysis population	Treatment group	Missing data replacement
FAS	Actual treatment received	Observed cases under treatment*
PP	Actual treatment received	Observed cases under treatment

** This analysis corresponds to analyses on completers (biopsy at week 24 performed, within maximum 14 days after last intake).*

5.2.3.6.2 Change in components

For each component (CRN-S, SAF-A, CRN-I and CRN-B scores), the following variables will be considered based on the change from baseline to Week 24 of:

- Absolute change of the component (quantitative variables)

- Change in the component (…Improvement of 2 points, Improvement of 1 point, No change, Worsening of 1 point, Worsening of 2 points…)
- Change in the component (Improvement of at least 1 point/No change/Worsening of at least 1 point)

Descriptive analysis

The population of analysis will be the FAS as described in section 4.3.3. Only the observed cases under treatment will be analysed (see section 4.1.6.3).

Endpoint will be summarized at Week 24 in a table using descriptive statistics by treatment group and diabetic status.

Sensitivity analysis

A single sensitivity analysis will be performed as detailed in table below. Each time, descriptive analysis will be performed as detailed above for main analysis.

Analysis population	Treatment group	Missing data replacement
PP	Actual treatment received	Observed cases under treatment

5.2.3.7 Change in component Fibrosis of CRN score and modified Fibrosis Ishak

5.2.3.7.1 Improvement or No worsening

The endpoints are the component CRN-F score and the modified Fibrosis Ishak score (modified ISHAK-F). For each score, the following variables will be considered based on the change from baseline to Week 24:

- Improvement of at least 1 point of the fibrosis score (Yes, No)
- No worsening of the fibrosis score (Yes, No)

Descriptive analysis

The population of analysis will be the FAS as described in section 4.3.3. The primary imputation method described in section 4.1.6.3 will be used for missing data replacement.

The number (% with its 95% CI) of improvement (Yes, No) and no worsening (Yes, No) at Week 24 will be summarized in a table using descriptive statistics by treatment group and diabetic status.

Evaluation of treatment effect (each dose versus placebo)

The same methodology as the one defined in the section 5.2.2.1 (paragraph 'Evaluation of treatment effect (each dose versus placebo)') will be implemented.

Sensitivity analyses

Several sensitivity analyses will be performed as detailed in table below. Each time, descriptive analysis will be performed as detailed above for main analysis.

Analysis population	Treatment group	Missing data replacement
FAS	Actual treatment received	Observed cases under treatment*
PP	Actual treatment received	Observed cases under treatment

** This analysis corresponds to analyses on completers (biopsy at week 24 performed, within maximum 14 days after last intake).*

Analysis by subgroups

Descriptive analysis will be performed in the FAS (primary imputation method) and among completers (Observed cases under treatment) for the following subgroups of interest:

- CRN-F score at baseline (F0-F1, F2-F3)

5.2.3.7.2 Change in component

For each fibrosis score (CRN-F and modified ISHAK-F scores), the following variables will be considered based on the change from baseline to Week 24 of:

- Absolute change of the score (quantitative variables)
- Change in the score (…Improvement of 2 points, Improvement of 1 point, No change, Worsening of 1 point, Worsening of 2 points…)
- Change in the score (Improvement of at least 1 point /No change/Worsening of at least 1 point)

Descriptive analysis

The population of analysis will be the FAS as described in section 4.3.3. Only the observed cases under treatment will be analysed (see section 4.1.6.3).

Endpoint will be summarized at Week 24 in a table using descriptive statistics by treatment group and diabetic status.

Sensitivity analysis

A single sensitivity analysis will be performed as detailed in table below. Each time, descriptive analysis will be performed as detailed above for main analysis.

Analysis population	Treatment group	Missing data replacement
PP	Actual treatment received	Observed cases under treatment

Analysis by subgroups

Descriptive analysis regarding CRN-F will be performed in the FAS (Observed cases under treatment) for the following subgroups of interest:

- CRN-F score at baseline (F0-F1, F2-F3)

5.2.3.8 Glucose metabolism

Main analysis

The population of analysis will be the FAS as described in section 4.3.3. Only the observed cases under treatment will be analysed (see section 4.1.6.3).

Only fasting results will be considered for fasting glucose, insulin, C-peptid and HOMA index. HbA1c and fructosamide results will be considered regardless of the fasting status.

- Descriptive analysis

Fasting glucose and HbA1c assessed at Screening, Baseline, Week 4, Week 14, Week 24 and Week 28, as well as insulin, C-peptid, fructosamide and HOMA index assessed at Week 0 and Week 24, will be described over time using descriptive statistics by treatment group and diabetic status, in terms of:

- Raw values
- Absolute change from baseline

The 95% CI of the mean will also be provided.

- Status over time (Normal-Normal, Normal-Abnormal, Abnormal-Normal, Abnormal-Abnormal)

The 2 timepoints prior to first intake will have to be analysed: screening and baseline.

One graph will also be provided describing the raw values (with 95% CI) by treatment group over time (including screening values)

The HOMA index will also be described qualitatively over time using descriptive statistics by treatment group and diabetic status (HOMA<3, ≥3).

- Absolute changes in HbA1c value will be described qualitatively over time using descriptive statistics by treatment group and diabetic status:
  - Decrease of HbA1c (Decrease of 1%, No change (Change within]-1% ; 1%[), Increase ≥ 1%).
  - Decrease of HbA1c (Decrease ≥ 0.5%, No change (Change within]-0.5% ; 0.5%[), Increase ≥ 0.5%)

- Evaluation of treatment effect (each dose versus placebo)

For fasting glucose, HbA1c, insulin and HOMA index, in order to evaluate each treatment dose versus placebo at week 24, a MMRM will be performed as detailed in section 4.1.5.
In order to take into account multiplicity of tests, the ascending Hochberg procedure will be applied (see section 4.1.5 for details).

- Time course of the response of each treatment group

For fasting glucose and HbA1c, in order to evaluate the time course of the response of each treatment group, a MMRM will be performed as detailed in section 4.1.5.
In order to take into account multiplicity of tests, the ascending Hochberg procedure will be applied at each time point (see section 4.1.5 for details).

Sensitivity analysis
None

Analysis by subgroups (descriptive analysis only)

- By diabetic status (Yes, No) for fasting glucose, insulin, C-peptid, HOMA index, fructosamide and HbA1c
- By HbA1c at baseline (<=6.5%, >6.5%) for HbA1c

5.2.3.9 Liver enzymes

The following table describes for each parameter the collection time and the type of analyses to be done.

Parameter	**Collection time**	**Main analyses (see section 5.2.3.8 describing the methodology)**	**Sensitivity analyses**	**Subgroup analyses**
ALT	Screening, Baseline, weeks 4, 14, 24 and 28	Descriptive analysis Treatment effect (each dose versus placebo) Time course of the response of each treatment group	None	By diabetic status (Yes, No)
AST	Screening, Baseline, weeks 4, 14, 24 and 28	Descriptive analysis Treatment effect (each dose versus placebo) Time course of the response of each treatment group	None	By diabetic status (Yes, No)
GGT	Screening, Baseline, weeks 4, 14, 24 and 28	Descriptive analysis Treatment effect (each dose versus placebo) Time course of the response of each treatment group	None	By diabetic status (Yes, No)
Alkaline Phosphatase	Screening, Baseline, weeks 4, 14, 24 and 28	Descriptive analysis	None	By diabetic status (Yes, No)
Total Bilirubin	Screening, Baseline, weeks 4, 14, 24 and 28	Descriptive analysis	None	By diabetic status (Yes, No)

5.2.3.10 Plasma lipids levels

The following table describes for each parameter the collection time and the type of analyses to be done.

Parameter	**Collection time**	**Main analyses (see section 5.2.3.8 describing the methodology)**	**Sensitivity analyses**	**Subgroup analyses**
Total Cholesterol	Screening, Baseline, weeks 4, 14, 24 and 28	Descriptive analysis Treatment effect (each dose versus placebo) Time course of the response of each treatment group	None	By diabetic status (Yes, No) By Statins at baseline (Yes, No)
HDL-C	Screening, Baseline, weeks 4, 14, 24 and 28	Descriptive analysis Treatment effect (each dose versus placebo) Time course of the response of each treatment group	None	By diabetic status (Yes, No) By Statins at baseline (Yes, No)
LDL-C	Screening, Baseline, weeks 4, 14, 24 and 28	Descriptive analysis Treatment effect (each dose versus placebo) Time course of the response of each treatment group	None	By diabetic status (Yes, No) By Statins at baseline (Yes, No)
Triglycerides	Screening, Baseline, weeks 4, 14, 24 and 28	Descriptive analysis Treatment effect (each dose versus placebo) Time course of the response of each treatment group	None	By diabetic status (Yes, No) By Statins at baseline (Yes, No)
Apo A1	Baseline, week 24	Descriptive analysis Treatment effect (each dose versus placebo)	None	By diabetic status (Yes, No) By Statins at baseline (Yes, No)
FFA	Baseline, week 24	Descriptive analysis	None	By diabetic status (Yes, No) By Statins at baseline (Yes, No)
Adiponectin	Baseline, week 24	Descriptive analysis Treatment effect (each dose versus placebo)	None	By diabetic status (Yes, No) By Statins at baseline (Yes, No)
Leptin	Baseline, week 24	Descriptive analysis	None	By diabetic status (Yes, No) By Statins at baseline (Yes, No)
APO B	Baseline, week 24	Descriptive analysis	None	By diabetic status (Yes, No) By Statins at baseline (Yes, No)

Parameter	**Collection time**	**Main analyses (see section 5.2.3.8 describing the methodology)**	**Sensitivity analyses**	**Subgroup analyses**
APO C3	Baseline, week 24	Descriptive analysis	None	By diabetic status (Yes, No) By Statins at baseline (Yes, No)
FGF21	Baseline, week 24	Descriptive analysis	None	By diabetic status (Yes, No) By Statins at baseline (Yes, No)

Only fasting results will be considered for analyses.
For adiponectin, folds being defined as the value at week 24 divided by baseline value will also be presented in the descriptive analysis.

5.2.3.11 Efficacy inflammatory markers

The following table describes for each parameter the collection time and the type of analyses to be done.

Parameter	**Collection time**	**Main analyses (see section 5.2.3.8 describing the methodology)**	**Sensitivity analyses**	**Subgroup analyses**
Fibrinogen	Baseline, week 24	Descriptive analysis Treatment effect (each dose versus placebo)	None	None
Hs-CRP	Baseline, week 24	Descriptive analysis Treatment effect (each dose versus placebo)	None	None
alpha2 macroglobulin	Baseline, week 24	Descriptive analysis	None	None
Haptoglobin	Baseline, week 24	Descriptive analysis	None	None
IL-13	Baseline, week 24	Descriptive analysis	None	None
IL-17a	Baseline, week 24	Descriptive analysis	None	None
IL-6	Baseline, week 24	Descriptive analysis	None	None
IL-1b	Baseline, week 24	Descriptive analysis	None	None
TNF-a	Baseline, week 24	Descriptive analysis	None	None
INFg	Baseline, week 24	Descriptive analysis	None	None

5.2.3.12 Efficacy fibrosis markers

The following table describes for each parameter the collection time and the type of analyses to be done.

Parameter	**Collection time**	**Main analyses (see section 5.2.3.8 describing the methodology)**	**Sensitivity analyses**	**Subgroup analyses**
TIMP-1	Baseline, week 24	Descriptive analysis	None	None
TIMP-2	Baseline, week 24	Descriptive analysis	None	None
Hyaluronic acid	Baseline, week 24	Descriptive analysis	None	None
P3NP	Baseline, week 24	Descriptive analysis	None	None
NFS	Baseline, week 24	Descriptive analysis Treatment effect (each dose versus placebo)	None	None
FIB-4 score	Baseline, week 24	Descriptive analysis Treatment effect (each dose versus placebo)	None	None
ELF score	Baseline, week 24	Descriptive analysis Treatment effect (each dose versus placebo)	None	None
MACK-3	Baseline, week 24	Descriptive analysis Treatment effect (each dose versus placebo)	None	None
FIBC3	Baseline, week 24	Descriptive analysis Treatment effect (each dose versus placebo)	None	None
ABC3D	Baseline, week 24	Descriptive analysis Treatment effect (each dose versus placebo)	None	None
Cytokeratin M30	Baseline, week 24	Descriptive analysis	None	None
Cytokeratin M65	Baseline, week 24	Descriptive analysis	None	None
MMP2	Baseline, week 24	Descriptive analysis	None	None
MMP9	Baseline, week 24	Descriptive analysis	None	None
Pro-C3	Baseline, week 24	Descriptive analysis Treatment effect (each dose versus placebo)	None	None

The following variables will also be described qualitatively over time using descriptive statistics by treatment group and diabetic status

- ELF score (No to mild fibrosis, moderate fibrosis, severe fibrosis, cirrhosis)
- NFS (Low probability of fibrosis F3-F4, Intermediate, High probability of fibrosis F3-F4)
- FIB-4 score (Low probability of fibrosis F3-F4, Intermediate, High probability of fibrosis F3-F4)
- MACK-3 score (No fibrosis, Fibrosis undefinable (grey zone), Fibrosis)

Moreover, as an exploratory analysis, the ELF score in class, the NFS in class and the FIB-4 score in class will be cross-tabulated with the CRN-F score (F0-F1, F2-F3): at baseline and then

at Week 24, regardless of treatment group. Similarly, the MACK-3 score in class will be cross-tabulated with the CRN-F score (F0, F1, F2, F3).

The ProC3, FIBC3 and ABC3D values will be described in each modality of the CRN-F score (F0-F1, F2-F3): at baseline and then at Week 24, regardless of treatment group.

5.2.3.13 Efficacy chemistry markers

The following table describes for each parameter the collection time and the type of analyses to be done.

Parameter	**Collection time**	**Main analyses (see section 5.2.3.8 describing the methodology)**	**Sensitivity analyses**	**Subgroup analyses**
Plasma Iron	Screening, week 24	Descriptive analysis	None	None
Transferrin	Screening, week 24	Descriptive analysis	None	None
Ferritin	Screening, week 24	Descriptive analysis	None	None

5.2.3.14 Improvement of ISHAK fibrosis by at least 2 stages with no worsening of NASH

The endpoints will be a binary variable (responder / non responder) based on the change from baseline to Week 24 of the ISHAK-F score and the worsening of NASH (see section 4.5.4.1.12).

Main analysis

The population of analysis will be the FAS as described in section 4.3.3. The primary imputation method described in section 4.1.6.3 will be used for missing data replacement.

- Descriptive analysis

The number (% with its 95% confidence interval) of responders and non-responders at Week 24 will be summarized in a table using descriptive statistics by treatment group and diabetic status.
The reason for non-response (Worsening of CRN-S score, ± Worsening of CRN-I score, ± Worsening of CRN-B score, ± No improvement of 2 stages in ISHAK-F score, No post-treatment biopsy available) will also be displayed.

- Evaluation of treatment effect (each dose versus placebo)

The same methodology as the one defined in the section 5.2.2.1 (paragraph 'Evaluation of treatment effect (each dose versus placebo)') will be implemented.

- Dose-response relationship

Moreover, the dose-response relationship will be assessed on the FAS (Primary imputation method and Observed cases under treatment), and on the PP (Observed cases under treatment) according to method detailed in section 4.1.5 (Cochran-Armitage test using PROC LOGISTIC with adjustment on diabetic status).

Sensitivity analyses

Several sensitivity analyses will be performed as detailed in table below. Each time, descriptive analysis, evaluation of treatment effect (each dose versus placebo) will be performed as detailed above for main analysis.

Analysis population	Treatment group	Missing data replacement
FAS	Actual treatment received	Observed cases under treatment*
PP	Actual treatment received	Observed cases under treatment

** This analysis corresponds to analyses on completers (biopsy at week 24 performed, within maximum 14 days after last intake).*

5.3 Safety data

5.3.1 Extent of exposure

The following parameters will be summarized in a table using descriptive statistics by treatment group in the safety set of patients:

- Treatment prematurely discontinued during study (Yes, No)
- Treatment duration (weeks)
- Overall persistence (%)
- Overall compliance at time of biopsy at week 24 (%)
- Overall compliance at time of biopsy at week 24 (%) based on lanifibranor bottles
- Compliance (%) at each visit

5.3.2 Display of adverse events

5.3.2.1 Overall summary of Treatment Emergent Adverse Events (TEAEs)

The following summary statistics will be given in the safety set of patients by treatment group (Lanifibranor 800mg, lanifibranor 1200mg, lanifibranor all, placebo):

- Number (%) of patients with at least one **TEAE**
- Number (%) of patients with at least one **TEAE related to treatment**
- Number (%) of patients with at least one **TESAE**
- Number (%) of patients with at least one **TESAE related to treatment**

- Number (%) of patients with a **fatal TESAE**
- Number (%) of patients with a **fatal TESAE related to treatment**

- Number (%) of patients with at least one **mild TEAE**
- Number (%) of patients with at least one **moderate TEAE**
- Number (%) of patients with at least one **severe TEAE**

- Number (%) of patients with at least one **severe TEAE related to treatment**
- Number (%) of patients with at least one **severe TESAE**
- Number (%) of patients with at least one **severe TESAE related to treatment**

- Number (%) of patients with at least one **TEAE leading to treatment permanent discontinuation**
- Number (%) of patients with at least one **TEAE leading to treatment permanent discontinuation related to treatment**

Corresponding number of events will also be provided for each type of AEs.

5.3.2.2 Overall Analysis of Treatment Emergent Adverse Events (TEAEs)

The number (%) of patients with at least one **TEAE** (and the corresponding number of events) will be described **by SOC and PT** by treatment group in the safety set of patients. In case a same patient presented the same AE (i.e. same AE as defined according to SOC and PT) several times during the study, only one occurrence per patient will be reported, but the total number of events will be given.

Same tables as this one will also be produced for:

- **TEAE related to treatment**
- **TESAE**
- **TESAE related to treatment**
- **Fatal TESAE**
- **Severe TEAE**
- **Severe TEAE related to treatment**
- **Severe TESAE**
- **Severe TESAE related to treatment**
- **TEAE leading to treatment permanent discontinuation**
- **TEAE leading to treatment permanent discontinuation related to treatment**

5.3.2.3 Analysis of Non-Treatment Emergent Adverse Events (non-TEAEs)

For Non-TEAEs, only a listing will be edited in the safety set of patients.

5.3.2.4 Analysis of Post-Treatment Adverse Events (PTAEs)

For PTEAEs, only a listing will be edited in the safety set of patients.

5.3.2.5 Analysis of Adverse Events in screen failure patients

A listing of all AEs experienced in screen failure patients will be edited.

5.3.3 Other safety analysis

5.3.3.1 Specific cardiac inflammatory safety: NT-pro-BNP

The population of analysis will be the Safety Set as described in section 4.3.3. Only the observed cases under treatment will be analysed (see section 4.1.6.3).

The NT-pro-BNP is collected at baseline and week 24. A listing of abnormal values at Baseline and/or Week 24 will be provided including absolute and relative changes from baseline.

5.3.3.2 Bone remodelling

The following table describes for each parameter the collection time and the type of analyses to be done.

Parameter	**Collection time**	**Main analyses (see section 5.2.3.8 describing the methodology)**	**Sensitivity analyses**	**Subgroup analyses**
B-Crosslaps	Baseline, week 24	Descriptive analysis	None	By gender
Osteocalcin	Baseline, week 24	Descriptive analysis	None	By gender

5.3.3.3 Laboratory tests for safety assessment

The following parameters will be considered for the analyses:

- Haematology
  - RBC count (10^12/L),
  - WBC count (10^9/L),
  - WBC differential: Neutrophil, Lymphocyte, Monocyte, Eosinophil, Basophil (10^9/L),
  - Reticulocytes (10^9/L),
  - Haemoglobin (g/L),
  - Haematocrit (L/L),
  - Platelet count (10^9/L),
  - Erythrocytes Mean Corpuscular Volume (MCV) (fL),
  - Mean Corpuscular Haemoglobin Concentration (MCHC) (g/L)
- Chemistry
  - Creatinine (µmol/L),
  - Urea (mmol urea/L),
  - Albumin (g/L),
  - Creatine PhosphoKinase (UI/L),
  - eGFR (mL/min/1.73m²)
- Liver/coagulation
  - INR

Main analysis

The population of analysis will be the Safety Set as described in section 4.3.4. Only the observed cases under treatment will be analysed (see section 4.1.6.3).

- Descriptive analysis

Each parameter will be described at each study visit using descriptive statistics by treatment group in the safety set of patients, in terms of:

- Raw values
- Absolute change from Baseline
- Status over time (Normal-Normal, Normal-Abnormal, Abnormal-Normal, Abnormal-Abnormal)

Then, for each parameter, will be provided a graph reporting the mean (95% CI) of the parameter by visit and treatment group.

Sensitivity analysis
None

Analysis by subgroups
None

5.3.3.4 Anthropometric and vital signs

The following vital signs parameters will be summarized in a table using descriptive statistics by treatment group at each study visit (from baseline to week 28) in the safety set of patients:

- Weight (kg),
- Systolic Blood Pressure (mmHg),
- Diastolic Blood Pressure (mmHg).

The corresponding relative changes from baseline will also be described by treatment group at each study visit.

Additionally, will be presented at each study visit the number (%) of patients presenting a relative change from baseline in weight (Decrease of ≥ 10%, Decrease from ≥ 5% to < 10%, No change (Change within]-5% ; 5%[), Increase from ≥ 5% to < 10%, Increase of ≥ 10%). A graph reporting the mean (95% CI) weight by visit and treatment group will be provided.

5.3.3.5 Electrocardiogram (ECG)

The following parameters will be considered for the analyses of ECG:

- Status over time (based on the conclusion of the central reader):
    - Normal or Abnormal NCS - Normal or Abnormal NCS
    - Normal or Abnormal NCS - Abnormal CS
    - Abnormal CS – Normal or Abnormal NCS
    - Abnormal CS - Abnormal CS
- QT duration corrected according to Fridericia formula (QTcF) (ms)
- QTcF > 450 ms (Yes, No)
- QTcF > 480 ms (Yes, No)
- QTcF > 500 ms (Yes, No)
- Absolute change from baseline in QTcF (ms)
- Absolute change from baseline ≥ 60 ms (Yes, No)
- Absolute change from baseline ≥ 30 ms (Yes, No)
- HR (beats/min)
- HR in categories (<40 beats/min, ≥40 and ≤ 120 beats/min, >120 beats/min)
- Relative change in HR from baseline (≤ 25 %, >25%)

Each parameter will be described at each study visit using descriptive statistics by treatment group overall and by gender in the safety set of patients.

Then, for QTcF and HR, will be provided a graph reporting the mean (+/- 95% CI) of the parameter by visit and treatment group.

A listing of abnormal CS interpretation at Baseline and/or over time will be provided.

5.4 Quality of Life

The endpoints will be the 10 sub-scores of the SF-36 and the global score of FFS (see sections 4.5.5.1 and 4.5.5.2).

Main analysis

The population of analysis will be the FAS as described in section 4.3.3. Only the observed cases under treatment will be analysed (see section 4.1.6.3).

- Descriptive analysis

Each score/sub-score will be described over time (Baseline and Week 24) using descriptive statistics by treatment group, in terms of:

- Raw values
- Absolute change from baseline

One graph will also be provided describing the raw values (with 95%CI) by treatment group over time.

5.5 Exploratory data

5.5.1 Liver biopsy

The following variables will be described by treatment and by diabetic status, for the biopsies at week 24:

- CRN-S score (S0, S1, S2, S3)
- CRN-S (quantitative)
- CRN-I score (Grades 0, 1, 2)
- CRN-I (quantitative)
- CRN-B score (Grades 0, 1, 2)
- CRN-B (quantitative)
- CRN NAS score (from 0 to 8)
- CRN NAS score (quantitative)
- SAF-I score (Grades 0, 1, 2)
- SAF-I (quantitative)
- SAF-A score (A2, A3, A4)
- SAF-A score (A2-A3, A4)
- SAF-A (quantitative)
- CRN-F score (F0, F1, F2, F3)
- CRN-F score (F0-F1, F2-F3)
- CRN-F score (quantitative)
- Fibrosis Stage (modified Ishak) (Stages 0, 1, 2, 3, 4, 5, 6)
- Fibrosis Stage (modified Ishak) (quantitative)
- Biopsy length (mm)
- Biopsy length (≤ 8, >8 mm)
- Iron overload intensity (Absent, mild, moderate, severe)
- Iron overload location (None, Macrophages, Hepatocytes, Both)

All other information collected in the biopsy form will be listed individually in Listings 16.2.

5.5.2 Fibroscan

The following variables will be described by treatment:

- TE / Stiffness (kPa)
- CAP ($dB.m^{-1}$)
- Probe used (M, XL)
- Probe used at Screening and Visit 3 (M-M, M-XL, XL-M, XL-XL)

If the same probes were used (ie M-M or XL-XL):

- Absolute change in TE / Stiffness (kPa)
- Absolute change in CAP ($dB.m^{-1}$)

All other information regarding the Fibroscan will be listed individually in Listings 16.2.

5.5.3 Alcohol consumption

The following parameters will be summarized in a table using descriptive statistics by treatment group at each study visit in the safety set of patients for males and then females:

- Alcohol consumption since last visit (Yes, No)
    - If consumption, drinks/day (quali)
- Drinks/day (quali) (this value will be defined as 0 for patient with no alcohol consumption)

5.5.4 Immunohistochemistry (semi-quantitative score of ballooning and stellate cell activation)

If deemed necessary at the time of the availability of the study results, complementary immunohistochemistry analyses could be performed within the year after the end of the study, and specific analyses analysis considered relevant in the scope of the study to understand the safety and efficacy of lanifibranor in patients with NASH could be performed. A separate dedicated SAP will cover this endpoint.

5.5.5 Pharmacokinetic data

The following variables will be summarized in a table using descriptive statistics by lanifibranor group at each study visit (Visit 1 and Visit 3) in the safety set of patients, overall, by gender (Male, Female), by BMI at baseline (Obese, Non-obese) and by age in class (<65, ≥65 years old):

- Trough values for lanifibranor and its 3 metabolites
- Metabolites ratio defined as the value of the metabolite/value of parent (Lanifibranor) for the 3 metabolites. If the value of parent is 0 or BLQ, then the ratio will be missing.

Four box plots for lanifibranor and its 3 metabolites displaying the trough values will be edited for each lanifibranor group overall.

Some values may be aberrant. In this purpose, only values collected before the treatment intake will be considered in the analyses. BLQ (Below Limit of Quantification) values will be considered as 0.

6 Tables, Listings and Graphs (TLG)

See appended document:
INVENTIVA_NATIVE_SAP_Mock_Up_TFLs_Version1.0_20200513.pdf

7 Template of tables, listings and graphs

See appended document:
INVENTIVA_NATIVE_SAP_Mock_Up_TFLs_Version1.0_20200513.pdf

8 Appendix 1 - Correspondence between patient number and country

Country number: first two digits of patient number	Country
00	Belgium
01	Italy
02	France
03	UK
04	Switzerland
05	Spain
06	Portugal
07	Poland
08	Germany
09	Czech Republic
10	Austria
11	Netherlands
12	Australia
13	Canada
14	Mauritius
15	Bulgaria
16	United States
17	Slovenia

9 Appendix 2 - Contents of statistical deliverables

See appended document: INVENTIVA_NATIVE_SAP_Mock_Up_TFLs

10 Appendix 3 – Strategy for analysis QC

See appended document: INVENTIVA_NATIVE_SAP_Mock_Up_TFLs

11 References

Reference 1

EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholoc fatty liver disease, Clinical Practice Guidelines, Journal of hepatology 2016 vol.64 1388-1402

Reference 2

P. Angulo, J.M. Hui, G. Marchesini, E. Bugianesi, J. George, G.C. Farrell, *et al.* The NAFLD fibrosis score: a non-invasive system that identifies liver fibrosis in patients with NAFLD. Hepatology, 45 (2007), pp. 846-854

Reference 3

Sterling, R. K., Lissen, E., Clumeck, N., Sola, R., Correa, M. C., Montaner, J., S. Sulkowski, M., Torriani, F. J., Dieterich, D. T., Thomas, D. L., Messinger, D. and Nelson, M. (2006), Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology, 43: 1317-1325.

Reference 4

Ralf Lichtinghagen, Daniel Pietsch, Heike Bantel, Michael P. Manns, Korbinian Brand, Matthias J. Bahr, The Enhanced Liver Fibrosis (ELF) score: Normal values, influence factors and proposed cut-off values, EASL European Association for the Study of the Liver, Journal of Hepatology

Reference 5

Hui Liu, Merck Research Labs, Merck & Co., Inc, Rahway, NJ, Cochran-Armitage Trend Test Using SAS

Reference 6

J. Boursier & all, Screening for therapeutic trials and treatment indication in clinical practice: MACK-3, a new blood test for the diagnosis of fibrotic NASH, Aliment Pharmacol Ther. 2018 May; 47(10):1387-139

Reference 7

Gradisar M, Lack L, Richards H, et al. The Flinders Fatigue Scale: preliminary psychometric properties and clinical sensitivity of a new scale for measuring daytime fatigue associated with insomnia. J Clin Sleep Med. 2007;3(7):722–728

Reference 8

Boyle M. and all, Performance of the PRO-C3 collagen neo-epitope biomarker in non-alcoholic fatty liver disease, JHEP Rep. 2019 Jul 4;1(3):188-198