



STUDY PROTOCOL

A placebo-controlled, proof-of-concept study to evaluate the safety and efficacy of Lanifibranor alone and in combination with the sodium-glucose transport protein 2 (SGLT2) inhibitor EmpaGliflozin in patiEnts with Non-alcoholic steatohepatitis (NASH) and type 2 Diabetes mellitus (T2DM)

Protocol identification: 337HNAS21016 (LEGEND)

EudraCT number: 2021-005057-87

Investigational medicinal products: IVA337 (lanifibranor), empagliflozin (Jardiance)

Development phase: 2a

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Version number: 6.0

Edition date: 22 Feb 2024

This study will be performed in compliance with the principles of Good Clinical Practice.

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INVESTIGATOR SIGNATURE PAGE

Study title: A placebo-controlled, proof-of-concept study to evaluate the safety and efficacy of lanifibranor alone and in combination with the sodium-glucose transport protein 2 (SGLT2) inhibitor empagliflozin in patients with non-alcoholic steatohepatitis (NASH) and type 2 diabetes mellitus (T2DM)

Study code: 337HNAS21016

I agree to conduct this study according to this protocol and any amendments and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

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Signature	Date

TABLE OF CONTENTS

SIGNATURE PAGE..... 2

INVESTIGATOR SIGNATURE PAGE..... 3

TABLE OF CONTENTS 4

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 8

1 **PROTOCOL SUMMARY 12**

1.1 **Synopsis..... 12**

1.2 **Study Design 25**

1.3 **Schedule of Activities (SoA) 26**

2 **INTRODUCTION..... 29**

2.1 **Study Rationale 29**

2.2 **Background..... 31**

2.2.1 Peroxisome Proliferator-Activated Receptor (PPAR) 32

2.2.2 Lanifibranor 32

2.2.3 Empagliflozin..... 34

2.3 **Risk/Benefit Assessment 35**

2.3.1 Known Potential Risks 35

2.3.2 Known Potential Benefits 36

2.3.3 Assessment of Potential Risks and Benefits 36

3 **OBJECTIVES AND ENDPOINTS 37**

3.1 **Primary, Secondary, and Exploratory Objectives(s), and Related Estimands 37**

3.1.1 Primary Objective 37

3.1.2 Secondary Objectives..... 37

3.2 **Primary, Secondary, Exploratory and Safety Endpoints..... 38**

3.2.1 Primary Efficacy Endpoint..... 38

3.2.2 Secondary Efficacy Endpoints 38

3.2.3 Safety Endpoints 38

4 **STUDY DESIGN..... 40**

4.1 **Overall Design 40**

4.2 **Scientific Rationale for Study Design..... 41**

4.3 **Justification for Dose 41**

4.4 **Data Monitoring Committee (DMC)..... 42**

4.5 **Study Procedures in Case of Crisis Situations 42**

4.6 **End of Treatment/Study Definitions 43**

5 **STUDY POPULATION 44**

5.1 **Inclusion Criteria 44**

5.2 **Exclusion Criteria 45**

5.3	Screen Failures	48
5.4	Strategies for Recruitment and Retention	48
6	INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)	50
6.1	Study Treatments	50
6.2	Study Drug Description	50
6.3	Description of IMPs	50
6.4	Dosing and Administration	51
6.5	Preparation/Handling/Storage/Accountability	52
6.5.1	Acquisition and Accountability	52
6.5.2	Formulation, Packaging and Labeling	52
6.5.3	Product Storage and Stability	54
6.6	Measures to Minimize Bias: Randomization and Blinding	54
6.7	Emergency Unblinding	55
6.8	Treatment Compliance	55
6.9	Overdose and Treatment	55
6.10	Concomitant Therapy	56
6.10.1	Allowable Medications for Standard Care or Precautions	56
6.10.2	Rescue Medication	56
6.10.3	Prohibited Medications	57
7	STUDY TREATMENT DISCONTINUATION AND PATIENT DISCONTINUATION/WITHDRAWAL	58
7.1	Study Withdrawal	58
7.2	Pregnancy	58
7.3	Temporary Interruption	59
7.4	Drug-Induced Liver Injury Monitoring and Stopping Rules	60
7.5	Overall Study Termination	61
8	STUDY ASSESSMENTS AND PROCEDURES	62
8.1	Efficacy Assessments	62
8.1.1	Clinical Laboratory Evaluations	62
8.1.3	Body Weight	63
8.1.4	Body Composition	63
8.2	Safety and Other Assessments	65
8.2.1	Safety Laboratory	66
8.2.2	SARS-CoV-2 Infection	67
8.2.3	Vital Signs	67
8.2.4	Physical Examination and Waist Circumference	67
8.2.5	Electrocardiogram	68
8.2.6	Dietary and Lifestyle Monitoring	68
8.2.7	Pharmacokinetic Evaluations	68
8.3	Adverse Events and Serious Adverse Events	69
8.3.1	Definitions of Adverse Event (AE)	69
8.3.2	Definition of Serious Adverse Event (SAE)	70
8.3.3	Suspected Unexpected Serious Adverse Reactions	71

8.3.4	Clinical Laboratory Abnormalities and Other Abnormal Assessments.....	71
8.3.5	Adverse Events of Special Interest (AESI).....	71
8.3.6	Classification of Adverse Events	72
8.4	Documenting and Reporting Adverse Events	74
8.4.1	Time Period and Frequency for Event Assessment and Follow-Up.....	74
8.4.2	Adverse Event Reporting	74
8.4.3	Serious Adverse Event Reporting	75
8.5	Reporting of Pregnancies	75
8.6	Safety Reporting Oversight.....	75
9	STATISTICAL CONSIDERATIONS	77
9.1	Statistical Hypotheses	77
9.2	Sample Size Determination	77
9.3	Populations for Analyses	78
9.4	Statistical Analysis	79
9.4.1	General Approach	79
9.4.2	Analysis of the Primary Efficacy Endpoint	80
9.4.4	Safety Analyses.....	87
9.4.5	Baseline Descriptive Statistics	88
9.4.6	Planned Interim Analyses	88
9.4.7	Subgroup Analyses	89
10	REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS	90
10.1	Informed Consent Process.....	90
10.2	Confidentiality and Privacy	91
10.3	Indemnity/Insurance.....	91
10.4	Central and Local Laboratory Use.....	91
10.5	Clinical Monitoring and Audits.....	91
10.6	Quality Assurance and Quality Control	91
10.7	Data Handling and Record Keeping	92
10.8	Protocol Deviations	92
10.9	Publication and Data Sharing Policy	93
10.10	Conflict of Interest Policy.....	93
11	PROTOCOL AMENDMENT HISTORY	94
12	REFERENCES.....	100
13	APPENDICES	105
13.1	Appendix A: Alcohol Comparison Table.....	105
13.2	Appendix B: Permitted and Prohibited Concomitant Medications	106
13.3	Appendix C: Guideline for Adverse Events requiring specific management	109

LIST OF TABLES

Table 1: Characterization of lanifibranor tablets 50

Table 2: Characterization of placebo.....51

Table 3: Characterization of empagliflozin tablets 51

Table 4: List of clinical laboratory parameters.....66

Table 5: Power depending on expected effect sizes 78

Table 6: Definition of on study and on-treatment observations periods 79

Table 7: Approach for the primary endpoints, intercurrent events and estimands.....81

LIST OF FIGURES

Figure 1: Study design.....25

Figure 2: Drug supply kit of lanifibranor or matching placebo.....53

Figure 3: Drug supply kit of lanifibranor and empagliflozin 53

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AMA	Anti-mitochondrial antibodies
ANA	Anti-nuclear antibodies
ANCOVA	Analysis of covariance
ASMA	Anti-smooth muscle antibodies
AST	Aspartate aminotransferase
BMI	Body mass index
BNP	Brain Natriuretic Peptide
CAP	Controlled attenuation parameter
CDMO	Contract distributing and manufacturing organisation
CFR	Code of Federal Regulations
CMH	Cochran–Mantel–Haenszel
CMV	Cytomegalovirus
CONSORT	Consolidated standards of reporting trials
CRF	Case report form
CRO	Contract research organization
CSR	Clinical study report
cT1	Corrected T1 relaxation time
CV	Cardiovascular
DBP	Diastolic blood pressure
DPP	Dipeptidyl peptidase
DILI	Drug-induced liver injury
DM	Diabetes mellitus
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ELF	Enhanced liver fibrosis
EMA	European Medicines Agency
EoS	End of study
EoT	End of treatment
FAS	Full analysis set
FAST	Fibroscan-AST score

FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GLP1-RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycated hemoglobin
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HOMA-IR	Homeostatic model assessment for insulin resistance
hsCRP	High-sensitive C-reactive protein
IA	Interim analysis
IAS	Interim analysis set
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDEAL	Iterative decomposition of water and fat with echo asymmetry and least squares estimation
IEC	Independent ethics committee
IgG	Immunoglobulin G
IL	Interleukin
IMP	Investigational medicinal product
INR	International normalized ratio
IR	Insulin resistance
IRB	Institutional Review Board
IU	International unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWRS	Interactive web response system
LC1	Anti-liver cytosol type 1
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDPE	Low-density polyethylene
LKM1	Anti-liver kidney microsomal type 1
LLN	Lower limit of normal range
LS	Least squares
LSM	Liver stiffness measurement

MACE	Major adverse cardiovascular events
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MOLLI	Modified look locker inversion recovery
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging proton density fat fraction
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Non-alcoholic steatohepatitis
NIT	Non-invasive test
NT-pro-BNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
P3NP	Procollagen type III N-terminal peptide
Pan-PPAR	pan-peroxisome proliferator-activated receptor
PCR	Polymerase chain reaction
PI	Principal investigator
PK	Pharmacokinetics
popPK	Population pharmacokinetics
PPAR	Peroxisome proliferator-activated receptor
PPS	Per protocol set
PTEAE	Post-treatment-emergent AEs
QD	Quaque die, once a day
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Steatosis-activity-fibrosis
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SARS-Cov2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety analysis set
SAT	Subcutaneous adipose tissue
SBP	Systolic blood pressure
SGLT2	Sodium-glucose co-transporter-2
SoA	Schedule of activities
SUSAR	Suspected unexpected serious adverse reactions
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent AE
TG	Triglycerides
TIMP-1	Tissue inhibitor of metalloproteinase 1
TPO	Anti-thyroid peroxidase antibody
TRAb	Anti-TSH receptor antibodies

TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
VAT	Visceral adipose tissue
VLDL	Very-low-density-lipoprotein
WBC	White blood cell count

1 **PROTOCOL SUMMARY**

1.1 **Synopsis**

Title	A placebo-controlled, proof-of-concept study to evaluate the safety and efficacy of lanifibranor alone and in combination with the sodium-glucose transport protein 2 (SGLT2) inhibitor empagliflozin in patients with non-alcoholic steatohepatitis (NASH) and type 2 diabetes mellitus (T2DM)
Short title	LEGEND (Protocol Number: 337HNAS21016)
Study site(s)	Approximately 30 sites across Europe and the United States of America (USA)
Study rationale	Therapeutic compounds that address the upstream metabolic and immune mediated pathways of NASH are also expected to be beneficial for T2DM. There is a clear rationale to assess combination therapy with drugs that have a complementary mechanism of action in the complex disease pathophysiology of patients with NASH who also have T2DM. SGLT2 inhibitors are approved for the treatment of T2DM. They have a beneficial effect on glucose metabolism, glycated hemoglobin (HbA1c), insulin resistance, inflammation through their inhibition of renal glucose reabsorption, and other pleiotropic metabolic effects, including weight loss. Lanifibranor, a pan-peroxisome proliferator-activated receptor (pan-PPAR) agonist, has beneficial effects on lipid and glucose metabolism, insulin resistance, as well as on steatohepatitis (hepatic injury and inflammation) and fibrosis as shown in the NATIVE Phase 2b study (NCT03008070). In this study in NASH patients, a sub-analysis on those patients with T2DM at baseline (i.e., with high baseline HbA1c > 6.5%), demonstrated significant improvements in glycemic control, with a substantial decrease in HbA1c under treatment with lanifibranor. The present LEGEND study is intended to confirm these preliminary findings. Further, it is expected that the therapeutic effect on the above-mentioned variables may increase when lanifibranor is combined with an SGLT2 inhibitor. In addition, the combination of lanifibranor with an SGLT2 inhibitor may improve tolerability of the PPAR agonist. While lanifibranor has an overall favorable safety profile, weight gain, peripheral edema and anemia have been observed in Phase 2 studies, mainly in female patients. Although weight gain with PPAR agonist therapy is considered to be metabolically healthy based on redistribution of visceral and subcutaneous fat, it may still be an undesirable effect. SGLT2 inhibitors induce weight loss and have a diuretic effect. They have also been shown to increase hematopoiesis. The proposed LEGEND study in the T2DM population is intended to: • Confirm as primary objective the lanifibranor effect versus placebo on glycemic control observed in the NATIVE Phase 2b study (NCT03008070) • Confirm a positive effect of the combination of lanifibranor with an SGLT2 inhibitor on glycemic control (i.e., conservation of the effect when associated with an SGLT2 inhibitor, no

Study endpoints	Primary efficacy endpoint • Absolute change in HbA1c from baseline (Week 0) to Week 24 Secondary efficacy endpoints The following endpoints will be evaluated at Week 24: • Change from baseline to Week 24 in liver tests (alanine aminotransferase [ALT], AST, gamma-glutamyl transferase (GGT), alkaline phosphatase [ALP], total and direct bilirubin) • Change from baseline to Week 24 in markers of glycemic control and insulin resistance (determination of hepatic insulin sensitivity, Homeostatic Model Assessment for insulin resistance [HOMA-IR], fasting insulin, fasting plasma glucose [FPG], fructosamine, adiponectin) • Binary endpoint defined as reaching HbA1c < 7.0% at Week 24, and no new antidiabetic treatment or increase in dosages of antidiabetic treatments • Binary endpoint defined as reaching HbA1c decrease $\geq 0.5\%$ at Week 24, and no new antidiabetic treatment or increase in dosages of antidiabetic treatments • Change from baseline to Week 24 in inflammatory markers (high-sensitivity C-reactive protein [hsCRP], Interleukin IL-6, Interleukin IL-1β) • Change from baseline to Week 24 in lipid parameters (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides [TG]) • Change from baseline to Week 24 in body weight • Binary endpoint defined as reaching body weight increase $\geq 5\%$ at Week 24 • Change from baseline to Week 24 in body composition as determined by MRI (including but not limited to: visceral adipose tissue [VAT], subcutaneous adipose tissue [SAT] and thigh SAT) Safety endpoints • Adverse events (AEs) • Adverse Events of Special Interest (AESIs): anemia, heart failure, aminotransferase elevation, bone fracture, peripheral edema, cholelithiasis, hypoglycemia and ovulation resumption • Serious adverse events (SAEs) including major adverse cardiovascular events (MACE) (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, hospitalization for acute coronary syndrome) • Physical examination • Vital signs (systolic and diastolic blood pressure [SBP, DBP], waist circumference) • Electrocardiogram (ECG) • Safety laboratory evaluations including N-terminal prohormone B-type natriuretic peptide (NT-pro-BNP)
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Study description	This proof-of-concept study will assess the safety and efficacy of the pan-PPAR agonist lanifibranor alone and in combination with the SGLT2 inhibitor empagliflozin in patients diagnosed with NASH and T2DM. The study is designed as a multinational, multicenter, three-arm, randomized, double-blind for lanifibranor and placebo, open-label for the combination lanifibranor plus empagliflozin, placebo-controlled, 24-week treatment study followed by a 4-week post-treatment follow-up visit. A total of 63 patients are planned to be randomized 1:1:1 to receive lanifibranor alone, or lanifibranor plus empagliflozin, or placebo. An interim analysis (IA) will be conducted once approximately half of the planned patients will be randomized, and have either completed the 24-week treatment period or prematurely discontinued from treatment earlier, that will constitute the Interim Analysis Set (IAS). At this time, all protocol-defined analyses will be performed. A data integrity plan will be developed detailing, among the patients not belonging to the IAS, how the blinding is maintained, how integrity of the trial will be

	protected and to ensure continued adherence to treatment and trial retention. The objective of this interim analysis will be: • To obtain preliminary information on observed effects sizes / variability allowing an early insight on the treatment effect on multiple mechanistic endpoints, helping supporting future decision making, both for the LEGEND study and in the overall lanifibranor clinical program • To stop recruitment should clear trends in study findings be observed thereby minimizing patient exposure with additional patients • To evaluate early signs on the impact on mechanistic endpoints, to determine whether to continue to perform more complex evaluations on study participants and to aid future decisions Recruitment will be paused once the first half of the planned patients are randomized. As this is a multicentre trial, some additional patients may have been randomized, and will continue to be followed in the study.
Study population	Adult patients diagnosed with non-cirrhotic NASH and T2DM, with at least 40% being male and at least 40% being female, in order to ensure there is a representative NASH population, as NASH prevalence is broadly comparable between males and females. [REDACTED] [REDACTED] Exclusion of cirrhosis at Screening will be based on histology or Non-Invasive Tests (NITs).
Eligibility criteria	Inclusion criteria For an eligible patient, all inclusion criteria must be answered “yes” at Screening and re-confirmed at the time of randomization procedure and at Baseline (i.e., before treatment initiation). Laboratory tests taken during the screening period will be used to determine eligibility. If information cannot be confirmed in the medical record, responses will be obtained in a patient interview: 1. Able to understand the nature of the study, willing and able to comply with the study procedures and restrictions, and willing to provide informed consent obtained before any study-related activities 2. The patient is willing to continue on the study in case of moving or relocating to a different region/city where there would be no active study site 3. Able to communicate meaningfully with the Investigator and legally competent to provide written informed consent 4. Male or female, aged ≥ 18 years at the time of signing informed consent 5. Diagnosis of NASH a. based on a historical (within 12 months prior to Screening) liver biopsy with a non-alcoholic fatty liver disease activity score (NAS) ≥ 4 with a score of one or more in each sub-component (steatosis, hepatocyte ballooning, lobular inflammation) and no documented cirrhosis in the last 12 months prior to Screening OR

	b. NASH at Screening: i. High Risk NASH defined as $cT1 \geq 875$ ms assessed by LiverMultiScan® OR ii. NASH defined as $cT1 \geq 825$ ms assessed by LiverMultiScan® and hepatic fat content $\geq 10\%$ assessed by MRI-PDFF 6. HbA1c at screening ≥ 7.0 and $\leq 10.0\%$, on diet alone, or on metformin ($\geq 1,000$ mg/day), and/or dipeptidyl peptidase 4 inhibitor (DPP-IVi) therapy. Doses have no qualitative change for 3 months prior to informed consent. These medicines will be continued at stable doses during the entire study. 7. Negative pregnancy test at Screening for females of childbearing potential or at least two-year post-menopausal. Women of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) have to use a highly effective method of contraception throughout the study and for one month after treatment discontinuation. Highly effective contraceptive methods are defined as follows: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (provided he is her sole sexual partner and he has received medical assessment of the surgical success), and true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient) whereas periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Exclusion criteria For an eligible patient, all the following exclusion criteria must be answered “no” at Screening and re-confirmed at time of randomization procedure and at Baseline (i.e., before treatment initiation), except for laboratory tests for which Screening results are used for randomization: <u>Liver-related:</u> 1. Documented causes of chronic liver disease other than NASH including, but not restricted to: a. Viral hepatitis, documented with i. Positive hepatitis B surface antigen (HBsAg) ii. Positive hepatitis C virus ribonucleic acid (RNA) (tested for in case of known cured hepatitis C virus [HCV] infection or positive HCV serology at Screening). Patients with a history of HCV infection can be included if HCV PCR is negative since more than 3 years. b. Drug-induced liver disease c. Autoimmune hepatitis (See Exclusion criterion 50 for more information) d. Wilson’s disease e. Hemochromatosis f. Primary biliary cholangitis
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	g. Primary sclerosing cholangitis h. α1-antitrypsin deficiency 2. Histologically documented liver cirrhosis (fibrosis stage F4), based on a historical biopsy (within 12 months prior to Screening); or diagnosis of cirrhosis at Screening based on clinic biochemical and imaging criteria (FibroScan® value confirmed ≥ 14 kPa and FIB-4 > 3.25 provided to the site by the central lab) 3. History or current diagnosis of hepatocellular carcinoma (HCC) 4. History of or planned liver transplant 5. Documented history of human immunodeficiency virus (HIV) infection 6. ALT or AST $> 5 \times$ upper limit of normal (ULN) at Screening 7. Abnormal liver function as defined by central laboratory evaluation of any of the following: - Albumin $<$ lower limit of normal range (LLN) - International normalized ratio (INR) ≥ 1.3 (unless patient is on anticoagulants) - Total bilirubin level ≥ 1.5 mg/dL (25.7 μmol/L) (Patients with a documented history of Gilbert's syndrome can be enrolled if direct bilirubin is ≤ 0.45 mg/dL (7.7 μmol/L)) 8. Hemoglobin < 110 g/L (11 g/dL) for females and < 120 g/L (12 g/dL) for males 9. White blood cell count (WBC) $<$ LLN. A lower count is acceptable in patients with benign ethnic neutropenia, if considered to be clinical insignificant by the investigator 10. Platelet count $< 140,000/\mu$L 11. Alkaline phosphatase (ALP) $> 2 \times$ ULN 12. Patient currently receiving any approved treatment for NASH or obesity 13. Current or recent history (< 5 years) of significant alcohol consumption, which is typically defined as higher than 30 g pure alcohol per day for men and as higher than 20 g pure alcohol per day for women (please also refer to Section 13.1). No binge drinking during the last year. Consuming 75 g pure alcohol (male), or 60 g pure alcohol (female), or more in about 2 hours 14. Administration of drugs known to produce hepatic steatosis in the 6 months prior to Screening (such as high-dose estrogens, methotrexate, tetracycline, or amiodarone) (see also Section 13.2) <u>Diabetes related:</u> 15. Diabetes mellitus other than type 2 (e.g., type 1, endocrinopathy, and genetic syndromes) 16. Diabetic ketoacidosis at Screening 17. Current treatment with glucagon-like peptide-1 receptor agonists (GLP-1RA), insulin or sulfonylurea or treatment within the last 3 months prior to Screening 18. Patients on pioglitazone in the last 12 months prior to Screening 19. Patients on any of the following medications unless the patient had no qualitative change in doses of such agents for the past 3 months before Screening: metformin, DPP-IVi, thiazide or furosemide diuretics, beta-blockers, or other chronic medications with known adverse effects on glucose tolerance levels. Patients may be taking
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	stable doses with no qualitative change of estrogens or other hormonal replacement therapy if the patient has been on these agents for the prior 3 months. Patients taking systemic glucocorticoids will be excluded. <u>Obesity related:</u> 20. Body mass index (BMI) > 45 kg/m² at Screening 21. Weight change > 5% in the 3 months prior to Screening 22. Introduction of an anti-obesity drug or restrictive bariatric surgery in the past 12 months prior to Screening or planned bariatric surgery through Week 24 23. Participation in an organized weight loss program (e.g., Weight Watchers[®], Jenny Craig[®]) in the past 6 months prior to Screening or planned participation through Week 24 <u>Cardiovascular related:</u> 24. History of (within 3 months prior to Screening) or current unstable cardiac dysrhythmias 25. NT-proBNP > 900 pg/mL 26. Unstable heart failure including: a. New, or worsening symptoms of coronary heart disease within the past 3 months prior to Screening b. Acute coronary syndrome within the past 6 months prior to Screening c. Acute myocardial infarction in the past 3 months prior to Screening d. Heart failure of New York Heart Association class (III-IV) or worsening congestive heart failure, or coronary artery intervention, within the past 6 months prior to Screening 27. Any other clinically significant cardiovascular event requiring hospitalization within 6 months before Screening 28. Uncontrolled hypertension at Screening (systolic blood pressure [SBP] > 160 mmHg and/or diastolic blood pressure [DBP] > 100 mmHg (under conditions described in Section 8.2.3.) 29. Stroke or transient ischemic attack within 6 months prior to Screening <u>General safety:</u> 30. Significant systemic or major illnesses other than liver disease, (including but not limited to those listed above) and pulmonary disease, organ transplantation, serious psychiatric disease, that, in the opinion of the Investigator, would preclude treatment with lanifibranor and/or empagliflozin and/or adequate follow-up 31. Any condition which, in the Investigator's opinion, might jeopardize a patient's safety or compliance with the protocol, or warrants exclusion from the study 32. Cancer: Presence or history of malignancy within 5 years prior to Screening and/or active neoplasm at Screening. History of cancer is
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	allowed only following 5 years of documented remission with the exception of resolved superficial non melanoma skin cancer 33. History of bladder disease and/or persistent hematuria within 6 months prior to Screening (transient hematuria which has been documented to have resolved within one week is acceptable), or current hematuria unless due to a urinary tract infection 34. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value < 60 mL/min as determined by Modification of Diet in Renal Disease [MDRD] 35. Total creatine kinase > 1.5 x ULN 36. History of pancreatitis, or confirmed pancreatic lipase > 1.3 x ULN, or > 2.0 x ULN upon repeated test within 3 weeks if on a DPP-IVi 37. Concomitant treatment with PPAR-α agonists (fibrates); if treatment with PPAR-α agonist is discontinued before the Baseline visit, it should be anticipated that triglycerides remain < 500 mg/dL during the study 38. Patients on Vitamin E at doses $\geq$ 400 IU/day; doses of $\geq$ 400 IU/day are allowed when no qualitative change in dose for 6 months prior to Screening 39. SARS-CoV-2 infections requiring hospitalization in the last 3 months or current SARS-CoV-2 infection confirmed by a validated test. (A SARS-CoV-2 test is not required for all patients at Screening visit but will be performed according to local standard practice). In case of previous asymptomatic or mild SAR-CoV-2 infection, the investigator should verify that abnormal lab tests due to COVID-19 are back to pre COVID-19 status before patient randomization. 40. Major surgery scheduled during the study 41. Known or suspected hypersensitivity to any of the ingredients of the investigational medicinal products (IMPs) 42. Rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption 43. Previous exposure to lanifibranor or empagliflozin 44. Osteopenia, or any other documented bone disease. Patient without documented osteopenia treated with vitamin D and/or calcium-based supplements for preventive reasons can be included. 45. Claustrophobia to a degree that prevents tolerance of MRI scanning procedure. Sedation is permitted at discretion of the Investigator. 46. 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 47. Present pregnancy/lactation or inability to adhere to adequate contraception in women of childbearing potential 48. Treatment with strong inducers or inhibitors of CYP2C8. When administered chronically, they should be replaced 3 months before Screening visit. If not administered chronically, they should be stopped at least 7 days before treatment initiation (See Section 6.7 and Section 13.2). Prior administration of other drugs (i.e. weight loss treatments, chronically administered medications) as specified in Section 13.2.
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	49. Participation in any clinical trial of an approved or non-approved investigational medicinal product/device within 3 months from Screening or five half-lives of the investigational drug from Screening, whichever is longer. Participation in non-interventional trials will be allowed with Sponsor approval. <u>Autoimmune related:</u> 50. Any patient with a predisposition to autoimmune liver disease, including: - Signs on previous liver biopsy suggestive of autoimmune liver disease (autoimmune hepatitis, immune cholangitis or overlap syndrome) - Family history of autoimmune liver disease in a first degree relative - Autoimmune thyroid disease: - Known diagnosis of autoimmune thyroid disease - Thyroid replacement hormone unless documented for reason of primary thyroid insufficiency (e.g. due to thyroidectomy, radiation therapy, etc.) - Positive autoimmune antibodies associated with abnormal thyroid function testing (TSH, T4 or free T3) - Anti-thyroid peroxidase antibody (TPO) - Anti-TSH receptor antibodies (TRAb) - History of or positive testing at screening for: - Anti-nuclear antibodies (ANA) at a dilution of 1:320 or greater - Anti-mitochondrial antibodies (AMA) - Anti-smooth muscle antibodies (ASMA) at a dilution of 1:320 or greater - Anti-liver kidney microsomal type 1 antibodies (LKM1) - Anti-liver cytosol type 1 antibody (LC1)
Investigational treatments	Tablets of lanifibranor 400 mg, administered on a daily dose of 800 mg lanifibranor or placebo, i.e., 2 tablets of 400 mg/placebo orally once daily (QD) during breakfast, for a total of 24 weeks Tablets of empagliflozin 10 mg/day administered orally once daily during breakfast, for a total of 24 weeks
Dose adjustment	No lanifibranor or empagliflozin dose adjustment is allowed in the study. Interruption of the IMP(s) due to AEs is allowed as per the Investigator's discretion and medical judgment for a maximum of 15 days, and should occur only once during the 24-week treatment period, taking into account that the IMP(s) will have to be administered during the last 15 days before Week 24.
Prohibited medication	If one of the following treatments is initiated during the study, a discussion should take place immediately between the site and the Sponsor to decide whether this new treatment is stopped or the patient withdrawn from the study treatment): - PPAR-γ agonists, PPAR-α agonists (fibrates) - Orlistat or bupropion - SGLT2 inhibitors, GLP-1 receptor agonists, sulfonylurea, insulin

	• Vitamin E (α-tocopherol) at a dose ≥ 400 IU/day • Treatment or anticipated initiation (for more than 14 consecutive days) of medications known to have an effect on NAFLD (e.g., oral corticosteroids > 5 mg/day of prednisone equivalent, methotrexate, tamoxifen, valproic acid, or amiodarone) • Drugs approved for the treatment of NASH (in the event that such drugs are approved during the course of the study) • Other investigational treatment whatever the indication • CYP2C8 strong inducers (e.g. rifampin). However, if medically necessary, these drugs may be taken for a maximum duration of 3 weeks. • CYP2C8 strong inhibitors, when systemically administered, i.e. by oral, intra-venous or intra-muscular route of administration (e.g. gemfibrozil, clopidogrel). • Herbal supplements: Herbal preparations should not be started during the course of the study for treatment of glycaemic control or liver health, or if there is a known concern with liver injury. Conditions associated with prohibited medications are detailed in Section 6.10.3 and Section 13.2.
Rescue medication	Rescue medication is defined as use of any new or additional antidiabetic medication, or increase in the dose of background antidiabetic medication above the baseline dose. The use of rescue medication in case of hyperglycemia will be permitted during the trial but only if the criteria below are met: • Week 1-12: Glucose level > 240 mg/dl (> 13.3 mmol/l) after an overnight fast, or > 400 mg/dl (> 22.2 mmol/l) in a randomly performed measurement • Week 13-24: Glucose level > 200 mg/dl (> 11.1 mmol/l) after an overnight fast, or > 400 g/dl (> 22.2 mmol/l) in a randomly performed measurement The above results should be confirmed, meaning that there is a minimum of two measurements, at least one of which should be performed after an overnight fast and on a different day to the initial (overnight fast or random) measurement. If fasting glucose levels remain at > 240 mg/dl (> 13.3 mmol/l) or > 200 mg/dl (> 11.1 mmol/l), depending upon the week of treatment, despite the initiation of rescue medication (and no further glucose lowering effect is anticipated by the Investigator), the patient should be withdrawn from the study. Sulfonylureas, metformin, DPP-IVi may all be given as rescue medication until the end of the trial. In case of no other clinical options, insulin can be used as rescue medication. Dosage will be left at the discretion of the Investigator. Rescue medication should be used in accordance with the local prescribing information, taking into account potential contraindications.

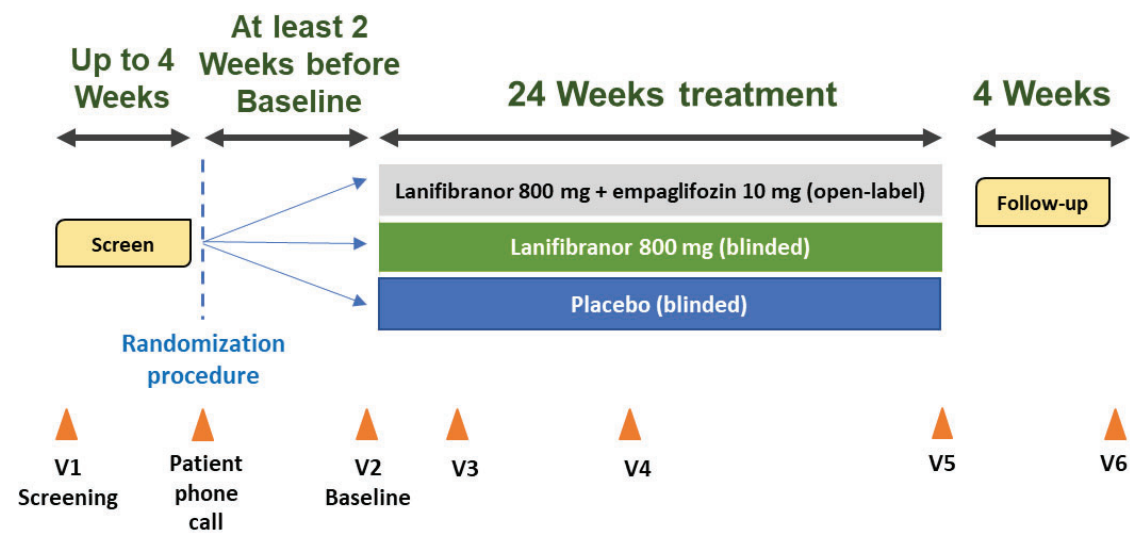
Study duration	The total time (from first patient enrolled to last patient finished) will be approximately 14 months (6 weeks screening period including randomization procedure, 24-week treatment and 4-week post-treatment follow-up for the last patient, with an estimated recruitment period of 6 months). At time of interim analysis, the Sponsor reserve the right to terminate the study should clear trends in study findings be observed. In that case, recruitment will not be re-initiated.
Participant duration	For an individual patient: 34 ± 2 weeks, i.e., 6 weeks screening period including randomization procedure, 24-week treatment and 4-week post-treatment follow-up
Total number of subjects	63 patients randomized (21 patients per treatment arm)
Statistical analyses	Randomization Randomization will be stratified by 2 stratifying factors: HbA1c at Screening ($< 7.5\%$, $\geq 7.5\%$) and by sex (Male, Female), because these factors are considered important prognostic covariates. Details will be provided in a dedicated randomization plan. Moreover, at least 40% males and at least 40% females will be randomized. Statistical considerations Final analysis will be performed on the Full Analysis Set (FAS) consisting of the randomized patients who received at least one dose of IMP. Interim analysis will be performed on the IAS consisting of approximately the first half of the (planned) randomized patients, who received at least one dose of IMP. The overall type I error of the study is 0.05 (2-sided). No alpha (type I error) adjustment will be considered for the interim analysis, i.e. still considering 0.05 (2-sided), this study being an exploratory proof-of-concept study. Estimands strategy will be clearly defined for the primary analyses in line with ICH E9 (R1) addendum, and intercurrent events will be handled through a combination of hypothetical and treatment-policy strategies. A hierarchical fixed testing procedure for the primary endpoint tests will be used; lanifibranor alone will be compared to placebo at the 2-sided 0.05 level on the primary endpoint, and, should this test pass, the combination will be tested at the same level. To assess the superiority of each active arm versus placebo on absolute change in HbA1c from baseline, a mixed model for repeated measures (MMRM) will be used with treatment group, time, treatment*time interaction as fixed effects, baseline outcome value and sex, as covariates and the patient effect as a random effect. Treatment effect on absolute change in HbA1c from baseline at Week 24 between each active arm and placebo will be estimated using this MMRM model with the contrast of interest at Week 24. MMRM is used to handle missingness because outcomes are measured repeatedly over time, and no explicit imputation will be done for missing data. The MMRM model is recognized to perform well under the missing at random (MAR) assumption for missing data. Since a low number of missing data is

	expected for the main endpoint in this rather short study, this assumption is deemed to be plausible for the main estimation. Supplementary analyses testing other assumptions will be developed in the protocol and Statistical Analysis Plan (SAP) of the study. To assess the treatment effect for continuous secondary endpoints, similar MMRM will be used, including additionally the stratifying factor HbA1c at Screening ($< 7.5\%$, $\geq 7.5\%$), as covariates in the model. To assess the treatment effect for categorical secondary endpoints, categorical outcome measures will be compared using Cochran–Mantel–Haenszel (CMH) test adjusted for the 2 stratifying factors, separately between each active arm and placebo. A popPK model will be developed using nonlinear mixed effect modelling (NONMEM) software. The model developed on rich sampling scheme from Phase 1/2 studies will be used as basis for this patients' model where concentrations will be obtained using a sparse sampling scheme. This model will be used to estimate popPK parameters such as clearance and volume of distribution. Sample size The sample size is based on the effect size of lanifibranor alone versus placebo (First test in the hierarchical procedure) on the change from baseline in HbA1c at Week 24, assuming an additive efficacy when empagliflozin is added to lanifibranor (Second test in the hierarchical procedure). Based on recent results of the Phase 2 trial NATIVE (NCT03008070), in the subpopulation of NASH with T2DM, the mean (standard deviation [SD]) absolute changes in HbA1c from baseline to Week 24 were -0.60 (0.54)% with lanifibranor 800 mg and $+0.10$ (0.53)% with placebo. Assuming an effect size of lanifibranor versus placebo of 0.60%, an expected SD of the change from baseline of 0.60%, a type I error of 0.05 (2-sided), an allocation ratio of 1:1, the required sample size per group is 21 patients with a power close to 90%. The total sample size is 63 patients overall, distributed into 21 patients in each group.
Interim analyses	An interim analysis on the IAS will be planned once approximately half of the planned patients are randomized, and have either completed the 24-week treatment period or prematurely discontinued from treatment earlier. Recruitment will be paused once half of the planned patients are randomized. Once the interim analysis results will be available, recruitment may be re-initiated, or, should clear trends in study findings be observed, recruitment may be stopped to minimize patient exposure with additional patients.
Safety rules for discontinuation or dose reduction	Reasons for permanent drug discontinuation include: • In the opinion of the Investigator, any AE, AESI, SAE, or significant change in a laboratory value that warrants permanent discontinuation of study drug therapy • Occurrence of a drug-induced liver injury (DILI) event requiring drug discontinuation

	• Occurrence of repeated hypoglycemic episodes without possibility for a down-titration of background therapy that may put the patient at risk with continued participation • Non-permitted concomitant medication • Female patients who are pregnant or women of childbearing potential who do not agree to use a highly effective method of contraception during the study • Non-compliance with the study treatment • Uncooperative patient
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1.2 Study Design

Figure 1: Study design



1.3 Schedule of Activities (SoA)

	Screening	Randomi- zation*	Baseline	Treatment period			Follow-up
Visit	Visit 1	NA	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time frame	Week -6 to Week 0**		Week 0	Week 4	Week 12	Week 24 EOT or Premature EOT***	4 weeks after last dose of study drug
Time window	Maximum -6 to -2 Weeks (latest) before Week 0	At least 2 Weeks before Week 0		± 3 days	± 6 days	± 6 days	± 7 days
Clinical assessments							
Informed consent	X						
Phone call to patient to re- confirm eligibility*		X					
Eligibility criteria ¹	X	X	X				
Demographics ²	X						
Alcohol intake ³	X		X	X	X	X	X
Medical and disease history	X	X	X				
Concomitant medications ⁴	X	X	X	X	X	X	X
Dietary and lifestyle monitoring	X		X	X	X	X	
Serious Adverse Events	X	X	X	X	X	X	X
Adverse events, AESI			X****	X	X	X	X
Physical examination ⁵	X		X	X	X	X	X
Vital signs ⁵	X		X	X	X	X	X
ECG ⁶	X					X	
IMP							
Randomization		X*					
Dispensing study drug			X		X		
Study drug intake			<----->				
Drug accountability ⁷				X	X	X	
Laboratory testing							
SARS-CoV-2 testing ⁸	X		X	X	X	X	X
Serology ⁹	X						
Urinalysis ¹⁰	X		X	X	X	X	X
Hematology ¹⁰	X		X	X	X	X	X
Liver tests ¹⁰	X		X	X	X	X	X
Monitoring of liver tests and INR ¹¹				Liver tests and INR have to be repeated at maximum every 6 weeks between 2 visits (W8 and W18)			
Serum chemistry ¹⁰	X		X	X	X	X	X
Renal function ¹⁰	X		X	X	X	X	X
Coagulation ¹⁰	X		X	X	X	X	X
NT-ProBNP	X		X	X	X	X	X
Inflammatory parameters ¹⁰			X			X	

- 5 Vital signs include assessments of SBP, DBP, and pulse rate. Physical examination includes assessments of height (only at Screening), body weight and waist circumference at all site visits. Fasting for at least 8 hours is required for body weight measurements. Other assessments that will be documented as part of physical examination include general appearance, thyroid gland palpation, the musculoskeletal system, central and peripheral nervous system, skin, lymph node palpation, and general assessments of the head, ears, eyes, nose, throat and neck as well as examinations of the respiratory, cardiovascular, and gastrointestinal systems including mouth.
- 6 Single ECG read locally (for details see [Section 8.2.5](#))
- 7 The Investigator (or designee) will confirm that patient understands and is following their dosing instructions properly at the Baseline and all subsequent visits. Compliance will be assessed at each visit by counting returned IMP against issues supplies, etc. and will be documented in the source documents and CRF. Any deviation from the correct use of the IMP will be recorded in the eCRF and compliance records. The IMP start and stop dates, including dates for IMP delays, will also be recorded in the eCRF.
- 8 SARS-CoV-2 test will be done locally according to local requirements at the time of each study visit.
- 9 Serology tests: HBV (HBsAg), HCV (HCV antibodies. If anti-HCV antibodies are detected, HCV RNA should be determined to differentiate past from current infection, only if no results of RNA dated from up to 3 years before screening are available on the medical history), HIV1 & 2 antibodies
- 10 Patient in fasted state for at least 8 hours. Please refer to [Table 4](#) for a detailed list of parameters.
- 11 Monitoring of liver tests = ALT, AST, GGT, ALP, total and direct bilirubin and INR. Those tests should be performed centrally or locally (on site or any accessible laboratory).
- 12 For women of childbearing potential, serum β -hCG at screening. Urine pregnancy test for all other site visits and at any time during the study if pregnancy is suspected or according to local regulations. Urine pregnancy test will be provided to the female patients at Baseline visit if needed. If the test is positive, the patient will stop treatment and contact the site immediately for premature end of treatment visit.
- 13 At Screening, thyroid function testing (TSH, T4 and free T3) and autoimmune antibodies should be performed by the central lab (when available), or by local assessment:
 - If performed by a local lab, it is not needed to repeat an autoimmune antibody if available within 12 months prior to screening
 - If performed by the central lab, all autoimmune antibodies will be tested at once

2 INTRODUCTION

2.1 Study Rationale

There is a strong association between T2DM and NAFLD/NASH with all being linked to the metabolic syndrome. T2DM is a chronic disease caused by insulin resistance and progressive β -cell failure [1]. Overall, T2DM is a progressive disease and patients will ultimately require multiple antidiabetic treatments to maintain glycemic control [2]. NAFLD is commonly felt to be the hepatic manifestation of the metabolic syndrome. Insulin resistance is the key pathophysiological event leading to clinical manifestation of the metabolic syndrome and thus, to the development of both NASH and T2DM. NAFLD can also be considered as clinical continuum, encompassing obesity to metabolic syndrome and diabetes. NAFLD/NASH patients typically display clinical features of metabolic syndrome including abdominal obesity, dyslipidemia, hypertension, insulin resistance and T2DM. Insulin resistance drives the development and progression of T2DM and NASH whereby development of NASH is a multi-step process [3]. Insulin resistance promotes transition from normal to fatty liver [4] while numerous additional factors ("hits") trigger the development of steatohepatitis in patients with steatosis.

The prognosis of NASH is determined both by progression of hepatic disease and by extrahepatic complications [5]. Hepatic fibrosis progression is the main hepatic complication of NASH [6][7] and can progress to cirrhosis, which over time leads to complications of decompensated cirrhosis and is associated with an increased risk for liver cancer [8][9]. Extrahepatic complications include an increased risk of cardiovascular events and cardiovascular morbidity that seems to be independent of other known cardio-metabolic risk factors [10]-[12]. Several studies have shown that patients with NASH have reduced survival compared to the age- and sex-matched general population [13] and that they are exposed to the risk of end-stage liver disease [8][12], HCC [8][14], and increased liver-related mortality [12].

It has been shown that the level of glycemic control can predict the severity of histological features of liver injury in NAFLD/NASH. In a longitudinal cohort study, higher mean HbA1c was associated with a higher grade of steatosis and ballooned hepatocytes, but not lobular inflammation [15].

The majority of patients with T2DM require pharmacological management, with lifestyle medication being supportive. In patients with NASH, although lifestyle medication is a mainstay, most patients fail to achieve clinical improvements. Pharmacological treatment of NASH is a significant unmet clinical need. While diet and lifestyle changes are always recommended as first-line therapy and can be efficient in reducing NASH histological lesions, most patients fail to reach these objectives and compliance with these measures is usually poor [16][17]. It is now recognized that insulin resistance is the main mechanism leading to fat accumulation in the liver and insulin-sensitizing agents such as glitazones [18] and metformin [19] have been proposed as putative treatments of NASH. However, although some studies suggest a moderate efficacy of glitazones (the early-phase studies have shown that at least half of treated patients have no or a suboptimal response to glitazones) [20]-[22]. A prospective study in patients with pre-diabetes or T2DM with NASH found that pioglitazone reduced liver fibrosis (histologically assessed), with reduced intrahepatic triglyceride content [23]. A meta-analysis of pioglitazone studies showed that in patients with pre-diabetes or T2DM there was significant liver histological improvements in steatosis, inflammation and ballooning [24].

Therapeutic compounds that address the upstream metabolic and immune mediated pathways of NASH are also expected to be beneficial for T2DM. Utilizing drug combinations targeting

multiple aspects of the metabolic syndrome has the potential to enhance relevant clinical outcomes in both T2DM and NASH. Clinical trials on diabetes drugs with beneficial effects on metabolic syndrome, such as pioglitazone and liraglutide, have shown improvements in liver histology, thereby supporting the use of such strategies for both T2DM and NASH [25]. There is a clear rationale to assess combination therapy with drugs that have a complementary mechanism of action in the complex disease pathophysiology of patients with NASH who also have T2DM.

SGLT2 inhibitors are approved for the treatment of T2DM. They have a beneficial effect on glucose metabolism, HbA1c, insulin resistance, inflammation through their inhibition of renal glucose reabsorption and other pleiotropic metabolic effects, including weight loss. SGLT2 inhibitors in combination with pioglitazone in T2DM have shown improved glycemic control, reduced body weight and lowered blood pressure compared with pioglitazone alone [26].

Lanifibranor, a pan-PPAR agonist, has beneficial effects on lipid and glucose metabolism, insulin resistance, as well as on steatohepatitis (hepatic injury and inflammation) and fibrosis as shown in the NATIVE Phase 2b study [27]. In this study in NASH patients, a sub-analysis on those patients with T2DM at baseline (i.e., with baseline HbA1c > 6.5%), demonstrated significant improvements in glycemic control, with a substantial decrease in HbA1c under treatment with lanifibranor. The present LEGEND study is intended to confirm these preliminary findings. Further, it is expected that the therapeutic effect on the above-mentioned variables may increase when lanifibranor is combined with an SGLT2 inhibitor.

In addition, the combination of lanifibranor with an SGLT2 inhibitor may improve tolerability of the PPAR agonist. While lanifibranor has an overall favorable safety profile, weight gain, peripheral edema and anemia have been observed in Phase 2 studies, mainly in female patients.

The weight gain observed with PPAR agonists is associated with a fat re-distribution that involves remodelling of abdominal fat tissue which can be considered to be metabolically healthy [28]. It has been demonstrated that the shift of fat distribution from visceral to subcutaneous adipose depots after pioglitazone therapy is associated with improvements in hepatic and peripheral tissue sensitivity to insulin. PPAR γ agonists have been shown to decrease both hepatic steatosis and visceral fat, improve peripheral, adipose tissue and liver insulin sensitivity [29]. Weight gain with pioglitazone is limited largely to gain in subcutaneous fat, with a reduction in visceral fat [30]. In the NATIVE Phase 2b study [27], lanifibranor was associated with improvements in markers of lipid metabolism, insulin resistance (fasting glucose, fasting insulin, HbA1c) and diastolic blood pressure, despite a third of patients having weight gain [31]-[33]. In contrast, SGLT2 inhibitors have been shown to induce body weight reductions.

In the NATIVE Phase 2b study, peripheral oedema occurred more frequently with lanifibranor than with placebo [27]. In this context, SGLT2 inhibitors have been associated with a consistent diuretic effect. [26] Anemia was observed more frequently with lanifibranor in the NATIVE Phase 2b study, whereas SGLT2 inhibitors have been shown to increase hematopoiesis, with elevations in erythropoietin, haemoglobin and hematocrit levels [34].

The LEGEND study in the T2DM population is intended to:

- Confirm as primary objective the lanifibranor effect versus placebo on glycemic control observed in the NATIVE Phase 2b study (NCT03008070)
- Confirm a positive effect of the combination of lanifibranor with an SGLT2 inhibitor on glycemic control (i.e., conservation of the effect when associated with an SGLT2 inhibitor, no deleterious effect, no negative interaction on glycemic control), while assessing the safety and tolerability, i.e., evaluation of the effect of lanifibranor in

combination with an SGLT2 inhibitor on AEs, weight gain, peripheral edema, and anemia as safety endpoints.

2.2 Background

A large proportion of patients with T2DM and NASH display typical features of metabolic syndrome including abdominal obesity, dyslipidemia, hypertension and insulin resistance.

T2DM accounts for 90 to 95% of all cases of diabetes and is an increasingly prevalent disease with an estimated 462 million affected people worldwide. Complications induced by hyperglycemia are currently the most frequent causes of adult-onset loss of vision, renal failure, and amputation in the industrialized world. Diabetes is also associated with macrovascular complications with a 2- to 5-fold increase in cardiovascular disease risk. The high frequency of complications leads to a significant reduction of quality of life and life expectancy [35][36]. NASH is an important condition closely associated with T2DM, with the prevalence of NASH being reported as high as 65% among patients with T2DM [37].

NAFLD is the hepatic manifestation of metabolic syndrome. Insulin resistance is the key pathophysiological event leading to the development of NAFLD and T2DM, both being manifestations of the metabolic syndrome. NAFLD is the most common chronic liver disease and affects about 25% of the overall population, which increases to over 90% for very obese individuals. A large proportion of patients with NAFLD display typical features of the metabolic syndrome or T2DM [38]. The subtype of NAFLD that is histologically categorized as non-alcoholic steatohepatitis (NASH) has a potentially progressive course leading to liver fibrosis, cirrhosis, HCC and liver transplantation.

To date, there are no approved medications to specifically treat NASH, although a significant proportion of patients with NASH do have T2DM, for which there are a number of therapeutically approved options. There is a need to evaluate therapies that address both NASH and T2DM, particularly combinations of drugs with complementary modes of action. The complex pathophysiology effecting both conditions means that therapeutic approaches require multiple treatments regulating lipid and glucose homeostasis as well as blood pressure control [39]. There is growing interest in developing novel therapeutic strategies that could target multiple metabolic disease components. There are several metabolic disease drug classes, either in development or already on the market, that modulate multiple targets or have multiple therapeutic actions. Combining different drug classes could serve as a starting point for developing novel multi-targeted molecules or combinations to treat metabolic diseases. It is important to choose targets modulating different components of the metabolic syndrome, ideally with a combination that has a synergistic effect, contributing to the efficacy and safety of the multi-target approach.

The strong association of NASH and T2DM, both being manifestations of the metabolic syndrome, provides a compelling rationale for investigating therapies that work on multiple mechanisms and combining treatments with synergistic effects. Utilizing drug combinations that target multiple aspects of the metabolic syndrome may enhance relevant clinical outcomes in both T2DM and NASH. A combination of the pan-PPAR agonist lanifibranor with the SGLT2i empagliflozin may fulfil these requirements.

2.2.1 Peroxisome Proliferator-Activated Receptor (PPAR)

The three PPAR isoforms are not only key players in the control of insulin sensitivity, and lipid and glucose metabolism, but also in the control of fibrogenic pathways leading to hepatic fibrosis. PPARs also have an important role in modulating inflammation in immune cells having differential therapeutic effects on hepatocytes, activated hepatic stellate cells and inflammatory macrophages.

PPAR- α is highly expressed in hepatocytes where it is involved in transport and β -oxidation of fatty acids [40][41]. PPAR- α expression in the liver of NASH patients negatively correlates with the severity of NASH [42].

PPAR- δ is involved in hepatic glucose utilization, lipoprotein metabolism and cell proliferation. Both PPAR- α and PPAR- δ have anti-inflammatory activities within the liver [43]-[45].

PPAR- γ is essentially expressed in adipose tissue, where it regulates insulin sensitivity and lipolysis, and in inflammation tissue [46]. In the liver, PPAR- γ is expressed in hepatic stellate cells, the key cells driving the hepatic fibrotic process [47][48], where it controls their activation.

Clinical evidence indicates that activation of PPAR- γ in NASH patients can improve circulating and histological markers of liver steatohepatitis and induces NASH reversal [48][49].

Overall, the three PPAR isoforms play an important role in several components of NASH, from hepatic triglyceride accumulation to fibrosis [47].

2.2.2 Lanifibranor

Lanifibranor is a pan-PPAR agonist that targets the three PPAR isotypes with a well-balanced potency. It activates all three PPAR isoforms. These isoforms are nuclear receptor proteins that regulate gene expression.

Lanifibranor in non-clinical models of NASH

In animal models reproducing NASH disease characteristics (CCl-4-induced liver fibrosis in mice, Methionine Choline Deficient Diet mice, Choline deficient mice, Alms1 mutant *foz/foz* mice), lanifibranor demonstrated a strong effect on all the key features of the disease with dose-dependent antidiabetic activity, decrease in adiposity index and levels of plasma triglycerides and very-low-density lipoprotein (VLDL) cholesterol, and with a rise in high-density lipoprotein (HDL) cholesterol, and hepato-protective effect. In addition, lanifibranor reverses liver fibrosis, the histological feature of NASH associated with long-term overall mortality.

Antidiabetic properties of lanifibranor were demonstrated in various animal models (db/db mice, diet-induced obesity mice, and Zucker diabetic fatty rats) as well as its anti-dyslipidemic effects (in apoA1 transgenic mice and Wistar-Ottawa-Karlsburg W rats).

Lanifibranor in patients with diabetes or NASH

In the Phase 2b S337.2.001 study in patients with T2DM treated with metformin, lanifibranor (n=47) showed its pan-PPAR agonism activities on key metabolic markers as triglycerides decrease (PPAR- α and β/δ -mediated), adiponectin increase (PPAR- γ mediated), and HDL cholesterol increase (PPAR- α and β/δ -mediated), with a good safety profile compared to placebo (n=14 patients).

In the Phase 2b IVA_01_337_HNAS_16_002 study (NATIVE), in NASH patients treated for 24 weeks with lanifibranor 800 mg or 1200 mg versus placebo, lanifibranor met the primary endpoint in the 1200 mg/day treatment group with 49.4% of patients achieving a 2-point reduction of the Steatosis-Activity-Fibrosis (SAF) score with no worsening of fibrosis at Week 24 compared to 27.2% on placebo ($p=0.004$).

Key secondary histological efficacy parameters showed a statistically significant difference at Week 24 compared to placebo in the Full Analysis Set (FAS) and subpopulation with F2/F3 fibrosis stage:

- Resolution of NASH and improvement of fibrosis: in the FAS population, 20.5% ($p=0.017$) of patients in the 800 mg/day treatment group and 31.3% ($p<0.001$) in the 1200 mg/day treatment group versus 7.4% in the placebo group. In the subgroup of patients with F2/F3, 23.5% ($p=0.012$) of patients in the 800 mg/day treatment group and 33.3% ($p<0.001$) in the 1200 mg/day treatment group versus 7.0% in the placebo group.
- Resolution of NASH and no worsening of fibrosis: in the FAS population, 32.5% ($p=0.043$) of patients in the 800 mg/day treatment group and 44.6% ($p<0.001$) in the 1200 mg/day treatment group versus 18.5% for placebo. In the subgroup of patients with F2/F3, 33.8% ($p=0.0011$) for the 800 mg/day treatment group and 44.4% ($p<0.001$) in the 1200 mg/day treatment group, versus 8.8% for placebo.
- Improvement of fibrosis by at least one stage and no worsening of NASH: in the FAS population, 42.2% ($p=0.011$) in the 1200 mg/day treatment group versus 23.5% for placebo, and 47.6% ($p=0.048$) versus 29.8% for placebo in the subgroup of patients with F2/F3).

In addition, statistically significant results in the FAS were obtained in both dose groups (800 mg/day and 1200 mg/day) regarding:

- Decrease of liver enzymes
- Improvement of lipid parameters (decrease in triglycerides and increase of HDL cholesterol)
- Decrease in insulin, fasting glucose, and Hb1Ac in patients with T2DM

Further, both lanifibranor groups showed a decrease in diastolic blood pressure from baseline. In the lanifibranor 1200 mg group there was a mean reduction of -2.4 mmHg at Week 4 which was maintained up to Week 24. In the lanifibranor 800 mg group, the decrease was linear from baseline up to Week 24 (-4.1 mmHg).

In the NATIVE study, a sub-analysis was performed on those patients with diabetes at baseline. Diabetes patients, who as expected had high values of HbA1c at baseline ($> 6.5\%$), showed a substantial decrease from baseline to Week 14 in HbA1c when treated with lanifibranor (800 mg and 1200 mg) which was maintained up to Week 24 (mean absolute changes from baseline at Week 24: -0.60% [SD: 0.54%] and -0.72% [SD: 0.65%] in the lanifibranor 800 mg and 1200 mg groups versus 0.10% [SD: 0.53%] in the placebo group). At Week 24, in the lanifibranor 800 mg and 1200 mg groups, 45.8% and 56.0% of diabetic patients with abnormal values at baseline progressed to normal Hb1Ac values (11/24 patients and 14/25 patients, respectively) versus only 4.2% on placebo (1/24 patients). Furthermore, HbA1c decreased by $\geq 0.5\%$ in 16 (55.2%) and 19 (61.3%) diabetic patients in the lanifibranor (800 mg and 1200 mg) groups versus 3 (9.4%) diabetic patients in the placebo group. A decrease $\geq 1\%$ was reported for 6 (20.7%) and 8 (25.8%) patients on lanifibranor and 1 (3.1%) on placebo.

2.2.3 Empagliflozin

Empagliflozin is an orally available, potent, and selective inhibitor of renal SGLT2. Its selective inhibition reduces renal reabsorption of sodium and glucose. This leads to both increased urinary sodium and glucose excretion. While urinary sodium excretion returns to normal within few days of empagliflozin administration, the effect on urinary glucose continues. Empagliflozin is approved in the USA (see Jardiance USPI), Europe (see Jardiance SmPC) and other regions for the treatment of T2DM.

In humans, empagliflozin predominantly showed linear pharmacokinetics (PK). Empagliflozin reaches peak levels at approximately 1.5 hours and showed a biphasic decline with the terminal elimination half-life ranging from 10 to 19 hours. Empagliflozin exposure increases with renal or hepatic impairment; however, no dose adjustment is recommended as the observed changes in exposure were not clinically meaningful. No clinically relevant PK interactions were observed with other oral antidiabetics, warfarin, verapamil, ramipril, simvastatin, digoxin, hydrochlorothiazide, torasemide, emfibrozil, rifampicin, probenecid or oral contraceptives [50].

In Phase 3 studies in T2DM treatment with empagliflozin 10 mg or 25 mg once daily for up to 24 weeks resulted in a reduction of HbA1c up to 0.82%, body weight reduction between 2-3 kg, and a decrease in SBP between 3-5 mmHg compared with placebo [50][51]. This was consistently observed with empagliflozin as monotherapy, add-on to metformin, metformin and sulfonylurea, pioglitazone with or without metformin, and to basal insulin with metformin and/or sulfonylurea. Phase 3 studies up to 104 weeks in T2DM support the long-lasting effect of empagliflozin. In clinical studies, empagliflozin was well tolerated in both healthy volunteers and patients with T2DM including patients with high cardiovascular risk up to a median duration of 2.6 years. The frequency of overall AEs, AEs leading to discontinuation and SAEs were comparable to placebo. There was no significant increase in frequency of hypoglycemia with empagliflozin compared to placebo except when used in combination with a sulfonylurea or basal insulin. In general, there was a small increase in frequency of urinary tract infection compared to placebo. There was an increase in frequency of genital infections with the use of empagliflozin. There was a small increase in total cholesterol, LDL cholesterol and HDL cholesterol, but no significant changes in triglycerides. No changes in electrolytes were observed with empagliflozin [50][51].

Empagliflozin has been evaluated in patients with Class II-IV heart failure and left ventricular ejection fraction $\leq 40\%$, in patients with and without T2DM. Empagliflozin has been shown to reduce the risk of cardiovascular death or hospitalization for heart failure and total hospitalizations for heart failure in both patients with and without diabetes [52].

Treatment with empagliflozin for 24 weeks was associated with improvement of liver steatosis and fibrosis in patients with NAFLD and T2DM as assessed by transient elastography [53]. Empagliflozin was also shown to reduce liver fat (measured by MRI-PDFF) and improve ALT in patients with T2DM and NAFLD [54]. These findings are in line with those observed across different SGLT2 inhibitors, which consistently have shown that SGLT2 inhibitors improve liver enzymes and liver fat in patients with T2DM and NAFLD [55].

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Clinical experience with medicinal products from the same therapeutic class identified the following important risks:

- Hypoglycemia
- Peripheral edema
- Heart failure
- Weight gain
- Anemia
- Liver injury
- Muscular toxicity
- Renal toxicity
- Ovulation resumption
- Bone fractures
- Cholelithiasis

Some of these risks have been observed during clinical development with lanifibranor in patients with NASH, including peripheral edema, weight gain and anemia. Most of these events were of mild or moderate intensity and none of them were assessed as serious.

An increase in liver tests with features of autoimmune disease has been observed in a few patients in the Sponsor Phase 3 trial in NASH with liver fibrosis (protocol 337HNAS20011 (NATiV3), IND 140010, EudraCT2020-004986-38) which is ongoing at time of this protocol amendment. Patients with a personal or close family history of autoimmune liver diseases or a personal history of autoimmune thyroid disease may be at a higher risk for this to occur. Patients with these conditions will not be eligible to enrol in the study. Any patient already enrolled in the study prior to the protocol version 6.0 should discuss the potential risks and benefits of continuing with their study doctor.

For empagliflozin (Jardiance), the following important risks have been observed from clinical experience or from post-marketing experience:

- Complicated urinary tract infection
- Genital infection
- Diabetic ketoacidosis with atypical presentation
- Urinary tract carcinogenicity
- Liver injury
- Bone fractures
- Amputation risk
- Pancreatitis

Other adverse reactions have been observed with empagliflozin including:

- Transient increase in serum creatinine
- Hypoglycemia (especially with insulin or sulfonylurea use for rescue).

Further evaluation of the risks for lanifibranor (alone or in combination with the SGLT2 inhibitor) will be performed during the ongoing clinical development, including the present study. Monitoring of safety and tolerability measures will be performed throughout this study with special attention to cardiovascular parameters (blood pressure, heart rate), electrolyte homeostasis, parameters of renal and hepatic function based on the mechanism of action of lanifibranor and empagliflozin, and the already known risks (see [Section 8.2](#) for further details).

Further, due to the absence of clinical data on the exposure of lanifibranor during pregnancy, women of childbearing potential have to be on highly effective contraceptive methods before considering enrolment in the study, until one month after the last study drug intake.

2.3.2 Known Potential Benefits

Based on the positive effects of lanifibranor on metabolic parameters in patients with T2DM and on histological features of NASH reported in [Section 2.2.2](#), it is anticipated that lanifibranor will be beneficial for the patients enrolled in this study. Previous clinical studies have demonstrated that lanifibranor induces anti-fibrotic, anti-inflammatory and beneficial vascular and metabolic changes in the body. In this study, patients receiving lanifibranor may experience an improvement in metabolic parameters, resolution of NASH and improvement of liver fibrosis.

SGLT2 inhibitors are approved for the treatment of T2DM. They have a beneficial effect on glucose metabolism, insulin resistance, inflammation through their inhibition of renal glucose reabsorption, and other pleiotropic metabolic effects, including weight loss. Lanifibranor has beneficial effects on lipid and glucose metabolism, insulin resistance, as well as on steatohepatitis (hepatic injury and inflammation) and fibrosis as shown in NATIVE Phase 2b study (NCT03008070). Therefore, it is expected that the therapeutic effect on these variables may increase when lanifibranor is combined with an SGLT2 inhibitor.

In addition, the combination of lanifibranor with an SGLT2 inhibitor may improve tolerability of the PPAR agonist. While lanifibranor has an overall favorable safety and tolerability profile, weight gain, peripheral edema and anemia were observed in Phase 2 studies. Although weight gain under PPAR agonist therapy is considered to be metabolically healthy based on redistribution of visceral and subcutaneous fat, it may still be an undesirable effect. SGLT2 inhibitors induce weight loss and have a diuretic effect. They were also shown to increase hematopoiesis. Therefore, the proposed study will allow evaluation of the effect of lanifibranor in combination with an SGLT2 inhibitor on weight, peripheral edema, and anemia as safety endpoints.

2.3.3 Assessment of Potential Risks and Benefits

On the basis of the risks of lanifibranor and empagliflozin (alone or in combination) that will be managed with the adequate mitigation plan as described above, and balanced with the beneficial effects of lanifibranor observed in the previous Phase 2 study in patients with T2DM and/or NASH, the benefit-risk profile of lanifibranor alone and in combination with empagliflozin is anticipated to be positive for the patients enrolled in this study.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary, Secondary, and Exploratory Objectives(s), and Related Estimands

3.1.1 Primary Objective

The primary objective of this study is to assess the effect of lanifibranor alone compared to placebo and the effect of lanifibranor in combination with empagliflozin compared to placebo on HbA1c after a 24-week treatment duration.

In line with ICH E9 (R1) addendum, five attributes (treatment, population, endpoint, intercurrent events, and population-level summary) were specified to translate the primary efficacy objective into treatment effects that are to be estimated (estimands), and are described in [Section 9.4.2.1](#).

The primary estimand is the comparison of lanifibranor alone and lanifibranor plus empagliflozin versus placebo on the change in HbA1c from baseline to end of treatment (Week 24), on the population initiating treatment with lanifibranor or lanifibranor plus empagliflozin, and excluding potential rescue medication (under the hypothetical strategy where patients would have continued their treatment during 24 weeks without rescue medication).

3.1.2 Secondary Objectives

The secondary objectives of this study are to assess the effect of lanifibranor alone compared to placebo and lanifibranor in combination with empagliflozin compared to placebo after a 24-week treatment duration on:

- Liver tests
- Markers of glycemic control and insulin resistance
- Inflammatory markers
- Lipid parameters
- Body weight and body composition

and to assess the safety and tolerability of lanifibranor alone and in combination with empagliflozin during the 24-week treatment period and the 4-week follow-up period.

[REDACTED]

3.2 Primary, Secondary, Exploratory and Safety Endpoints

3.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the absolute change in HbA1c from baseline (Week 0) to Week 24.

3.2.2 Secondary Efficacy Endpoints

The following secondary endpoints will be evaluated at Week 24:

- Change from baseline to Week 24 in liver tests (ALT, AST, GGT, ALP, total and direct bilirubin)
- Change from baseline to Week 24 in markers of glycemic control and insulin resistance (determination of hepatic insulin sensitivity, HOMA-IR, fasting insulin, FPG, fructosamine, adiponectin)
- Binary endpoint defined as reaching HbA1c < 7.0% at Week 24, and no new antidiabetic treatment or increase in dosages of antidiabetic treatments
- Binary endpoint defined as reaching HbA1c decrease $\geq 0.5\%$ at Week 24, and no new antidiabetic treatment or increase in dosages of antidiabetic treatments
- Change from baseline to Week 24 in inflammatory markers (hsCRP, IL-6, IL-1 β)
- Change from baseline to Week 24 in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, TG)
- Change from baseline to Week 24 in body weight
- Binary endpoint defined as reaching body weight increase $\geq 5\%$ at Week 24
- Change from baseline to Week 24 in body composition as determined by MRI (including but not limited to: VAT, SAT, thigh SAT)

3.2.3 Safety Endpoints

- AEs
- AESIs: anemia, heart failure, aminotransferases elevation, bone fracture, peripheral edema, cholelithiasis, hypoglycemia and ovulation resumption
- SAEs including MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, hospitalization for acute coronary syndrome)
- Physical examination
- Vital signs (SBP, DBP, waist circumference)
- ECG
- Safety laboratory evaluations including NT-pro-BNP

•	[REDACTED]
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4 STUDY DESIGN

4.1 Overall Design

This proof-of-concept study will assess the safety and efficacy of the pan-PPAR agonist lanifibranor alone and in combination with the SGLT2 inhibitor empagliflozin in patients diagnosed with NASH and T2DM. The study will assess the impact on safety (including body weight changes), metabolic parameters, inflammatory markers, body composition, liver function, and improvement in hepatic steatosis and fibrosis.

The study is designed as a multinational, multicenter, three-arm, randomized, double-blind for lanifibranor and placebo, open-label for the combination lanifibranor plus empagliflozin, placebo-controlled, 24-week treatment study followed by a 4-week post-treatment visit.

A total of 63 patients are planned to be randomized 1:1:1 to receive:

- Lanifibranor 800 mg QD for 24 weeks or
- Matching placebo QD for 24 weeks or
- Lanifibranor 800 mg QD plus empagliflozin 10 mg QD for 24 weeks.

Moreover, at least 40% males and at least 40% females will be randomized.

Patients who drop out after randomization but before first study drug administration will be replaced. Patients who drop out after randomization and have already received at least one dose of study drug will not be replaced.

An interim analysis will be conducted once approximately half of the planned patients will be randomized, and have either completed the 24-week treatment period or prematurely discontinued from treatment earlier, that will constitute the Interim Analysis Set (IAS). At this time, all protocol-defined analyses will be performed.

A data integrity plan will be developed detailing, among the patients not belonging to the IAS, how the blinding is maintained, how integrity of the trial will be protected and to ensure continued adherence to treatment and trial retention.

The objective of this interim analysis will be:

- To obtain preliminary information on observed effects sizes / variability allowing an early insight on the treatment effect on multiple mechanistic endpoints, helping supporting future decision making, both for the LEGEND study and in the overall lanifibranor clinical program
- To stop recruitment should clear trends in study findings be observed thereby minimizing patient exposure with additional patients
- To evaluate early signs on the impact on mechanistic endpoints, to determine whether to continue to perform more complex evaluations on study participants and to aid future decisions

Recruitment will be paused once the first half of the planned patients are randomized. As this is a multicentre trial, some additional patients may have been randomized, and will continue to be followed in the study.

For study design and schedule of activities see also [Section 1.2](#) and [Section 1.3](#), respectively.

4.2 Scientific Rationale for Study Design

The patient population in this trial will be insufficiently controlled patients with T2DM with a documented diagnosis of NASH. This study is planned to enroll 63 patients, distributed into 21 patients in each group.

The trial has a 1:1:1 randomization scheme: lanifibranor or matching placebo as double-blinded treatment, and an open-label arm of lanifibranor in combination with empagliflozin (see [Figure 1](#)). The randomization will be stratified by HbA1c at Screening ($< 7.5\%$, $\geq 7.5\%$) and sex (Male, Female). Details will be provided in a dedicated randomization plan.

As described in [Section 2.1](#) the major purpose of this study is to confirm as primary objective the lanifibranor effect versus placebo on glycemic control observed in the NATIVE Phase 2b study. For that reason, a double-blind design was chosen for the lanifibranor and matching placebo arm to allow the assessment of the effect of lanifibranor versus placebo on HbA1c (primary endpoint) and other endpoints for glycemic control, liver tests, inflammatory markers, lipid parameters and body composition. The effects of lanifibranor versus placebo on liver fat content, hepatic fibrosis, NASH and liver biomarkers will also be explored.

This study is planned to randomize a population with at least 40% being male and at least 40% being female in order to ensure there is a representative NASH population, as NASH prevalence is slightly higher in males compared to females.

Another purpose of this study is to perform an initial assessment for any potential positive effect of the combination of lanifibranor with an SGLT2 inhibitor on the investigated efficacy parameters and to assess the tolerability of the combination treatment. For this purpose, an open-label design is deemed to be sufficient, for this proof-of-concept study.

There is a clear rationale to assess combination therapy with drugs that have a complementary mechanism of action in the complex disease pathophysiology of patients with NASH who also have T2DM.

SGLT2 inhibitors are approved for the treatment of T2DM. They have a beneficial effect on glycemic control, inflammation through their inhibition of renal glucose reabsorption and other pleiotropic metabolic effects, including weight loss. Lanifibranor, a pan-PPAR agonist, has beneficial effects on lipid and glucose metabolism, insulin resistance, as well as on steatohepatitis (hepatic injury and inflammation) and fibrosis. Overall, it is hypothesized that combination of lanifibranor with an SGLT2 inhibitor might have beneficial add-on effects on the above-mentioned parameters.

In addition, the combination of lanifibranor with an SGLT2 inhibitor may improve the safety and tolerability of the PPAR agonist (see [Section 2.1](#)). This study will allow evaluation of the effect of lanifibranor in combination with an SGLT2 inhibitor on body weight, peripheral edema, and anemia as safety endpoints.

To avoid confounding factors, the prohibited concomitant medications include those known to affect NASH, diabetes medications other than those specified in the protocol and other drugs with pharmacological activity on some of the same PPAR targets as lanifibranor (see [Section 6.10.3](#) and [Section 13.2](#) for additional information).

4.3 Justification for Dose

In the Phase 2b NATIVE study, in patients with highly active NASH, lanifibranor doses of 800 mg QD and 1200 mg QD over 24 weeks were well tolerated and showed the potential for improvement of the histological features of NASH as well as the accompanying metabolic,

glycemic and dyslipidemic abnormalities of the disease (see [Section 2.2](#)). At Week 24, mean change from baseline in body weight was comparable for lanifibranor 800 mg and 1200 mg QD with 2.4 kg and 2.7 kg, respectively. The subset of patients in the NATiVE study with diabetes showed improved glycemic control (HbA1c) at both lanifibranor doses. Lanifibranor was well tolerated with overall comparable safety findings for both doses while some adverse reactions were observed more frequently with the 1200 mg dose.

Besides, efficacy and safety of lanifibranor in NASH is assessing both lanifibranor 800 mg and 1200 mg QD in the Phase 3 NATiV3 study. This LEGEND study which a POC study design will assess lanifibranor 800 mg QD, which from Phase 2b study data has a comparable efficacy and safety profile with the higher 1200 mg dose in the subset of T2DM patients. The use of lanifibranor 800 mg QD in this POC study will allow appropriate endpoint assessments, at the same time minimizing any dose related adverse reactions.

All of this support the use of 800 mg as daily doses in this Phase 2 POC study to characterize metabolic and body weight/composition effects in patients with NASH and T2DM.

Empagliflozin 10 mg QD is the recommended starting dose for the treatment of adult patients with insufficiently controlled T2DM. Empagliflozin 10 mg QD was shown to result in similar HbA1c, body weight and SBP improvements as seen with empagliflozin 25 mg in Phase 3 studies in patients with T2DM. The safety profile of empagliflozin 10 mg was comparable to empagliflozin 25 mg QD across studies. The overall balance of efficacy and safety supports the use of empagliflozin 10 mg QD in this Phase 2 study in patients with NASH and T2DM [\[50\]\[56\]](#).

4.4 Data Monitoring Committee (DMC)

Due to the limited study duration (treatment duration of only 24 weeks), the short period of enrolment (estimated 6 months) and the limited number of subjects to be included (n=63), the Sponsor considers there is no need to have a DMC in this LEGEND study. Medical monitoring will be conducted by Investigators and medical monitors from the CRO/Sponsor and according to the measures detailed hereafter in [Section 8.2](#).

Experience during clinical trials conducted with lanifibranor is estimated to be around 940 subjects; among them, subjects with T2DM have been treated in the study 337.2.001, or in the phase 2 study NATiVE where an independent DMC was in place. In this study, lanifibranor was well tolerated and no serious adverse reactions were reported. For the ongoing phase 3 study NATiV3, an independent DMC will review the safety data from included patients (NASH diabetic and non-diabetic patients with fibrosis stages F2-F3) on a regular basis. Furthermore, the safety profile of empagliflozin, alone or in combination, in patients with T2DM has been characterized since its first marketing authorization in 2014. Information in terms of safety for the combination of lanifibranor and empagliflozin is lacking and will be obtained during this LEGEND clinical study where patients will be closely monitored and appropriate safety measures are part of the study procedures.

4.5 Study Procedures in Case of Crisis Situations

Additional precautions will be implemented in case of crisis situations (e.g., COVID-19 epidemic, political strife, natural disaster) to protect patient safety, particularly in the event that a patient is unable to physically come to the site for an on-site visit, come to the site to be dispensed IMP or if the patient contacts the site to report an AE/SAE that prevents their coming to the site.

If a defined crisis situation be declared, the relevant regulatory agencies/IRBs/ECs will be notified in parallel of these measures, as appropriate. These additional precautions remain in effect only until the local government, health authorities, and/or other regulatory bodies lift the ban on any lockdown/isolation requirements/guidelines.

In addition, the Sponsor has prepared plans that may be implemented as needed to provide secure delivery of the study drug to the patient at home, and to have at home patient assessments by a nurse or other health care provider as medically necessary.

These solutions can be applied depending on the Investigator's judgment of each case and the patient's agreement. The alternative solutions can be implemented in response to a crisis prior to the notification or submission to and approval of regulatory agencies and ECs.

Before implementing any of these options for a patient, the site will contact the patient to check whether he/she agrees with the off-site procedures and this will be documented in the patient's source.

Each investigational study site must comply with local public health rules, and temporary measures may be implemented immediately by the Sponsor to comply with local authority's requirements/restrictions.

In accordance with regulatory guidance, if planned on-site monitoring visits are no longer possible, the Sponsor reserves the right to use central and remote monitoring programs to maintain oversight of the clinical sites.

4.6 End of Treatment/Study Definitions

A patient is considered to have completed the treatment if he or she has finished his/her 24-week treatment period, and not completed if the patient prematurely discontinued his/her treatment before Week 24.

The follow-up (post last dose of study treatment) will be considered completed if the patient completed the last visit scheduled 4 weeks after last dose, as shown in the SoA, [Section 1.3](#).

If the randomized patient has died during trial, 'date of study completion' is the date of death.

The End of treatment and End of Study will be documented by the completion of the End of Treatment (EoT) form, respectively End of Study (EoS) form, collecting the reasons of treatment discontinuation and/or follow-up not completed.

5 STUDY POPULATION

5.1 Inclusion Criteria

For an eligible patient, all inclusion criteria must be answered “yes” at Screening and re-confirmed at time of randomization procedure and at Baseline (i.e., before treatment initiation). Laboratory tests taken during the screening period will be used to determine eligibility. If information cannot be confirmed in the medical record, responses will be obtained in a patient interview:

1. Able to understand the nature of the study, willing and able to comply with the study procedures and restrictions, and willing to provide informed consent obtained before any study-related activities
2. The patient is willing to continue on the study in case of moving or relocating to a different region/city where there would be no active study site
3. Able to communicate meaningfully with the Investigator and legally competent to provide written informed consent
4. Male or female, aged ≥ 18 years at the time of signing informed consent
5. Diagnosis of NASH
 - a. based on a historical (within 12 months prior to Screening) liver biopsy with a non-alcoholic fatty liver disease activity score (NAS) ≥ 4 with a score of one or more in each sub-component (steatosis, hepatocyte ballooning, lobular inflammation) and no documented cirrhosis in the last 12 months prior to Screening OR
 - b. NASH at Screening:
 - i. High Risk NASH defined as cT1 ≥ 875 ms assessed by LiverMultiScan® OR
 - ii. NASH defined as cT1 ≥ 825 ms assessed by LiverMultiScan® and hepatic fat content $\geq 10\%$ assessed by MRI-PDFF
6. HbA1c at screening ≥ 7.0 and $\leq 10.0\%$, on diet alone, or on metformin ($\geq 1,000$ mg/day), and/or DPP-IVi therapy. Doses have no qualitative change for 3 months prior to informed consent. These medicines will be continued at stable doses during the entire study.
7. Negative pregnancy test at Screening for females of childbearing potential or at least two-year post-menopausal. Women of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) have to use a highly effective method of contraception throughout the study and for one month after treatment discontinuation. Highly effective contraceptive methods are defined as follows: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (provided he is her sole sexual partner and he has received medical assessment of the surgical success), and true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient) whereas periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

5.2 Exclusion Criteria

For an eligible patient, all the following exclusion criteria must be answered “no” at Screening and re-confirmed at time of randomization procedure and at Baseline (i.e., before treatment initiation), except for laboratory tests for which Screening results are used for randomization:

Liver-related:

1. Documented causes of chronic liver disease other than NASH including, but not restricted to:
 - a. Viral hepatitis, documented with
 - i. Positive hepatitis B surface antigen (HBsAg)
 - ii. Positive hepatitis C virus RNA (tested for in case of known cured HCV infection or positive HCV serology at Screening). Patients with a history of HCV infection can be included if HCV PCR is negative since more than 3 years.
 - b. Drug-induced liver disease
 - c. Autoimmune hepatitis (See Exclusion criterion 50 for more information)
 - d. Wilson’s disease
 - e. Hemochromatosis
 - f. Primary biliary cholangitis
 - g. Primary sclerosing cholangitis
 - h. α 1-antitrypsin deficiency
2. Histologically documented liver cirrhosis (fibrosis stage F4), based on a historical biopsy (within 12 months prior to Screening); or diagnosis of cirrhosis at Screening based on clinic biochemical and imaging criteria (FibroScan[®] value confirmed ≥ 14 kPa and FIB-4 > 3.25 provided to the site by the central lab)
3. History or current diagnosis of HCC
4. History of or planned liver transplant
5. Documented history of HIV infection
6. ALT or AST $> 5 \times$ ULN at Screening
7. Abnormal liver function as defined by central laboratory evaluation of any of the following:
 - a. Albumin $<$ LLN
 - b. INR ≥ 1.3 (unless patient is on anticoagulants)
 - c. Total bilirubin level ≥ 1.5 mg/dL (25.7 μ mol/L) (Patients with a documented history of Gilbert’s syndrome can be enrolled if direct bilirubin is ≤ 0.45 mg/dL (7.7 μ mol/L))
8. Hemoglobin < 110 g/L (11 g/dL) for females and < 120 g/L (12 g/dL) for males
9. WBC $<$ LLN. A lower count is acceptable in patients with benign ethnic neutropenia, if considered to be clinical insignificant by the investigator
10. Platelet count $< 140,000/\mu$ L
11. ALP $> 2 \times$ ULN
12. Patient currently receiving any approved treatment for NASH or obesity
13. Current or recent history (< 5 years) of significant alcohol consumption, which is typically defined as higher than 30 g pure alcohol per day for men and as higher than 20 g pure alcohol per day for women (please also refer to [Section 13.1](#)). No binge drinking during the last year. Consuming 75 g pure alcohol (male), or 60 g pure alcohol (female), or more in about 2 hours

14. Administration of drugs known to produce hepatic steatosis in the 6 months prior to Screening (such as high-dose estrogens, methotrexate, tetracycline, or amiodarone) (see also [Section 13.2](#))

Diabetes related:

15. Diabetes mellitus other than type 2 (e.g., type 1, endocrinopathy, and genetic syndromes)
16. Diabetic ketoacidosis at Screening
17. Current treatment with GLP-1RA, insulin or sulfonylurea or treatment within the last 3 months prior to Screening
18. Patients on pioglitazone in the last 12 months prior to Screening
19. Patients on any of the following medications unless the patient has no qualitative change in doses of such agents for the past 3 months before Screening: metformin, DPP-IVi, thiazide or furosemide diuretics, beta-blockers, or other chronic medications with known adverse effects on glucose tolerance levels. Patients may be taking stable doses with no qualitative change of estrogens or other hormonal replacement therapy if the patient has been on these agents for the prior 3 months. Patients taking systemic glucocorticoids will be excluded.

Obesity related:

20. BMI > 45 kg/m² at Screening
21. Weight change > 5% in the 3 months prior to Screening
22. Introduction of an anti-obesity drug or restrictive bariatric surgery in the past 12 months prior to Screening or planned bariatric surgery through Week 24
23. Participation in an organized weight loss program (e.g., Weight Watchers[®], Jenny Craig[®]) in the past 6 months prior to Screening or planned participation through Week 24

Cardiovascular related:

24. History of (within 3 months prior to Screening) or current unstable cardiac dysrhythmias
25. NT-proBNP > 900 pg/mL
26. Unstable heart failure including:
 - a. New, or worsening symptoms of coronary heart disease within the past 3 months prior to Screening
 - b. Acute coronary syndrome within the past 6 months prior to Screening
 - c. Acute myocardial infarction in the past 3 months prior to Screening
 - d. Heart failure of New York Heart Association class (III-IV) or worsening congestive heart failure, or coronary artery intervention, within the past 6 months prior to Screening
27. Any other clinically significant cardiovascular event requiring hospitalization within 6 months before Screening
28. Uncontrolled hypertension at Screening (SBP > 160 mmHg and/or DBP > 100 mmHg (under conditions described in [Section 8.2.3.](#))
29. Stroke or transient ischemic attack within 6 months prior to Screening

General safety:

30. Significant systemic or major illnesses other than liver disease, (including but not limited to those listed above) and pulmonary disease, organ transplantation, serious psychiatric disease, that, in the opinion of the Investigator, would preclude treatment with lanifibranor and/or empagliflozin and/or adequate follow-up
31. Any condition which, in the Investigator's opinion, might jeopardize a patient's safety or compliance with the protocol, or warrants exclusion from the study

32. Cancer: Presence or history of malignancy within 5 years prior to Screening and/or active neoplasm at Screening. History of cancer is allowed only following 5 years of documented remission with the exception of resolved superficial non melanoma skin cancer
33. History of bladder disease and/or persistent hematuria within 6 months prior to Screening (transient hematuria which has been documented to have resolved within one week is acceptable), or current hematuria unless due to a urinary tract infection
34. Renal impairment measured as eGFR value < 60 mL/min as determined by Modification of Diet in Renal Disease [MDRD]
35. Total creatine kinase > 1.5 x ULN
36. History of pancreatitis, or confirmed pancreatic lipase > 1.3 x ULN, or > 2.0 x ULN upon repeated test within 3 weeks if on a DPP-IVi
37. Concomitant treatment with PPAR- α agonists (fibrates); if treatment with PPAR- α agonist is discontinued before the Baseline visit, it should be anticipated that triglycerides remain < 500 mg/dL during the study
38. Patients on Vitamin E at doses $\geq$ 400 IU/day; doses of $\geq$ 400 IU/day are allowed when no qualitative change in dose for 6 months prior to Screening
39. SARS-CoV-2 infections requiring hospitalization in the last 3 months or current SARS-CoV-2 infection confirmed by a validated test. (A SARS-CoV-2 test is not required for all patients at Screening visit but will be performed according to local standard practice). In case of previous asymptomatic or mild SAR-CoV-2 infection, the investigator should verify that abnormal lab tests due to COVID-19 are back to pre COVID-19 status before patient randomization.
40. Major surgery scheduled during the study
41. Known or suspected hypersensitivity to any of the ingredients of the IMPs (see [Table 1](#) to [Table 3](#))
42. Rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
43. Previous exposure to lanifibranor or empagliflozin
44. Osteopenia, or any other documented bone disease. Patient without documented osteopenia treated with vitamin D and/or calcium-based supplements for preventive reasons can be included.
45. Claustrophobia to a degree that prevents tolerance of MRI scanning procedure. Sedation is permitted at discretion of the Investigator.
46. 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
47. Present pregnancy/lactation or inability to adhere to adequate contraception in women of childbearing potential
48. Treatment with strong inducers or inhibitors of CYP2C8. When administered chronically, they should be replaced 3 months before Screening visit. If not administered chronically, they should be stopped at least 7 days before treatment initiation (See [Section 6.7](#) and [Section 13.2](#)). Prior administration of other drugs (i.e. weight loss treatments, chronically administered medications) as specified in [Section 13.2](#).
49. Participation in any clinical trial of an approved or non-approved investigational medicinal product/device within 3 months from Screening or five half-lives of the investigational drug from Screening, whichever is longer. Participation in non-interventional trials will be allowed with Sponsor approval.

Autoimmune related:

50. Any patient with a predisposition to autoimmune liver disease, including:
- a. Signs on previous liver biopsy suggestive of autoimmune liver disease (autoimmune hepatitis, immune cholangitis or overlap syndrome)
 - b. Family history of autoimmune liver disease in a first degree relative
 - c. Autoimmune thyroid disease:
 - i. Known diagnosis of autoimmune thyroid disease
 - ii. Thyroid replacement hormone unless documented for reason of primary thyroid insufficiency (e.g. due to thyroidectomy, radiation therapy, etc.)
 - iii. Positive autoimmune antibodies associated with abnormal thyroid function testing (TSH, T4 or free T3)
 - (3) Anti-thyroid peroxidase antibody (TPO)
 - (4) Anti-TSH receptor antibodies (TRAb)
 - d. History of or positive testing at screening for:
 - i. Anti-nuclear antibodies (ANA) at a dilution of 1:320 or greater
 - ii. Anti-mitochondrial antibodies (AMA)
 - iii. Anti-smooth muscle antibodies (ASMA) at a dilution of 1:320 or greater
 - iv. Anti-liver kidney microsomal type 1 antibodies (LKM1)
 - v. Anti-liver cytosol type 1 antibody (LC1)

5.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this trial may be re-screened once. In the event of re-screening, a new informed consent must be obtained, and a new patient number will be generated.

A Screening laboratory value, blood pressure and pulse measurements can be repeated based on the Investigator's discretion, if he/she believes that there is a good reason that the repeat test will be different than the original one. Only the laboratory value that needs to be repeated should be analyzed (and not the full set of parameters tested at Screening). In addition, a sample will have to be redrawn during the screening period in case a laboratory test that must be checked as part of an eligibility criterion could not be properly analyzed due to technical issues.

5.4 Strategies for Recruitment and Retention

Patient recruitment will be a key challenge in this study due to the challenge of identifying patients with T2DM diagnosed with NASH, limited number of experienced investigators, relatively low disease awareness and adequate imaging tools.

To support recruitment, sites will be proactively engaged and managed through protocol training and the monitoring of screening and recruitment activities. Working with sites will create site-specific recruitment plans with patient pathway roadmaps that highlight all routes for patient identification.

To support retention, patients, Principal Investigators (PIs), and study staff must be well educated on lanifibranor/empagliflozin and NASH trial requirements. Contact with study patients throughout treatment will help ensure the study stays top-of-mind, while also helping with retention and study compliance.

6 INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)

6.1 Study Treatments

Patients enrolled in this study will be randomized 1:1:1 to receive

- Lanifibranor 2 tablets of 400 mg (total dose 800 mg) QD for 24 weeks OR
- Matching placebo two tablets QD for 24 weeks OR
- Lanifibranor 2 tablets of 400 mg (total dose 800 mg) plus empagliflozin one tablet of 10 mg, QD for 24 weeks

6.2 Study Drug Description

Lanifibranor, a new chemical entity (4-[1-(1,3-benzothiazol-6-ylsulfonyl)-5-chloro- 1H-indol-2-yl]butanoic acid), is an almost white to light brown colored solid.

Structural formula, including relative and absolute stereochemistry:

- Molecular Formula: C₁₉H₁₅Cl N₂O₄S₂
- Molecular weight: 434.92
- Chirality: No asymmetric carbon
- Polymorphism: beta-form crystal

6.3 Description of IMPs

The details of the IMPs are given in [Table 1](#) to [Table 3](#).

Table 1: Characterization of lanifibranor tablets

Name / brand name	Lanifibranor
Strength / formulation	400 mg / film-coated tablet for oral use
Composition	
Packaging	Packaged in round plastic bottles made of high-density polyethylene (HDPE) with round plastic child-resistant tamper-evident screw cap of polypropylene (PP) fitted with a white low-density polyethylene (LDPE) capsule containing 2 g of silica gel. Two bottles of 30 tablets are placed into a carton to get a 4-week kit.
Manufacturer	
Storage	In original container, at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

Table 2: Characterization of placebo

Name / brand name	Placebo
Strength / formulation	NA / film-coated tablet for oral use
Composition	
Packaging	Packaged in round plastic bottles made of HDPE with round plastic child-resistant tamper-evident screw cap of PP fitted with a white LDPE capsule containing 2 g of silica gel. Two bottles of 30 tablets are placed into a carton to get a 4-weeks kit.
Manufacturer	
Storage	In original container, at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

Table 3: Characterization of empagliflozin tablets

Name / brand name	Empagliflozin / Jardiance
Strength / formulation	10 mg film-coated tablet for oral use
Composition	Tablet core: Lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, colloidal anhydrous silica (colloidal silicium dioxide), magnesium stearate Film coating: Hypromellose, titanium dioxide (E171), talc, Polyethylene glycol (Macrogol 400), iron oxide yellow (E172)
Packaging	The 4-weeks kit contains three child-proof wallets, each wallet containing one blister of 10 tablets.
Manufacturer	Boehringer Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim Pharma GmbH & Co. KG (tablets); Eurofins CDMO, AmatsiGroup SAS (kits)
Storage	In original container, at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

6.4 Dosing and Administration

Lanifibranor (two 400 mg tablets) or its matching placebo (two tablets) will be orally taken by patients once a day (QD) with breakfast. Empagliflozin (Jardiance, one 10 mg tablet) will also be orally taken by patients once a day together with breakfast. Patients receiving the combination of lanifibranor and empagliflozin will take all three tablets together with breakfast, whereby the order of tablets does not matter.

No lanifibranor or empagliflozin dose adjustment is allowed during the study. For temporary dose interruptions see [Section 7.3](#).

The first dose of IMP(s) will be administered on-site, under study staff supervision after each patient is shown and trained on how to use the IMP supply kits.

Because patients will attend all site visits while fasting, the study treatment will be administered at the investigational site with breakfast and the IMP intake will occur under study staff supervision and timing will be collected.

6.5 Preparation/Handling/Storage/Accountability

6.5.1 Acquisition and Accountability

Drug accountability of all patient kits received at site is the responsibility of the Investigator. Returned (used/partly used and/or unused), expired, or damaged patient kits can be stored at room temperature and must be stored separately from non-allocated patient kits.

An individual patient supply of study drugs may be shipped to the homes of study participants under the following conditions: 1) such clinical trial material shipment is permitted by local institution policy, 2) shipment is by a secure, trackable method and documentation of shipment and receipt is retained with the patient or pharmacy records, and 3) the material is shipped in packaging that monitors and records internal package temperature.

Clinical trial material exposed to temperature excursions should be replaced. In the patient's home, clinical trial material must be stored under the conditions stated on the container labels and the Pharmacy Study Manual. Unused material and empty containers should be returned to the study site to enable the pharmacy to maintain accountability records.

Non-allocated patient kits including expired or damaged products must be accounted as unused at the latest at closure of the trial site. The Interactive Web Response System (IWRS) will allocate patient kits to the patient at randomization and each dispensing visit, through assignment of treatment number. The patient kits will be dispensed to each patient as required according to treatment group. The correct patient kit number(s) must be dispensed to the patient.

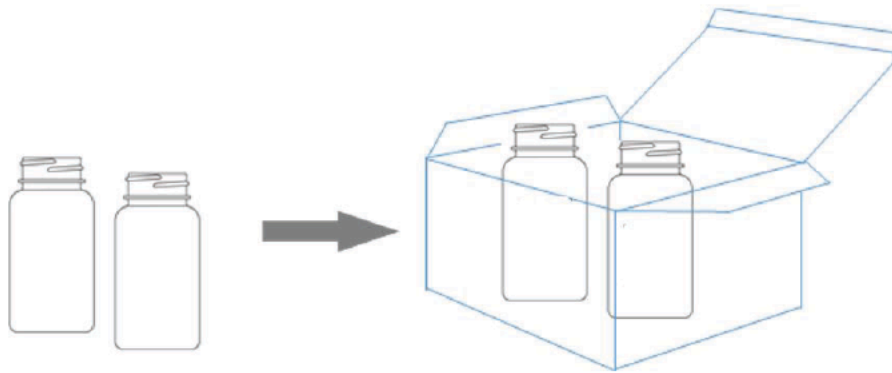
The IMPs must be accounted for at tablet level and either recorded as used/partly used, unused, or lost. Returned bottles must be sent for destruction to the contract development and manufacturing organization, thus may not be re-allocated to new patients. Patients must be instructed to return all used, partly used, and unused patient kits including empty packaging material at each dispensing visit and at EoT Visit. Destruction of patient kits and corresponding IMPs can be performed on an ongoing basis and will be done according to local procedures after accountability is completed and reconciled by the monitor.

Every effort must be made to have the IMPs returned to the contract development and manufacturing organization. However, in exceptional circumstances, the investigational site may request to destroy all or part of the IMPs. The destruction of IMPs should only be made with Sponsor's written authorization.

Any destruction of IMPs at site must be documented by a certificate of destruction, dated and signed by the appropriate site staff, allowing clear identification of the batches, quantities, kit number, and/or patient number. In addition, destruction of IMPs must be documented in the IWRS.

6.5.2 Formulation, Packaging and Labeling

The IMPs lanifibranor and matching placebo used in this clinical proof-of-concept trial are packaged in round plastic bottles made of HDPE with round plastic child-resistant tamper-evident screw cap of PP fitted with a white LDPE capsule containing 2 g of silica gel. Two bottles of 30 tablets are placed into a carton to get a 4-weeks kit (see [Figure 2](#)).

Figure 2: Drug supply kit of lanifibranor or matching placebo

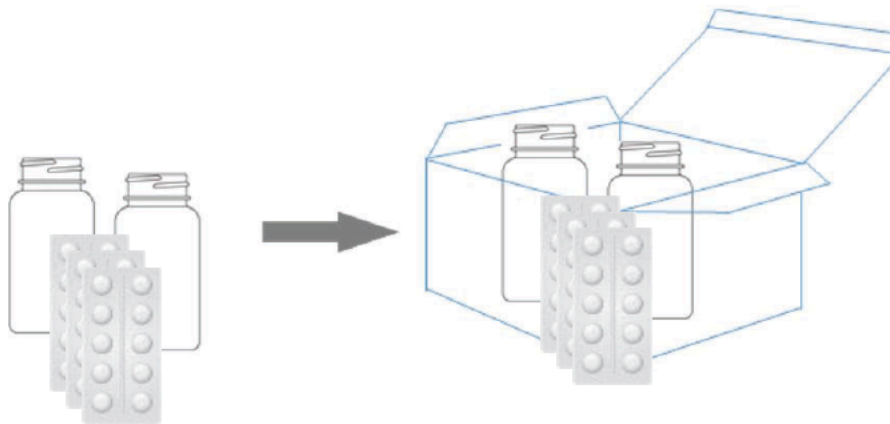
The kit design is based on a 4-week treatment and contains 2 bottles of 30 tablets. The daily dose (two tablets) will be composed either:

- 800-mg daily dose treatment kit: (L+L)
- Placebo daily dose treatment kit: (P+P).

Where P denotes the placebo tablet and L denotes the active (lanifibranor) tablet (400 mg).

The IMP empagliflozin (Jardiance) will be supplied in its commercially available form, i.e., three blisters of 10 tablets, also corresponding to a 4-week treatment. Each blister will be in a child-proof wallet.

The kit design is based on a 4-week treatment and contains two bottles of 30 tablets of lanifibranor 400 mg and three child-proof wallets containing 1 blister of 10 tablets of empagliflozin 10 mg (see [Figure 3](#)).

Figure 3: Drug supply kit of lanifibranor and empagliflozin

If the patient's study drug supply is lost, damaged or destroyed, the study center must be notified immediately.

6.5.3 Product Storage and Stability

Lanifibranor or matching placebo

The IMP should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). It should be stored in the original containers (i.e., bottles).

Provided the IMP is stored in the original container (see [Figure 2](#)) below 25°C and based on the results of the ongoing stability studies, the shelf life will be extended. Furthermore, the stability data over 6 months at 40°C/75% relative humidity demonstrate that temperature excursions (e.g., during shipment, storage) will not significantly affect the stability of lanifibranor 400-mg film-coated tablets.

Empagliflozin (Jardiance)

The IMP should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). It should be stored in the original containers (i.e., blisters) (see [Figure 3](#)).

6.6 Measures to Minimize Bias: Randomization and Blinding

Combination treatment with lanifibranor plus empagliflozin in this study will be open-label. Treatment assignments to lanifibranor alone or matching placebo in this study will be blinded to the patients, Investigator/study staff, and Sponsor's study team conducting the trial. Investigators will remain blinded to each patient's assigned study treatment (only lanifibranor alone or placebo) unless an unblinding is necessary.

In the event of a Quality Assurance audit, the auditor(s) will be allowed to access the unblinded study treatment records at the site(s) to verify that randomization has been done correctly.

The IWRS will be programmed with blind-breaking instructions. The study blind may be broken if, in the opinion of the Investigator, it is in the patient's best interest to know the study treatment assignment. Sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency. In this case, Sponsor must be notified within 24 hours after breaking the blind. The date and reason why the blind was broken must be recorded in the source documentation.

The randomization procedure will be performed as soon as all eligibility criteria can be confirmed during a phone call and at the latest 2 weeks before the Baseline visit, by the investigator using the IWRS system, to allow the treatment ordering and treatment shipment/delivery to the site, so that treatments are available at time of baseline visit for dispensation to patient.

Randomization will be stratified by 2 stratifying factors: HbA1c at Screening ($< 7.5\%$, $\geq 7.5\%$) and by sex (Male, Female), because these factors are considered important prognostic covariates. Randomization will not be stratified by center due to the high number of expected centers versus the low number of patients in this study. Details will be provided in a dedicated randomization plan.

Moreover, to ensure a representative NASH population, at least 40% males and 40% females will be randomized. Sites will be informed regularly, on an ongoing basis, of the number of males and females enrolled, and will be requested to stop the screening of males or females when the threshold of 40% will be reached.

6.7 Emergency Unblinding

Unblinding will be controlled through the randomization system. The code for a particular patient may be broken in a medical emergency if knowing the actual treatment would influence the treatment of the patient. Whenever a code is broken, the person breaking the code must print the Code Break Confirmation Notification generated by the IWRS, record the reason, and sign and date the document.

The Sponsor must be notified prior to unblinding, except in cases where an immediate need for unblinding exists for reasons of patient's safety at which time the Investigator can unblind the patient prior to notifying the Sponsor. However, the Investigator will have the final decision and unilateral right for unblinding in matters involving the safety of study participants.

When the code is broken, the treatment allocation will be accessible to the Investigator and the Sponsor Global Safety department. If IWRS is not accessible at the time of code break the IWRS helpdesk should be contacted. If the code has been broken, the patient must discontinue treatment with IMP and a treatment discontinuation session (i.e., EoT visit) must be completed in IWRS.

In some situations, the Investigator may unblind the study treatment if the appropriate future medical management of the patient necessitates knowledge of the current treatment. Although it is advantageous to retain the blind for all patients prior to final study analysis, when an AE may be assessed as related to the IMP, serious and unexpected or otherwise judged reportable on an expedited basis, it is recommended that the blind should be broken only for that specific patient, by the Sponsor, even if the Investigator has not broken the blinding. If the blind for a patient has been broken, the reason will be required to be fully documented in the source documents.

6.8 Treatment Compliance

Study medication compliance will be measured by drug accountability. The Investigator should maintain records of the delivery of study medication to the study center, the inventory at the study center, the use of study treatments for each patient, and the return of study treatments to the Sponsor. The Investigator shall be responsible for ensuring that the records adequately document that the patients were provided the doses specified in the protocol and that all study treatment received from the Sponsor is reconciled.

6.9 Overdose and Treatment

For this study, an overdose is defined as any intake of lanifibranor/matching placebo or empagliflozin (Jardiance) greater than:

- 2 tablets of lanifibranor/matching placebo per day in any study arm
- 2 tablets of empagliflozin (Jardiance) per day in the open-label arm

either reported spontaneously by the patient or noticed during drug accountability by the site.

In the event of an overdose, the Investigator/treating physician should:

- Contact the Medical Monitor immediately
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study treatment should be interrupted or whether the dose should be reduced
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdose

- Report the overdose (see [Section 8.4.2](#) for AE reporting instructions).

6.10 Concomitant Therapy

Any medication or vaccine that the patient is receiving at the time of the informed consent form (ICF) signature or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Details of any concomitant medication must be recorded at the first visit. Changes in concomitant medication must be recorded at each visit as they occur. The information collected for each concomitant medication includes trade name or generic name, indication, start date and stop date, or continuation. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

A summary of permitted/prohibited concomitant medication is provided in [Section 13.2](#).

6.10.1 Allowable Medications for Standard Care or Precautions

Treatment used for the underlying medical condition

Treatments are allowed within certain restrictions (described above and below) and provided there has been no qualitative change in dose (changes having minimal clinical impact like temporary cessation/change between class of drugs are allowed) **for at least 3 months before inclusion in the study.**

- **Type 2 diabetes:** Metformin, DPP-IVi.
- **Antiplatelets agents:** The antiplatelets agents (incl. low-dose aspirin, ticlopidine, prasugrel, ticagrelor) are allowed (but not clopidogrel).

In addition, statins are allowed to treat hyperlipidemia.

If a symptomatic medication is needed to treat AEs that may be related to IMP(s), the Investigator will inform the Principal Investigator about the concomitant medication given.

6.10.2 Rescue Medication

Rescue medication is defined as use of any new or additional antidiabetic medication, or increase in the dose of background antidiabetic medication above the baseline dose.

The use of rescue medication in case of hyperglycemia will be permitted during the trial but only if the criteria below are met:

- Week 1-12: Glucose level > 240 mg/dl (> 13.3 mmol/l) after an overnight fast, or > 400 mg/dl (> 22.2 mmol/l) in a randomly performed measurement
- Week 13-24: Glucose level > 200 mg/dl (> 11.1 mmol/l) after an overnight fast, or > 400 mg/dl (> 22.2 mmol/l) in a randomly performed measurement

The above results should be confirmed, meaning that there is a minimum of two measurements, at least one of which should be performed after an overnight fast and on a different day to the initial (overnight fast or random) measurement. If fasting glucose levels remain at > 240 mg/dl (> 13.3 mmol/l) or > 200 mg/dl (> 11.1 mmol/l), depending upon the week of treatment, despite the initiation of rescue medication (and no further glucose lowering effect is anticipated by the Investigator), the patient should be withdrawn from the study.

Sulfonylureas, metformin, DPP-IVi may all be given as rescue medication until the end of the trial. In case of no other clinical options, insulin can be used as rescue medication. Dosage will be left at the discretion of the Investigator. Rescue medication should be used in accordance with the local prescribing information, taking into account potential contraindications.

6.10.3 Prohibited Medications

Prohibited medications listed in this protocol or that meet the criteria of a prohibited medication by class or substrate may not be used in this study. If one of the following treatments is initiated during the study, a discussion should take place immediately between the site and the Sponsor to decide whether this new treatment is stopped or the patient withdrawn from the study treatment (for further details see [Section 13.2](#)):

- PPAR- γ agonists, PPAR- α agonists (fibrates)
- Orlistat or bupropion
- SGLT2 inhibitors, GLP-1 receptor agonists, sulfonylurea, insulin
- Vitamin E (α -tocopherol) at a dose ≥ 400 IU/day
- Treatment or anticipated initiation (for more than 14 consecutive days) of medications known to have an effect on NAFLD (e.g., oral corticosteroids > 5 mg/day of prednisone equivalent, methotrexate, tamoxifen, valproic acid, or amiodarone)
- Drugs approved for the treatment of NASH (in the event that such drugs are approved during the course of the study)
- Other investigational treatment whatever the indication
- CYP2C8 strong inducers (e.g. rifampin). However, if medically necessary, these drugs may be taken for a maximum duration of 3 weeks.
- CYP2C8 strong inhibitors, when systemically administered, i.e. by oral, intra-venous or intra-muscular route of administration (e.g. gemfibrozil, clopidogrel).
- Herbal supplements: Herbal preparations or vitamin supplements should not be started during the course of the study for treatment of glycaemic control or liver health, or if there is a known concern with liver injury.

7 STUDY TREATMENT DISCONTINUATION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1 Study Withdrawal

A patient may decide to withdraw consent for participation in the study at any time at his/her own request, without the need to justify. The Investigator also has the right to withdraw patients in case of safety concerns, protocol deviations or administrative reasons. Since an excessive rate of withdrawals can render the study uninterpretable, the unnecessary withdrawal of patients should be avoided.

Reasons for withdrawal include, but are not limited, to the following:

- Withdrawal of consent
- Withdrawal by subject (i.e., patient decision)
- Lost to follow-up, death
- Any AE, laboratory abnormality or illness which, in the opinion of the Investigator, indicates that continued treatment with study therapy and participation in the trial is not in the best interest of the subject
- Persisting hyperglycemia as defined in [Section 6.10.2](#) despite the initiation of rescue medication and no further glucose lowering effect is anticipated by the Investigator
- Major protocol deviation: e.g., lack of compliance with scheduled visits, non-compliance with study treatment, treatment with prohibited medication during the study
- Any deterioration in cardiac status
- Drug-induced Liver Injury (DILI) (see [Section 7.4](#))
- Investigator's decision for any other reason (e.g., occurrence of AEs which require specific management, see [Section 13.3](#))

If a patient discontinues the treatment, the Investigator will make reasonable efforts to obtain the reason and to perform a premature EOT visit as soon as possible, and another safety follow-up visit 4 weeks after the last dose of study drug. The reason and the date of withdrawal must be documented in the eCRF. If a patient discontinues the study for safety reasons, the outcome must be known.

In the case of withdrawal due to pregnancy (see [Section 7.2](#)), the patient will be followed until outcome, at least on a quarterly basis for follow-up evaluation of the pregnancy, fetus, delivery and new born. In the case of withdrawal due to an AE the patient will be followed until resolution of the AE, or until in the opinion of the Investigator the event has stabilized, and the patient is referred to the primary physician for appropriate management of the ongoing event. Reasonable efforts will be made to contact a patient who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health.

Health data and biological samples collected during the whole participation of the patient will be analyzed at the end of the study, and the biological samples stored up to one year after the completion of the study and destroyed.

7.2 Pregnancy

Lanifibranor should not be used during pregnancy. Females of childbearing potential must practice a consistent and proper use of a highly effective method of contraception throughout the study and for one month after treatment discontinuation.

Accepted highly effective contraceptive methods are defined as follows: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner (provided he is her sole sexual partner and he has received medical assessment of the surgical success), and true sexual abstinence (when this is in line with the preferred and usual lifestyle of the patient) whereas periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Females of childbearing potential are defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause.

A serum pregnancy test will be performed at Screening for women of childbearing potential. They should be asked about the potential for pregnancy at every scheduled study visit throughout the trial. In addition, a urine pregnancy test will be performed at every site visit throughout the trial and at any time during the study if pregnancy is suspected.

Female patients must be instructed to discontinue the study drug immediately and inform the Investigator as soon as possible once they are aware of being pregnant or suspect that they are pregnant during the study or within one month of the last dose of IMP. In case of pregnancy, the study treatment should be discontinued and the procedures detailed in [Section 8.5](#) should be followed.

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

All pregnancies of female partners of male patients exposed to study medication should also be reported using the corresponding pregnancy form, provided that pregnant female partners have signed an informed consent.

The Investigator will contact the patient at the expected time of delivery for follow-up.

The process that must be followed for reporting of the pregnancy, and of the pregnancy outcome and any associated AEs, is set out in [Section 8.5](#).

7.3 Temporary Interruption

Interruption of the IMP due to AEs is allowed as per the Investigator's discretion and medical judgment for a maximum of 15 days. If treatment is interrupted, whatever the cause is, the duration and reason for the interruption should be clearly documented.

For example, in case of peripheral edema, weight gain, or anemia, the IMP can be interrupted for a maximum of 15 days, based on the Investigator's discretion and medical judgment.

This temporary discontinuation of the IMP should occur only once during the 24-week treatment period, whenever necessary, including for the patient's convenience, taking into account that the IMP will have to be administered during the last 15 days before the Week 24 visit.

7.4 Drug-Induced Liver Injury Monitoring and Stopping Rules

The following guidelines describe DILI monitoring and stopping rules. Guidelines differ depending on whether pre-treatment ALT/AST are normal or elevated.

- Pre-treatment ALT/AST is the mean of two ALT/AST values taken at Screening and Baseline visits at least two weeks apart.
- In cases where there is a significant difference between the two values (an increase at least 50% at Baseline compared to Screening), a third measurement will be performed 2 weeks after starting treatment to decide if the patient can continue on study.
- Monitoring and stopping rules will depend on the patients mean pre-treatment ALT or AST values ($<1.5 \times \text{ULN}$ or $\geq 1.5 \times \text{ULN}$).

Emergence of $\text{ALP} \geq 2 \times \text{ULN}$ is not typical of NASH and should prompt an evaluation for an alternative etiology including DILI. For DILI suspicion monitoring, the local laboratory may be used in order to provide information more quickly to the Investigator who will then notify the Sponsor.

For patients with mean pre-treatment ALT or AST $<1.5 \times \text{ULN}$:

ALT or AST ≥ 3 but $< 5 \times \text{ULN}$: perform close monitoring.

If during retest:

- ALT or AST remains ≥ 3 but $< 5 \times \text{ULN}$: continue study treatment with monitoring once a week
- ALT or AST increases to $\geq 5 \times \text{ULN}$: discontinue study treatment

ALT or AST $\geq 5 \times \text{ULN}$: perform close monitoring

If during retest:

- ALT or AST remains $\geq 5 \times \text{ULN}$: discontinue study treatment
- ALT or AST decreases to $< 5 \times \text{ULN}$: continue study treatment with monitoring once a week

Discontinue study treatment immediately and initiate close monitoring in the following cases:

- ALT or AST $\geq 8 \times \text{ULN}$
- ALT or AST $\geq 5 \times \text{ULN}$ for more than 2 weeks
- ALT or AST $\geq 3 \times \text{ULN}$, and total bilirubin $\geq 2 \times \text{ULN}$ or $\text{INR} > 1.5$
- ALT or AST $\geq 3 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$)

For patients with mean pre-treatment ALT or AST $\geq 1.5 \times \text{ULN}$:

- ALT or AST $\geq 3 \times \text{Baseline}$ or $\geq 300 \text{ U/L}$ (whichever comes first): perform close monitoring

If during retest:

- ALT or AST remains $\geq 3 \times \text{Baseline}$ value but $< 300 \text{ U/L}$: continue study treatment with monitoring once a week

Discontinue study treatment immediately and initiate close monitoring in the following cases:

- ALT or AST $\geq 5 \times \text{Baseline}$ or $\geq 500 \text{ U/L}$ (whichever occurs first)

- ALT or AST $\geq 2 \times$ Baseline or ≥ 300 U/L (whichever occurs first), and total bilirubin $\geq 2 \times$ ULN or INR > 1.5
- ALT or AST $\geq 2 \times$ Baseline or ≥ 300 U/L (whichever occurs first) with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$)

Close monitoring includes repeat ALT, AST, ALP, INR, CK, eosinophils and total bilirubin within 48 to 72 hours; follow-up for symptoms and initiation of evaluation for competing etiologies of abnormal liver tests including testing for viral and autoimmune hepatitis.

SARS-CoV-2 infection will be evaluated by a validated test in patients under monitoring for potential DILI.

If a patient meets discontinuation criterion, continue monitoring until the lab elevations/symptoms have resolved or stabilized, or until a determination of a cause unrelated to the study drug is made.

7.5 Overall Study Termination

Both the Investigator and the Sponsor reserve the right to terminate the study at any time.

Especially at time of interim analysis, the Sponsor reserve the right to terminate the study should clear trends in study findings be observed. In that case, recruitment will not be re-initiated. Final analysis will then be performed including the additional patients that may have been randomized but not considered in the first half of the total randomized patients.

Should this become necessary, the procedures will be agreed after consultation between the two parties. In terminating the study, the Sponsor and the Principal Investigator will ensure that adequate consideration is given to the protection of the best interests of the patients. The Sponsor will also inform the regulatory authorities and the IRBs/IECs as specified by the applicable regulatory requirement(s).

Furthermore, the premature study discontinuation may occur due to other reasons including but not limited to Regulatory Authority decision, favourable opinion withdrawn by the IECs/IRBs, new scientific evidence becomes available during the study that could affect the patient's safety or change in the benefit risk analysis of the study.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

Efficacy assessments will be performed as scheduled (see SoA [Section 1.3](#)) according to calendar days.

Patients must attend all site visits in a fasting state. Fasting is defined as no intake of food or liquids, except for water. IMP and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood sampling has been performed. If the patient is not fasting as required, the patient must be called in for a retest within the visit window to have the fasting procedures done. Fasting is required for body weight/composition measurements and blood sampling (at least 8 hours), Velacur and FibroScan measurements (at least 3 hours), and LiverMultiScan measurements (at least 2 hours).

8.1.1 Clinical Laboratory Evaluations

Efficacy clinical laboratory parameters are described as endpoints in [Section 3.2.1](#) and [Section 3.2.2](#). Please refer to [Section 8.2.1](#), [Table 4](#) for the list of efficacy laboratory parameters evaluated in this study.

Clinical laboratory tests for hematology, total chemistry panel, and specialized chemistry will be performed according to the SoA in [Section 1.3](#). All blood samples will be collected after at least 8 hours fasting and before trial drug administration.

Further details about sample handling, shipment, and assay procedures can be found in the Investigator Site File (ISF) (Central Laboratory Manual).

This study will use central laboratories for clinical biology, and pharmacovigilance assessment processing and will provide laboratory information to the study centers according to the standard of the institution and regional requirements. However, the use of local laboratories is allowed in cases where initiation of IMPs or safety follow-up is time-sensitive and the central laboratory results will not be available in time, see also [Section 10.4](#). If the patient is not able to go to the study center due to extraordinary circumstances, as described in [Section 4.5](#), some assessments may be obtained at the patient's home by a trained clinical professional.





8.1.3 Body Weight

Body weight will be measured in a fasting state at visits shown in the SoA [Section 1.3](#). The body weight should be measured with an empty bladder, without shoes, and only wearing light clothing. Pockets should be emptied of heavy objects (i.e., keys, coins etc). Body weight has to be recorded with one decimal (kg or lb) and using the same digital scale throughout the study. The scale used in the study center will be calibrated according to the directions for use.

The Investigator should provide standard recommendations to all patients related to diet and exercise.

See also the Guideline for Adverse Events Requiring Specific Management in [Section 13.3](#).

8.1.4 Body Composition

MRI assessments will be performed at screening and Week 24 with the patient in fasted state (at least 2 hours after food or beverage).

MRI assessment for body composition will include but is not limited to: L3 visceral adipose tissue (VAT)/ subcutaneous adipose tissue (SAT) and thigh SAT (left and right)

L3 VAT/SAT

The cross-sectional area of VAT and the cross-sectional area of SAT are measured in the axial plane at the third lumbar vertebra (L3). 3D multi-echo gradient echo pulse sequences covering the abdomen are acquired and processed to provide an image of fat on which measurements are performed through the semi-automated delineation of the VAT and SAT areas. The output is measurements of VAT and SAT in cm^2 .

Thigh SAT

The cross-sectional area of SAT is measured in the thighs (each separately) in the axial plane at a location 20 cm inferior to the top of the femoral head. 3D multi-echo gradient echo pulse sequences covering the abdomen are acquired and processed to provide an image of fat on which measurement is performed through the semi-automated delineation of the SAT areas. The output is SAT in cm^2 .





8.2 Safety and Other Assessments

The timing and frequency of safety assessments are described in SoA [Section 1.3](#).

All visits are expected to be performed on site. However, the conduct of any phone visits instead of on-site visits will be based on the discretion of the investigator if medically necessary and if the patient cannot come to the site, e.g. due to pandemic period. Each phone visit must be documented in the eCRF. These phone visits will be limited, and not possible for screening, baseline and EOT or premature EOT visits.

During phone visit, the investigator or study staff conducting the visit will ask the patient to report all of the following safety information in the eCRF regarding:

- New AEs
- Resolution or worsening of any ongoing AEs
- Any change in diet or lifestyle
- Alcohol intake
- Any change in concomitant therapies (medication or dose)
- Any change in concomitant procedures
- For women of childbearing potential:
 - Any change of status (women no longer consider of childbearing potential)
 - Results of home pregnancy tests (if applicable)
 - Any change of contraceptive method
 - Any delay of menstruations
- Study drug dosing and study status:
 - Dates of any study drug interruption since the last dispensation and reason*
 - End of Treatment (if applicable): Date of last dose of study drug and reason*

* If the reason is related to an AE, collect all required details.

8.2.1 Safety Laboratory

Laboratory parameters to be evaluated in this study are listed in [Table 4](#).

Table 4: List of clinical laboratory parameters

	Parameter	Eligibility criterion	Efficacy endpoint	Safety parameter
SARS-Cov2 ¹	SARS-Cov2 PCR	X	--	X
Serology ²	HBsAg, anti-HCV, HIV1 & 2 antibodies	X	--	--
Autoimmunity	ANA, AMA, ASMA, LKM1, LC1, TPO, TRAb	X		
Hematology	Complete blood count: leukocytes (WBC) plus differential count (neutrophils, eosinophils, basophils, lymphocytes, monocytes), reticulocytes, platelets, erythrocytes, Hb, hematocrit, MCV, MCH, MCHC	X	--	X
Liver tests	ALT, AST, GGT, ALP, total and direct bilirubin	X	X	X
Serum chemistry	Electrolytes (Na, K, Ca, Ph, Bicar), CPK, pancreatic lipase, pancreatic amylase	X	--	X
Renal function	Serum creatinine, urea, albumin, eGFR	X	--	X
Coagulation	INR, aPTT	X	--	X
Cardiac test	NT-proBNP	X	--	X
Inflammatory parameters	hsCRP, IL-1beta, IL-6		X	X
Glycemic control	HbA1c, HOMA-IR, fasting insulin, FPG, fructosamine, adiponectin, ketones	X (HbA1c only)	X	X (FPG only)
Lipid parameters	Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides	--	X	X
Biomarkers related to NASH and fibrosis	Included but not limited to: TIMP-1, hyaluronic acid, P3NP, Pro-C3, cytokeratin CK18M30 and M65, MMP2, MMP9	--	exploratory	--
Serum iron biomarkers	Iron, ferritin, transferrin, iron binding capacity, vitamin B12, folate, LDH, haptoglobin	--	--	X
Pregnancy test	β-hCG (serum test at screening, urine test at all other visits)	X	--	X
Urinalysis	pH-value, glucose, protein, blood, nitrite, bilirubin, urobilinogen and leukocytes, blood, ketones	X	--	X

1 SARS-CoV-2 testing will be done according to local requirements at the time of each study visit.

- 2 If anti-HCV antibodies are detected, HCV RNA should be determined to differentiate past from current infection, only if no results of RNA dated from up to 3 years before screening are available on the medical history)

All blood samples will be collected after an overnight fast (at least 8 hours) and prior to study drug intake. Further details about sample handling, shipment, and assay procedures are provided in the Central Laboratory Manual which is located in the ISF.

This study uses central laboratories however, the use of local laboratories is allowed in cases where safety follow-up is time-sensitive and the central laboratory results will not be available in time. For the monitoring of liver tests and the autoimmune tests at screening the use of local laboratories is allowed.

8.2.2 SARS-CoV-2 Infection

Patients who are SARS-CoV-2 positive at Screening will not be enrolled in the study.

All patients will be asked if they have been tested or have symptoms of SARS-CoV-2 infection at Screening and throughout the study. Patients who have received a COVID vaccine have the date(s) of inoculation and type of the vaccine documents as previous treatment. Similarly, any COVID vaccine administered during the course of the study will be reported as concomitant treatment.

Patients enrolled in the study who are tested positive for COVID-19 will be evaluated by a physician, and will be managed according to standard of care

8.2.3 Vital Signs

Vital signs including SBP, DBP, and pulse rate will be performed at the visits specified in SoA [Section 1.3](#).

The method for measuring SBP and DBP needs to follow the standard clinical practice at site, but, as a minimum, the following guidelines must be adhered to:

- Avoid caffeine, smoking, and exercise at least 30 min prior to measuring the blood pressure
- Blood pressure should be measured in a sitting position, with the legs uncrossed, the back and arms supported
- The patient should be sitting for 5 min before the measurement is taken.

Three consecutive recordings will be taken and the average value will be noted in the source document and on the eCRF. The same arm and an appropriate cuff size should be used for blood pressure measurement at all visits.

8.2.4 Physical Examination and Waist Circumference

Physical examination

Physical examination will be performed at the visits specified in the SoA in [Section 1.3](#). Physical examination must be recorded in the patient's medical record and should include:

- Height at Screening
- General appearance
- Thyroid gland palpation

- Respiratory system
- Cardiovascular system
- Gastrointestinal system including mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Lymph node palpation
- Head, ears, eyes, nose, throat and neck.

Any abnormal, clinically significant findings at the Screening visit will be recorded as an ongoing medical condition present at Screening (on the Medical and Surgical History form).

Waist circumference

The waist circumference is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest and will be measured at the specified visits given in the SoA [Section 1.3](#).

One waist measurement must be performed and is measured in the horizontal plane with one decimal using a non-stretchable measuring tape. The same measuring tape should preferably be used throughout the study.

The patient should be measured in a standing position with an empty bladder and wearing light clothing. The patient should be standing, feet together with arms at the side, and waist accessible. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The patient should be asked to breathe normally.

8.2.5 Electrocardiogram

Standard 12-lead ECGs will be performed at the specified visits given in the SoA [Section 1.3](#).

The patient number, date of birth or age in case date of birth is not allowed, the date and actual time of the tracing, and the study code had to appear on each page of the tracing. The ECGs should be performed after patient has rested in supine position for 10 min.

Original ECG tracings together with a paper copy if ECG is printed on a thermal paper, appropriately signed, will be archived at the study site.

Additional unscheduled ECG recordings can be performed at the Investigator's discretion at other visits than the planned ECG visits. If unscheduled ECGs are recorded and submitted for central assessment, the reason should be documented and an AE reported (if applicable).

8.2.6 Dietary and Lifestyle Monitoring

Each patient's diet stability and exercise habits will be evaluated and documented at the specified visits given in the SoA [Section 1.3](#).





8.3 Adverse Events and Serious Adverse Events

8.3.1 Definitions of Adverse Event (AE)

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical study participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition
- Significant or unexpected worsening or exacerbation of the condition/indication under study
- A new condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study
- An overdose as defined on [Section 6.9](#)
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study drug or a concurrent medication

- Pre- or post-treatment events that occur as a result of protocol mandated procedures (e.g., invasive protocol defined procedures, modification of a patient's previous drug treatment regimen)

An AE does not include:

- Medical or surgical procedures (e.g., colonoscopy, biopsy). The medical condition that leads to the procedure is an AE
- Day to day fluctuations of pre-existing disease or conditions present or detected at the start of the study that overall do not worsen
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied unless more severe or more frequent than expected for the patient's condition
- Any previously-scheduled medical or surgical procedure that is known to the patient at Baseline should be documented in the physical examination section of the Baseline assessment in the source documents

8.3.2 Definition of Serious Adverse Event (SAE)

An SAE is any event that meets any of the following criteria:

- Results in death.
- Life-threatening: An AE is life-threatening if the patient was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that, if it had occurred in a more severe form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Hospitalization: AEs requiring hospitalization should be considered SAEs. Hospitalization for elective surgery, or for procedures planned prior to the patient providing informed consent, or routine clinical procedures that are not the result of an AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria. In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Disability/incapacity: an AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.
- Results in a congenital anomaly/birth defect.
- An important medical event: The event may not result in death, be life-threatening, or require hospitalization. However, the event will be considered an SAE when, based upon appropriate medical and scientific judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include: intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is defined as an untoward and unintended response to a study drug, which is not listed in the applicable product information, and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, is a medically important event, or is a congenital anomaly or birth defect, and is assessed as causally related to the IMP(s).

8.3.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities without clinical significance should not be recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis abnormalities) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE or SAE, as applicable. In addition, laboratory or other abnormal assessments (e.g. in ECGs, or vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in [Section 8.3.1](#) and [Section 8.3.2](#). If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased Hb).

8.3.5 Adverse Events of Special Interest (AESI)

In addition, from study drug first intake and until 30 days after last intake, the following AEs will be reported as AESI, within 7 days of awareness whenever possible, in order to collect further safety information whether or not these events are SAEs. Further details for the following events are provided in the Guideline for Adverse Events Requiring Specific Management included in [Section 13.3](#).

Hypoglycemia

Any hypoglycemia event will be reported as AESI in order to further document this potential risk, including signs, symptoms, circumstances, concomitant treatments and plasma glucose levels whenever available.

Hypoglycemia will be treated according to standard practice. In case of reoccurrence, specifically if the hypoglycemia is documented with low blood glucose level, recommendations will be given to the patient to consult the physician who prescribed him/her the antidiabetic treatment, for a potential adaptation of its dosage.

See also the Guideline for AEs Requiring Specific Management ([Section 13.3](#)).

Peripheral edema

Any peripheral edema event will be reported as AESI and recommendations are given to the Investigator through the Guideline for Adverse Events Requiring Specific Management in order to manage these AEs in a homogeneous manner across sites whenever possible.

Heart Failure

Any cardiac event will be reported as an AESI. The management of any heart failure is also described in the Guideline for AEs Requiring Specific Management ([Section 13.3](#)).

Ovulation resumption

As some patients with polycystic ovarian syndrome and premenopausal anovulatory women are also at risk for NASH and will be enrolled in this study, any ovulation resumption event will be reported as an AESI. This will also raise the Investigators' awareness about the potential pregnancy in these anovulatory women at Screening.

See also the Guideline for AEs Requiring Specific Management ([Section 13.3](#)).

Bone fractures

Any bone fracture will be reported as AESI in order to document all fractures by an X-ray report (if available). Bone fractures will be managed according to standard of care.

See also the Guideline for AEs Requiring Specific Management ([Section 13.3](#)).

Cholelithiasis

Any cholelithiasis event will be reported as an AESI. Cholelithiasis will be managed according to standard of care.

See also the Guideline for AEs Requiring Specific Management ([Section 13.3](#)).

Anemia

Any anemia will be reported as AESI and recommendations will be given to the Investigators through the Guideline for Adverse Events Requiring Specific Management in order to manage these AEs in a homogeneous manner across sites whenever possible.

Aminotransferase elevation

Any occurrence of increased aminotransferase (AST or ALT) will be reported as AESI(s) when ALT or AST $\geq 3 \times$ ULN for patients with Baseline ALT/AST $< 1.5 \times$ ULN or ALT or AST $\geq 3 \times$ pre-treatment for patients with Baseline ALT or AST $\geq 3 \times$ mean pre-treatment value or ≥ 300 IU/L if mean pre-treatment ALT or AST $\geq 1.5 \times$ ULN is confirmed 48 to 72 hours after its first occurrence. Recommendations will be given to Investigators through the Guideline for Adverse Events Requiring Specific Management in order to manage these AEs in a homogenous manner across sites whenever possible.

8.3.6 Classification of Adverse Events

All AEs will be assessed and documented by the Investigator according to the categories detailed below.

8.3.6.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in [Section 8.3.1](#) and [Section 8.3.2](#).

8.3.6.2 Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild:** Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

- **Moderate:** Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- **Severe:** Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

8.3.6.3 Causality

Investigators are required to systematically assess the causal relationship between the AEs and SAEs and the exposure to blinded treatment (blinded arms) and exposure to each of the IMPs (lanifibranor or empagliflozin (Jardiance) for open-label arm) using the following definitions:

- **Related:** The AE follows a reasonable temporal sequence to IMP administration, and it cannot be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications)
- **Not Related:** The AE does not follow a reasonable sequence from IMP administration, or it can be reasonably explained by the patient's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications)

8.3.6.4 AE Related Dosing Changes and Interruptions

The Investigator or designee will record the action taken for the AE in the eCRF. Actions taken will include:

- **Dose not changed:** The medication schedule was not changed because of the AE.
- **Drug interrupted:** The medication schedule was modified by temporarily terminating the prescribed regimen of medication, because of the AE.
- **Drug withdrawn:** The medication schedule was modified through termination of the prescribed regimen of medication, because of the AE.
- **Not applicable** (for example: the medication schedule had already been terminated, before onset of the AE).
- **Unknown**

8.3.6.5 Outcome

The outcome of the AE is to be documented as follows:

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

8.4 Documenting and Reporting Adverse Events

8.4.1 Time Period and Frequency for Event Assessment and Follow-Up

AE reporting begins at the time of the first study-related activity after the patient has signed the informed consent and continues until the last study visit. The events must be recorded in the applicable eCRF forms in a timely manner according to timelines below.

All AEs must be recorded by the Investigator and any designees on an AE form within the eCRF. The diagnosis should be reported if available. If no diagnosis is available, the Investigator or designee should record each sign and symptom as individual AEs using separate AE forms within the eCRF.

During the study all AEs and SAEs should be followed proactively by the Investigator until the event resolves or the condition stabilizes to a level acceptable to the Investigator, until the event is otherwise explained, or until the patient is lost to follow-up. At the time the patient's study participation ends, all ongoing AEs and SAEs should be evaluated for resolution. New or updated information will be recorded in the originally completed eCRF and the Investigator will submit any updated SAE information to the Sponsor within 24 hours of receipt of the information.

The Investigator must ensure that the recording of the worst-case severity and seriousness of an event is kept throughout the trial. Worsening of an unresolved AE must be reported as follow-up with reassessment of severity and/or seriousness of the event.

Queries or follow-up requests from the Sponsor must be responded to **within 14 calendar days** from the date of receipt of the request, unless otherwise specified in the follow-up request.

SAEs after end of trial: If the Investigator becomes aware of an SAE with a suspected causal relationship to the IMP(s) occurring to a patient after the patient has ended the trial, the Investigator should report this SAE to the Sponsor within the same timelines as for SAEs during the trial.

8.4.2 Adverse Event Reporting

At each visit, the Investigator, or delegate, will determine whether or not any AEs have occurred. Non leading questions such as "How are you feeling today?" or "Have you had any health concerns since your last visit?" should be used to elicit the patient to report any possible AEs. If any AEs have occurred, they will be recorded in the AE section of the eCRF and in the patient's source documents. If known, the diagnosis should be recorded, in preference to listing the individual signs and symptoms.

The Investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the patient to discontinue the study treatment/study.

AESIs will be specifically identified in the eCRF as part of AE and SAE reporting.

AESIs occurring after the first intake of IMP are reported to the sponsor through a specific AESI form, within 7 days of awareness whenever possible.

8.4.3 Serious Adverse Event Reporting

The SAE page will collect data surrounding the event (e.g., the nature of the symptom[s], time of onset in relation to initiation of therapy, duration, intensity, and whether or not therapy was interrupted or discontinued). The Investigator's assessment of the probable cause of the event will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic test reports, and procedures as well as all pertinent medical information related to the event will also be collected.

For each SAEs, an SAE page must be completed in addition to the AE page within the eCRF, immediately, without undue delay and no later than **within 24 hours of the Investigator's first knowledge of the SAE**. If several diagnoses occur at the same time or atypical symptoms are reported (for example, atypical jaundice associated with myocardial infarction), a separate form should be completed for each SAE.

8.5 Reporting of Pregnancies

Female patients of childbearing potential must practice a consistent and proper use of a highly effective method of contraception throughout the study and for one month after treatment discontinuation (see also [Section 7.2](#)).

Female patients must be instructed to notify the Investigator immediately if they become pregnant during the trial or within one month of the last dose of IMP. The Investigator must report any pregnancy in patients who have received IMP(s).

Pregnancies of female partners of male patients exposed to study medication within one month of the last dose of the male patient should also be reported using the corresponding pregnancy form, provided that pregnant female partners have signed an informed consent.

All pregnancies occurring during this study, in female patients or in the female partners of male patients will be recorded on a pregnancy page in the eCRF and a separate pregnancy notification page will be completed by the Investigator and sent to the Sponsor by fax or email within 24 hours of awareness.

The Investigator must follow the pregnancy and until the pregnancy outcome and the newborn infant is one month of age. The Investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the fetus and newborn infant to the Sponsor electronically (e.g., in PDF format), or by fax or email.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE on the appropriate AE or SAE page in the eCRF. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

8.6 Safety Reporting Oversight

In accordance with ICH GCP, the Sponsor (or designee) will inform Investigators of "findings that could affect adversely the safety of patients, impact the conduct of the trial, or alter the IEC/IRB's approval/favorable opinion to continue the trial".

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The Sponsor will

comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators. To support compliance with these requirements, the Investigator must provide requested information in a timely manner.

An Investigator who receives an Investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with the reference safety information (i.e., lanifibranor Investigator's Brochure [IB] and empagliflozin (Jardiance) EU Summary of Product Characteristics [SmPC]), and will notify the IRB/IEC, if appropriate, according to local requirements.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The following confirmatory one-sided hypotheses will be tested (let the mean treatment difference in HbA1c from baseline be defined as $\mu = \text{active treatment} - \text{placebo}$):

- Superiority of lanifibranor 800 mg alone versus placebo on change from baseline in HbA1c at Week 24
 - $H_{\text{Lani}, 0}: \mu \geq 0\%$ against $H_{\text{Lani}, 1}: \mu < 0\%$.
- Superiority of lanifibranor 800 mg plus empagliflozin versus placebo on change from baseline in HbA1c at Week 24
 - $H_{\text{Lani+E}, 0}: \mu \geq 0\%$ against $H_{\text{Lani+E}, 1}: \mu < 0\%$

Operationally the hypotheses will be evaluated by two-sided tests at the 5% significance level.

The hypotheses will be tested using a hierarchical fixed testing procedure. Lanifibranor alone will be compared to placebo at the 2-sided $\alpha = 0.05$ level (H_{Lani}), and, should this test pass, the combination will be tested at the same level ($H_{\text{Lani+E}}$).

9.2 Sample Size Determination

The sample size calculation was done by using SAS Version 9.4.

The sample size is based on the effect size of lanifibranor alone versus placebo (First test in the hierarchical procedure) on the change from baseline in HbA1c at Week 24, assuming an additive effect when empagliflozin is added to lanifibranor (Second test in the hierarchical procedure).

Based on recent results of the Phase 2 trial NATIVE (NCT03008070), in the subpopulation of NASH with T2DM, the mean (SD) absolute changes in HbA1c from baseline to Week 24 were -0.60 (0.54)% with lanifibranor 800 mg and +0.10 (0.53)% with placebo, leading to an adjusted mean difference [95% Confidence Interval] of -0.69% [-0.95; -0.42], obtained from an MMRM model.

Assuming an effect size of lanifibranor versus placebo of 0.60%, an expected SD of the change from baseline of 0.60%, a type I error of 0.05 (2-sided), an allocation ratio of 1:1, the required sample size per group is 21 patients with a power close to 90%.

The total sample size is then 63 patients overall, distributed in 21 patients in each group.

Table 5 shows the sensitivity of the power to a variety of scenarios of effect size (mean $\pm$ SD), with 2-sided alpha of 5%.

Table 5: Power depending on expected effect sizes

Mean difference between the two groups	Standard deviation	Power
0.4	0.5	76%
0.4	0.6	56%
0.5	0.5	89%
0.5	0.6	75%
0.5	0.7	62%
0.6	0.5	97%
0.6	0.6	89%*
0.6	0.7	77%
0.7	0.5	99%
0.7	0.6	96%
0.7	0.7	89%

* Effect size retained for the study

9.3 Populations for Analyses

The following populations are defined for the study:

FAS: The FAS consists of all randomized patients who received at least one dose of the assigned IMP, regardless of whether they prematurely discontinued randomized treatment or experienced any other intercurrent event.

‘Received at least one dose of the assigned IMP’ for the combination arm means that at least one dose of the two treatments empagliflozin and lanifibranor are to be received concomitantly, to be considered in the FAS.

IAS: The IAS consists of the first half of the planned randomized patients from the FAS.

Per Protocol Set (PPS): All patients in the FAS who do not have any major protocol deviations up to the time of their Week 24 efficacy assessment.

Patients with major deviations will be listed during the blind review and the reason for exclusion will be provided. Protocol deviations will be identified and classified at the data review meeting.

Safety Analysis Set (SAS): All patients who received at least one dose of IMP. Patients in the SAS will be analyzed and summarized based on the treatment they actually received.

‘Received at least one dose of IMP’ for the combination arm means that at least one dose of lanifibranor is to be received to be considered in the SAS.

The number of patients in each analysis set, and the number excluded and associated reasons will be summarized by treatment group and overall.

In addition, the following periods will be defined for the purpose of reporting.

Table 6: Definition of on study and on-treatment observations periods

Period	Description
On study	This observation period refers to the time interval during which the patient is assessed throughout the trial. The on study period is determined as: From the date of baseline visit until the earliest of: • End of Study date, scheduled to take place 4 weeks after last dose of study treatment, • Withdrawal of consent, • Last contact with the patient (for those who were lost to follow-up), • Death.
On-treatment	This observation period refers to the duration whereby patients are considered treated with the study treatment. For AEs, the on-treatment period is defined as: From the date of first dose of study treatment until the earliest of: • The last date of study treatment + 30 days, • The last date of the on study period (defined above). For all other assessments, the on-treatment period is defined as: From the date of first dose of study treatment until the last dose of study treatment + 3 days.
On-treatment without rescue medication	This observation period is a subset of the on-treatment observation period, where subjects are considered treated with study treatment, but have not initiated any rescue medications. Specifically, it starts at date of first dose of study treatment and the end date is the first date of any of the following: • The last dose of study treatment + 3 days • Initiation of rescue medication.

Data points collected outside an observation period will be treated as missing in the analysis. Baseline data will always be included in an observation period.

9.4 Statistical Analysis

9.4.1 General Approach

A SAP, covering the interim and final analyses, will include further technical descriptions of the analyses outlined within this section alongside more comprehensive details of all analyses to be performed for this study, and handling of missing values. Amendments to derivations and analyses may be implemented prior to unblinding of treatment allocations. Indeed, the SAP will be finalized before the interim analysis. Any deviations from this original statistical plan, after unblinding of treatment allocations at time of IA, will be described in an SAP amendment and/or justified in the clinical study report.

Baseline is defined as the last available assessment prior to or on the date of the Baseline visit for all patients, unless otherwise specified.

Continuous data will be summarized by treatment group using the number of observations available (n), mean, SD, minimum, quartile 1, median, quartile 3, and maximum. Categorical data will be summarized by treatment group using the count of patients and percentage.

In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from Baseline) by scheduled visits will be provided on observed cases (i.e., including only patients who have non-missing assessments at a given visit).

9.4.2 Analysis of the Primary Efficacy Endpoint

9.4.2.1 Estimands

In line with ICH E9 (R1) addendum, 5 attributes (treatment, population, endpoint, intercurrent events, and population-level summary) have been specified to translate the primary efficacy objective into treatment effects that are to be estimated (estimands).

1. The treatment conditions of interest are lanifibranor 800 mg administered daily (blinded), lanifibranor 800 mg administered daily plus empagliflozin (open-label), and are compared with placebo administered daily (blinded).
2. Adults with non-cirrhotic NASH and T2DM are the targeted patient population defined by list of in- and exclusion criteria.
3. The treatment effect is assessed at Week 24 by comparing absolute changes in HbA1c from baseline in each active arm versus placebo.
4. Intercurrent events are handled through a combination of treatment-policy strategy and hypothetical strategy (see [Table 7](#)).
5. The population-level summary of the treatment effect will be quantified by comparing at Week 24 the model-adjusted absolute changes in HbA1c from baseline (least squares mean), supported by the model-adjusted mean difference (of the absolute changes in HbA1c from baseline) between active arm compared to placebo, obtained through an MMRM model, adjusted on baseline HbA1c value detailed in [Section 9.4.2.2](#).

The constructed estimand assesses the expected glycemic benefit in a future population that results from subjects initiating treatment with lanifibranor or lanifibranor+empagliflozin excluding potential rescue medication(s).

Table 7: Approach for the primary endpoints, intercurrent events and estimands

Analysis	Population	Intercurrent events	Estimand strategy	Measures of intervention effect	1. Missing data imputation 2. Statistical model 3. Summary measures
Primary	Adults with non-cirrhotic NASH and T2DM defined by list of in- and exclusion criteria	Premature treatment discontinuation: - Due to safety reason - Not due to safety reason	Treatment policy The data collected at the follow-up visit (4 weeks after the intercurrent event) will be considered as per study design*.	Effect of the initially randomized treatments regardless of treatment discontinuation	1. Missing data at Week 24 not replaced (no explicit imputation) 2. MMRM model used to handle missingness under MAR assumption. 3. At Week 24: - model-adjusted absolute changes in HbA1c from baseline (least squares mean), - model-adjusted mean difference (of the absolute changes in HbA1c from baseline) between active arm compared to placebo, obtained through an MMRM model, adjusted on baseline HbA1c value and sex, autoregressive covariance matrix of order 1 with unequal variance (ARH(1))
		Intake of a rescue medication**	Hypothetical strategy*** The data at Week 24 (after the intercurrent event) will not be considered, even if collected, and set to missing.	Effect of the initially randomized treatments had all patients remained on their randomized treatment throughout the study, i.e., effect assuming patients did not initiate rescue medication	
		Low compliance to treatment	Treatment policy The data at Week 24 (after the intercurrent event) will be used.	Effect of the initially randomized treatments regardless of adherence to randomized treatment	
* As per study design, the patient will be asked to come for a follow-up safety visit 4 weeks after the premature treatment discontinuation, and will then be withdrawn from the study. ** Introduction of a new antidiabetic drug (patients without antidiabetics at baseline), and/or dosing increase of the antidiabetics ongoing at Baseline *** The hypothetical estimand assesses the glycemic benefit a future subject is expected to achieve if initiating treatment with lanifibranor or lanifibranor+empagliflozin excluding potential rescue medication(s). Accordingly, only data collected prior to initiation of rescue medication will be used to draw inference. This will avoid confounding from rescue medication.					

Table 7: Approach for the primary endpoints, intercurrent events and estimands

Analysis	Population	Intercurrent events	Estimand strategy	Measures of intervention effect	1. Missing data imputation 2. Statistical model 3. Summary measures
Supplementary 1 (Statistical methodology changed)	As primary	As primary	As primary		1. As primary 2. As primary 3. Using AR(1) or unstructured variance covariance matrix (UN) rather than ARH(1)
Supplementary 2 (Estimand strategy changed: treatment-policy for rescue medications)	As primary	Premature treatment discontinuation: - Due to safety reason - Not due to safety reason	As primary	As primary	As primary
		Intake of a rescue medication	Treatment policy The data at Week 24 (after the intercurrent event) will be used.	Effect of the initially randomized treatments regardless of initiation of rescue medication	
		Low compliance to treatment	As primary	As primary	
This estimand assesses the expected glycemic benefit in a future population that results from subjects initiating treatment with lanifibranor or lanifibranor+empagliflozin including potential rescue medication(s).					
This estimand is based on FAS using the on study period (see Section 9.3).					
Supplementary 3 (Estimand strategy changed: hypothetical strategy for premature discontinuation)	As primary	Premature treatment discontinuation: - Due to safety reason - Not due to safety reason	Hypothetical strategy The data at Week 24 (after the intercurrent event) will be set to missing.		As primary
		Intake of a rescue medication	As primary	As primary	
		Low compliance to treatment	As primary	As primary	
The hypothetical estimand assesses the glycemic benefit a future subject is expected to achieve if initiating and continuing treatment with lanifibranor or lanifibranor+empagliflozin. Accordingly, only data collected prior to discontinuation of trial product or initiation of rescue medication will be used to draw inference.					

Table 7: Approach for the primary endpoints, intercurrent events and estimands

Analysis	Population	Intercurrent events	Estimand strategy	Measures of intervention effect	1. Missing data imputation 2. Statistical model 3. Summary measures
This estimand is based on FAS using the on-treatment without rescue medication period (see Section 9.3).					
Supplementary 4 (Missing data imputation and Statistical model changed, under MAR assumption)	As primary	Premature treatment discontinuation: - Due to safety reason - Not due to safety reason	As primary	As primary	1. Missing data will be multiply imputed under a ‘missing at random (MAR)’ assumption: borrow information from patients in the same treatment arm. 2. 1000 complete datasets will be generated. For every completed data set, analysis of covariance (ANCOVA) model. 3. At Week 24: - model-adjusted absolute changes in HbA1c from baseline (least squares mean), - model-adjusted mean difference (of the absolute changes in HbA1c from baseline) between active arm compared to placebo, obtained through an ANCOVA model, adjusted on baseline HbA1c value and sex. Overall inference is obtained by applying Rubin’s rules on the estimates obtained from every imputed/completed data set.
		Intake of a rescue medication			
		Low compliance to treatment			
Each supplementary analysis only modifies one aspect of the primary analysis at a time, in line with the addendum ICH E9 R1 recommendations. Here, the statistical methodology is changed.					

Table 7: Approach for the primary endpoints, intercurrent events and estimands

Analysis	Population	Intercurrent events	Estimand strategy	Measures of intervention effect	1. Missing data imputation 2. Statistical model 3. Summary measures
Supplementary 5 (Missing data imputation and Statistical model changed, under a pattern mixture model)	As primary	Premature treatment discontinuation	Hypothetical strategy The data at Week 24 (after the intercurrent event) will be missing.	As primary	As Supplementary 4
		- Due to safety reason	Data considered not missing at random (nMAR), missing data at Week 24 borrowed from placebo arm patients.		
		- Not due to safety reason	Data considered MAR, missing data at Week 24 borrowed from patients in the same treatment arm.		
		Intake of a rescue medication	Hypothetical strategy Data considered not missing at random (nMAR), missing data at Week 24 borrowed from placebo arm patients.		
		Low compliance to treatment	As primary		
		In this analysis only missing data at week 24 for subjects who discontinue treatment due to safety reason (treatment-related AE) will be imputed to resemble the distribution of the week 24 values observed in the placebo treatment arm.			
Supplementary 6 (Treatment arm changed)	As primary	As primary	As primary	As primary	As primary, but using actual treatment received rather than randomized treatment
Supplementary 7 (Covariates added)	As primary	As primary	As primary	As primary	As primary, but adding some baseline characteristics as covariate. Details will be added in the SAP

Table 7: Approach for the primary endpoints, intercurrent events and estimands

Analysis	Population	Intercurrent events	Estimand strategy	Measures of intervention effect	1. Missing data imputation 2. Statistical model 3. Summary measures
Supplementary 8 (Per protocol)	Per protocol population (see Section 9.3)	As primary	As primary	As primary	As primary

9.4.2.2 Statistical Methodology

The primary endpoint ‘Absolute change in HbA1c from baseline at Week 24 (%)’ will be calculated for each patient as: HbA1c value at Week 24 – HbA1c value at Baseline, see Baseline definition in [Section 9.4.1](#).

Descriptive analyses:

HbA1c, absolute and relative changes in HbA1c will be summarized at Baseline and at each post-treatment visit as defined in [Section 9.4.1](#). Shift table between normal and abnormal values at Baseline and Week 24 will also be provided. Line plots of means with whiskers extending to the upper and lower bounds of the 95% CI over time will be displayed from baseline to Week 28, at each measured visit, for raw data, absolute and relative changes from baseline.

Evaluation of treatment effect using MMRM:

To assess the superiority of each active arm versus placebo on absolute change in HbA1c from Baseline, the primary analysis for the primary estimand will be a MMRM (see [Table 7](#)).

The model will include all post-baseline HbA1c measurements collected at scheduled visits as dependent variables, excluding HbA1c measurements collected post-rescue medication.

The independent effects included in the model will be treatment group, time, treatment*time interaction as fixed effects, baseline outcome value and sex as covariates and the patient effect as a random effect.

Treatment effect on absolute change in HbA1c from baseline at Week 24 between each active arm and placebo will be estimated using this MMRM model with the contrast of interest at Week 24.

The treatment effect will be quantified by providing the least squares mean (LSMean) treatment estimates of the three arms, treatment differences (lanifibranor 800 mg alone – placebo and lanifibranor 800 mg + empagliflozin - placebo), Standard Error (SE) and 95%CI. Corresponding two-sided p-value comparing each active group to placebo will be given at Week 24.

In the MMRM model, an autoregressive covariance matrix of order 1 with unequal variance (ARH(1)) will be considered. It is assumed that the variance at each time point is not the same and tends to increase due to an increase over time of withdrawals and treatment responders. It is also assumed that two consecutive measures are correlated (r) and the correlation decreases with the time interval between visits. This structure is more flexible than AR(1) because variances can be unequal but is consuming less degrees of freedom than the fully unstructured variance covariance matrix (UN).

To investigate the sensitivity of the primary analysis results, supplementary analyses will be performed for the primary estimand (see [Table 7](#)). Detailed description of statistical methods (multiple imputation of missing data, ANCOVA methodology, Rubin’s methods...) will be detailed in the SAP.

9.4.2.3 Missing Data Considerations at Week 24

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. This analysis assumes that the missing data mechanism is MAR. Since a low number of missing data is expected for the main endpoint in this rather short study, this assumption is deemed to be plausible for the main estimation.

Indeed, the proportion of missing data is expected to be low based on the NATIVE Phase 2 trial (NCT03008070), and missing data will mainly be due to withdrawal from trial (without follow-up visit performed) or lost to follow-up, or initiation of rescue medication.

Under this assumption MAR, the statistical behaviour of the missing data (given the observed responses and model fixed effects and covariates) is assumed to be the same as the observed data, i.e. the method provides an unbiased estimate of the treatment effect that would have been observed if all patients had continued on-treatment for the full study duration.

The supplementary analyses (see [Table 7](#)) will evaluate the sensitivity of the results due to the impact of missing data.

The number of missing HbA1c data at Week 24 and the reason for missingness will be reviewed during the trial, and additional analyses may be planned in the SAP if needed.

9.4.3 Analysis of the Secondary [REDACTED] Endpoints

For quantitative variables, descriptive analyses as defined in [Section 9.4.1](#) will be conducted. To assess the treatment effect, similar analyses as those described for the primary endpoint will be conducted, using MMRM models, including additionally the stratifying factors HbA1c at Screening ($< 7.5\%$, $\geq 7.5\%$), as covariates in the model.

For qualitative/categorical variables, descriptive analyses as defined in [Section 9.4.1](#) will be conducted. To assess the treatment effect for categorical secondary endpoints, categorical outcome measures will be compared using Cochran–Mantel–Haenszel (CMH) test adjusted for the 2 stratifying factors, separately between each active arm and placebo.

No multiplicity adjustment when testing for treatment effect on secondary/exploratory endpoints will be done. P-values will be considered exploratory.

Additional details will be described in the SAP.

9.4.4 Safety Analyses

All safety analyses will be performed on the SAS. Safety assessments defined in [Section 8.2](#) and [8.3](#) will be reported descriptively, using the on-treatment period.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and classified as either non- treatment-emergent AEs (pre-treatment AEs, post-treatment AEs) or treatment-emergent AEs (TEAEs) as follows:

- Non-Treatment-Emergent AE (NTEAE), i.e., Pre-treatment AEs are events that start prior to the date of first dose of study treatment.
- Post-Treatment-Emergent AEs (PTEAE) are events that start more than 30 days after stop of study treatment.
- TEAEs are events with start date on or after the date of first dose of study treatment and up to 30 days after date of last dose of study treatment, and events with start date prior to the date of first dose of study treatment whose severity worsens on or after the date of first dose of study treatment.

An overview table will summarize the number and percentage of patients with at least one NTEAE, PTEAE, and at least one of the following TEAEs: any TEAE; any TEAE by severity (mild, moderate, severe); treatment-related TEAE; TEAE leading to treatment discontinuation; treatment-related TEAE leading to discontinuation; SAE; treatment-related SAE; SAE leading to death; treatment-related SAE leading to death; SAE leading to treatment discontinuation.

The number and percentage of patients reporting each TEAE and the absolute count of TEAEs will be summarized by system organ class (SOC) and preferred term (PT), overall and by sex. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending frequency overall total.

Graphical representation of the most frequent AE will be displayed.

NTEAE, TEAE and PTEAE will be listed.

No statistical comparisons of AEs between treatment groups will be performed.

Laboratory quantitative data, as well as **vital signs**, **ECG** data including raw values, absolute and relative changes from baseline, will be summarized overall and by sex as defined in [Section 9.4.1](#) over time by treatment group. Line plots of means with whiskers extending to the upper and lower bounds of the 95% CI over time will be also displayed from baseline to Week 28, at each measured visit.

For other details on summaries of safety assessments, please refer to the SAP.

9.4.5 Baseline Descriptive Statistics

Baseline data and patient characteristics will be summarized on the IAS (interim analysis), FAS and PPS (final analysis), by treatment group, and overall. Medical history will be coded using MedDRA dictionary, and will be summarized by SOC and PT names in each treatment group and overall. Prior and concomitant medications will be coded using WHO Drug dictionary, and will be summarized by SOC and PT names in each treatment group and overall.

9.4.6 Planned Interim Analyses

An interim analysis will be conducted once approximately half of the planned patients will be randomized, and have either completed the 24-week treatment period or prematurely discontinued from treatment earlier, that will constitute the Interim Analysis Set (IAS).

No alpha (type I error) adjustment will be considered for the interim analysis, i.e. still considering 0.05 (2-sided), this study being an exploratory proof-of-concept study.

Recruitment will be paused once the first half of the patients are randomized. Once the interim analysis results will be available, recruitment may be re-initiated, or, should clear trends in study findings be observed*, recruitment may be stopped thereby minimizing patient exposure with additional patients.

* Clear trends such as significantly positive results, negative results or absence of discernable trends will be defined by the Sponsor during review/interpretation of interim results, based on results regarding the primary objective and some secondary objectives.

In general, endpoints will be analyzed using the same approach as described in [Sections 9.4.1](#), [9.4.2](#) and [9.4.3](#). Safety assessments will be reported descriptively using the same approach as described in [Section 9.4.4](#).

At time of the interim analysis, a snapshot of the database will be cleaned and locked for interim analysis. The analysis will be performed using all data available at time of the snapshot, in the subpopulation of patients belonging to the IAS.

Prior to the database lock for interim analysis, a data integrity plan will be produced to describe the unblinding process restricted to patients from the IAS, and will describe, among the patients not from the IAS and followed during the study, how the blinding is maintained, how integrity of the trial will be protected and to ensure continued adherence to treatment and trial retention.

The SAP will detail all analyses to be performed.

9.4.7 Subgroup Analyses

Subgroups will include but not limited to: HbA1c at screening ($< 7.5\%$, $\geq 7.5\%$) and sex (Male, Female). For details on subgroup analyses, please refer to the SAP.



10 REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Sponsor or its representatives will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, for clinical studies: European Directive 2001/20/CE and translation into national laws, European Regulation 536/2014 (if applicable), and all other applicable local regulations

10.1 Informed Consent Process

Prior to starting participation in the study, each patient will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Patients will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Patients will be given an opportunity to ask questions about the study prior to providing consent for participation.

Patients will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable. The patient will be given a copy of the signed ICF, and the original will be maintained with the patient's records.

Patients must be re-consented to the most current version of the ICF(s) approved by IRB/EC during their participation in the study.

10.2 Confidentiality and Privacy

Patients will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Patient and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual patients or Investigators will be redacted according to applicable laws and regulations.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law and applicable local regulations. The level of disclosure must also be explained to the patient. The patient must also be informed that his/her medical records may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

10.3 Indemnity/Insurance

All patients participating in the study will have insurance coverage arranged by the Sponsor, which is in line with applicable laws and/or regulations.

10.4 Central and Local Laboratory Use

As described in [Section 1.3](#) and in [Section 8.1.1](#), central laboratories will be used for clinical biology assessments.

However, in the interest of patient safety, local laboratories may be used for some assessments in cases where initiation of IMP(s) or safety follow-up is time-sensitive and the central laboratory results will not be available in time.

For the monitoring of liver tests and the autoimmune tests at screening the use of local laboratories is allowed.

10.5 Clinical Monitoring and Audits

The Investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or its representative may conduct audits either remotely or in-person at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of CRFs with source documents. Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator (or designee) should contact the Sponsor/CRO immediately if this occurs. All medical records (progress notes) must be available for audit. The Investigator must agree to participate with audits conducted at a convenient time in a reasonable manner.

10.6 Quality Assurance and Quality Control

The following data quality steps will be implemented:

- All patient data relating to the study will be recorded on eCRF unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Pre-defined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a Risk Management Plan. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.7 Data Handling and Record Keeping

All individual, patient-specific study data will be entered, in a timely fashion via the eCRF, into a validated system in compliance with US 21 CFR Part 11 and EU EMA Guideline on computerized systems and electronic data in clinical trials. All data generated from external sources (e.g., central laboratory, pharmacodynamics, ECG central readers) and transmitted to the Sponsor or designee electronically will be integrated with the patient's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each patient who signs an ICF and undergoes any Screening procedures, according to the eCRF completion instructions. The Sponsor, or designee, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study site staff.

The Investigator will sign and date the eCRF via the electronic data capture (EDC) system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, the data queries, and the site notifications.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents, including records of patients, source documents, CRFs, and the IMP(s) inventory, must be kept on file.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) (US site) or in the study site archive for at least 5 years after the end of the study (UK site) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.8 Protocol Deviations

A protocol deviation is any non-compliance with the clinical trial protocol (ref. ICH GCP). The non-compliance may be either on the part of the patient, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The site Investigator is responsible for knowing and adhering to the reviewing IEC/IRB requirements.

Protocol deviations will be identified and classified through the blind review as ‘leading to exclusion of the patient from the PPS’ or not.

Only patients with deviations ‘leading to exclusion from the PPS’ will be discussed in the Clinical Study Report (CSR).

The status of protocol deviations will be defined by the Sponsor before database lock by judging the importance of the influence of the deviations upon the primary efficacy endpoint.

10.9 Publication and Data Sharing Policy

All relevant data and information will be reported in a CSR submitted to the Investigator coordinators for review, comments, and signature. The final CSR will be used for further development of the IMP and regulatory submissions.

No information provided by the Sponsor to the Investigators for the purposes of performing the study, will be published, or passed on to a third party, without prior written approval by the Sponsor.

The Investigators will have full access to all of the study data and will take complete responsibility for the integrity of the data and the relevance of the data analysis and reporting.

The study will be registered by the Sponsor in the ClinicalTrials.gov database and in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT). Summary of results will be made publicly available through the European Union Clinical Trials Register. The PI or anyone else working on the study will submit all proposed publications, papers, abstracts, or other written materials or an outline of any proposed oral presentation related to the study to Sponsor at least one month prior to (i) submission of such written materials for publication, or (ii) any proposed oral disclosure to a third party. Sponsor shall have the right to comment on such written material/outline and to take any necessary action to protect its intellectual property; the PI, in determining the final form of disclosure, shall consider such comments in good faith. Notwithstanding any of the above, the PI or anyone else working on the study may not include any confidential information unrelated to the study in any such publication or disclosure.

The Investigator will provide the Sponsor with complete test results and all data derived from the study in accordance with the protocol.

Only the Sponsor and its authorized contractor may make information obtained during the study available to regulatory agencies, except as required by regulation.

Patients will be informed of the overall outcome of the study by their PI or will be invited to a meeting arranged by the Sponsor or patient organization where the trial results will be presented.

10.10 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

11 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	21/12/2021	Initial version	
2.0	25/01/2022	- Clarification regarding prohibited medication: treatment with substrates of CYP2B6 and CYP2C8, CYP2C8 strong inducers and CYP2C8 strong inhibitors excluded. - Modification in study parameters: eGFR no-longer BSA normalized - Clarification regarding SAR-CoV-2 infection - Clarification of rational, background and study design - Clarification regarding randomization process	- Driven by the preliminary results of the Drug-Drug Interaction study 337HVPK21014 - In Renal Impairment guidances, FDA and EMA recommend expressing GFR in mL/mn because renal clearance of a drug is proportional to individual GFR and not to BSA-standardized GFR. - General protocol clarification
2.1 FR	18/03/2022	Version submitted only to French CA - Update of exclusion criteria N°36 with patient with history of pancreatitis excluded - Update of the guideline for Adverse Events requiring specific management related to hypoglycemia to include blood glucose monitoring in accordance with local guidelines/clinical practice	- Aligned with empagliflozin labelling (special warnings and precautions) - To ensure appropriate clinical monitoring for patients with persisting hypoglycemia
3.0	08/04/2021	Version including changes submitted to French CA as well as other changes - Clarification regarding stratifying factors in the randomization process - Addition of a randomization procedure before Baseline visit, allowing the treatment ordering and treatment shipment/delivery to the site. - Update of patient individual study duration - Update of exclusion criteria N°1 - Update of exclusion criteria N°2	- General protocol clarification - Addition of randomization procedure to be in line with the study IMP supply strategy. - Due to addition of randomization procedure - Clarification of the criteria - Clarification of the imaging criteria for the diagnosis of cirrhosis

Version	Date	Description of Change	Brief Rationale
		- Addition of the possibility to perform phone call visit if medically needed [REDACTED] - Update of the AESI reporting period - Update of the drug-Induced Liver Injury Monitoring and Stopping Rules - Update of the guideline for Adverse Events requiring specific management related to Anemia, heart failure, Aminotransferase elevation, Bone fracture, Peripheral Oedema, Cholelithiasis, Hypoglycaemia, Ovulation resumption and Weight gain. - Update of the guideline for Adverse Events requiring specific management related to hypoglycemia to include blood glucose monitoring in accordance with local guidelines/clinical practice [REDACTED] - Update of the Known Potential Risks of empagliflozin - List of clinical laboratory parameters updated (HIV-1 and HIV-2 antibodies and serum ketones measures) - Justification for dose updated to clarify the choice of 800 mg dosage for lanifibranor - Update of exclusion criteria N°36 with patient with history of pancreatitis excluded	- To ensure appropriate patient follow-up in case on-site visit is not possible. [REDACTED] - To be in line with lanifibranor AESI reporting guidelines. - To align with lanifibranor Adverse Events management guidelines across the clinical development programme. - To align with lanifibranor Adverse Events management guidelines across the clinical development programme. - To ensure appropriate clinical monitoring for patients with persisting hypoglycemia [REDACTED] - Aligned with empagliflozin labelling - To document the history of HIV infection and to ensure appropriate monitoring for the risk of ketoacidosis due to the use of empagliflozin - Additional clarification on the justification of the lanifibranor dose selected - Aligned with empagliflozin labelling (special warnings and precautions)

Version	Date	Description of Change	Brief Rationale
		• Addition of one footnote related to patient rescreening to the Schedule of Activities • Update of the allowable Medications for Standard Care or Precautions • Addition of a reference added regarding the definition of NASH • Update of the Adverse Event Reporting guidance • Update of the guideline for Adverse Events requiring specific management related to Anemia	• To allow the use of previous LMS result for patient re-screening. • Clarification that patients who have clinically insignificant changes in the listed concomitant medications are eligible • Definition of NASH (using cT1 > 825 ms and MRI-PDFF > 10%), corresponding to the inclusion criterion 5 revised. • To precise the AESI reporting timelines applicable for the study. • Correction of an error regarding temporary treatment discontinuation recommendation. • To clarify the guidance for specific AESI anemia reporting.

Version	Date	Description of Change	Brief Rationale
5.0	19 Oct 2023	- Update of the secondary endpoint related to body composition determined by MRI - Addition of an interim analysis (IA) - Update of the exclusion criteria N°48 - Addition of the overall study termination - Deletion of Anti-SARS-Cov2-IgM as serological test in case of aminotransferase elevation	- To allow more flexibility in the analysis of body composition imaging - To obtain preliminary information on observed effects sizes / variability allowing an early insight on the treatment effect on multiple mechanistic endpoints - To refer to the full list of permitted and prohibited concomitant medications - To clarify that both Investigator and Sponsor can terminate the study at any time, especially at time of IA - To align with the central lab testing availability

Protocol 337HNAS21016
LEGEND

Version 6.0
22 Feb 2024

Version	Date	Description of Change	Brief Rationale
6.0	22 Feb 2024	• Update of the exclusion criteria n°1 • Addition of the exclusion criteria n°50 related to autoimmunity and addition of corresponding laboratory parameters • Addition of liver tests and INR monitoring • Addition of the possibility to use local laboratories for the above tests • Update of the known potential risks	• To mimic the recommendations issued by the Data Monitoring Committee for the Phase 3 study, NATiV3 (IND140010 EudraCT 2020-004986-38), in patients with NASH and liver fibrosis

12 REFERENCES

- [1] De Fronzo RA. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. *Diabetes* 2009; 58(4): 773-795.
- [2] Turner RC, Cull CA, Frighi V. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. *JAMA* 1999; 281(21): 2005-2012.
- [3] Day CP, James OF. Steatohepatitis: a tale of two “hits”? *Gastroenterology* 1998; 114(4): 842–845.
- [4] Sanyal AJ, Campbell-Sargent C, Mirshahi F, et al. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology* 2001; 120(5): 1183–1192.
- [5] Ratzliff V, Poynard T. Assessing the outcome of nonalcoholic steatohepatitis? It’s time to get serious. *Hepatology* 2006; 44(4): 802–805.
- [6] Ratzliff V, Giral P, Charlotte F, et al. Liver fibrosis in overweight patients. *Gastroenterology* 2000; 118(6): 1117–1123.
- [7] Ratzliff V, Poynard T. NASH: a hidden and silent fibroser finally revealed? *J Hepatol* 2005; 42(1): 12–14.
- [8] Ratzliff V, Bonyhay L, Martino VD, et al. Survival, liver failure, and hepatocellular carcinoma in obesity-related cryptogenic cirrhosis. *Hepatology* 2002; 35: 1485–1493.
- [9] Sanyal AJ, Banas C, Sargeant C, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. *Hepatology* 2006; 43(4): 682–689.
- [10] Targher G. Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: the plot thickens. *Diabet Med* 2007; 24(1): 1–6.
- [11] Francque SM, van der Graaff D, Kwanten WJ. Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysiological mechanisms and implications. *J Hepatol* 2016; 65(2): 425-443.
- [12] Ekstedt M, Franzén LE, Mathiesen UL, et al. Longterm follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006; 44(4): 865–873.
- [13] Adams LA, Lymp JF, Sauver JS, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; 129(1): 113–121.
- [14] Bugianesi E, Leone N, Vanni E, et al. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002; 123(1): 134–140.
- [15] Alexopoulos A-S, Crowley MJ, Wang Y, et al. Glycemic control predicts severity of hepatocyte ballooning and hepatic fibrosis in nonalcoholic fatty liver disease. *Hepatology* 2021; 74(3): 1220-1233.

- [16] Ratziu V, Vispo M, Tahiri M, et al. Can metabolic steatohepatitis be treated? *Gastroenterol Clin Biol* 2007; 31(3): 333–340.
- [17] Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. *Gastroenterology* 2015; 149(2): 367–378.
- [18] Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006; 355(22): 2297–2307.
- [19] Bugianesi E, Gentilcore E, Manini R, et al. A randomised controlled trial of metformin versus vitamin E or prescriptive diet in nonalcoholic fatty liver disease. *Am J Gastroenterol* 2005; 100(5): 1082–1090.
- [20] Ratziu V, Giral P, Jacqueminet S, et al. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomised placebocontrolled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. *Gastroenterology* 2008; 135(1): 100–110.
- [21] Musso G, Gambino R, Tabibian JH, et al. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. *PLoS Med* 2014; 11(7): e1001680.
- [22] Pavlides M, Banerjee R, Tunnicliffe EM, et al. Multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease severity. *Liver Int Off J Int Assoc Study Liver* 2017; 37(7): 1065–1073.
- [23] Bril F, Kalavalapalli S, Clark VC, et al. Response to pioglitazone in patients with nonalcoholic steatohepatitis with vs without type 2 diabetes. *Clin Gastroenterol Hepatol* 2018; 16(4): 558-566.
- [24] Lian J, Fu J. Pioglitazone for NAFLD patients with prediabetes or type 2 diabetes mellitus: A meta-analysis. *Front Endocrinol (Lausanne)* 2021; 12: 615409.
- [25] Blazina I, Selph S. Diabetes drugs for nonalcoholic fatty liver disease: a systematic review. *Syst Rev* 2019; 8(1): 295.
- [26] Liao H-W, Wu Y-L, Sue Y-M, et al. Sodium-glucose cotransporter 2 inhibitor plus pioglitazone vs pioglitazone alone in patients with diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. *Endocrinol Diabetes Metab* 2019; 2(1): e00050.
- [27] Francque SM, Bedossa P, Ratziu V, et al. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. *N Engl J Med* 2021; 385(17): 1547-1558.
- [28] Miyazaki Y, Mahankali A, Matsuda M et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab* 2002;87(6): 2784–2791.
- [29] Leonardini A, Laviola L, Perrini S, et al. Cross-Talk between PPARgamma and insulin signaling and modulation of insulin sensitivity. *PPAR Res* 2009; 2009: 818945.

- [30] Gastaldelli A, Sabatini S, Carli F, et al. PPAR-gamma-induced changes in visceral fat and adiponectin levels are associated with improvement of steatohepatitis in patients with NASH. *Liver Int* 2021; 41(11): 2659-2670.
- [31] Francque S, Cooreman M, Bausin M et al. The pan-PPAR agonist lanifibranor significantly improves cardiovascular risk biomarkers in patients with NASH. *J Hepatol* 2021;75(2): s268.
- [32] Francque S, Cooreman M, Bausin M et al, Lanifibranor therapy improves markers of lipid metabolism, insulin resistance, liver injury and fibrosis in patients with NASH and F2 and F3 fibrosis stages: a subgroup analysis of the phase 2b NATIVE study. *J Hepatol* 2021 July; 75(2): s268-s269.
- [33] Francque SM, Bedossa P, Ratzu V et al. Efficacy of the panPPAR agonist lanifibranor on the histological endpoints NASH resolution and fibrosis regression is similar in type-2 diabetic and non-diabetic patients: additional results of the native phase 2b trial in non-cirrhotic NASH. In the liver meeting digital experience™. AASLD.
- [34] Sano M, Goto A, Possible mechanism of hematocrit elevation by sodium glucose cotransporter 2 inhibitors and associated beneficial renal and cardiovascular effects. *Circulation*. 2019;139: 1985–1987.
- [35] Khan MAB, Hashim MJ, King JK, et al. Epidemiology of type 2 diabetes – global burden of disease and forecast trends. *J Epidemiol Glob Health* 2020; 10(1): 107-111.
- [36] IDF Diabetes Atlas 9th Edition 2019. <https://www.diabetesatlas.org>
- [37] Dufour JF, Scherer R, Balp M-M, et al. The global epidemiology of nonalcoholic steatohepatitis (NASH) and associated risk factors – a targeted literature review. *Endocrine and Metabolic Science* 2021; 3: 100089.
- [38] Younossi ZM. Non-alcoholic fatty liver disease – A global public health perspective. *Public Health* 2019; 70(3): 531-544.
- [39] Lillich FF, Imig JD, Proschak E. Multi-target approaches in metabolic syndrome. *Front Pharmacol* 2021 Mar 12; 11: 554961.
- [40] Lefebvre P, Chinetti G, Fruchart JC, Staels B. Sorting out the roles of PPAR in energy metabolism and vascular homeostasis. *J Clin Invest* 2006; 116: 571-580.
- [41] Zambon A, Gervois Ph, Pauletto P, et al. Modulation of hepatic inflammatory risk markers of cardiovascular diseases by PPAR-activators: clinical and experimental evidence. *Arterioscler Thromb Vasc Biol* 2006; 26: 977-986.
- [42] Francque S, Verrijken A, Caron S, et al. PPAR α gene expression correlates with severity and histological treatment response in patients with non-alcoholic steatohepatitis. *J Hepatol* 2015; 63(1): 164-173.
- [43] Lee C, Olson P, Hevener A, et al. PPAR δ regulates glucose metabolism and insulin sensitivity. *Proc Natl Acad Sci USA* 2006; 103: 3444-3449.

- [44] Tailleux A, Wouters K, Staels B. Roles of PPARs in NAFLD: Potential therapeutic targets. *Biochim Biophys Acta BBA - Mol Cell Biol Lipids* 2012; 1821: 809-818.
- [45] Odegaard JI, Ricardo-Gonzalez RR, Red Eagle A, et al. Alternative M2 Activation of Kupffer cells by PPAR δ ameliorates obesity-induced insulin resistance. *Cell Metab* 2008; 7: 496-507.
- [46] Lalloyer F, Staels B. Fibrates, glitazones, and peroxisome proliferator-activated receptors. *Arterioscler Thromb Vasc Biol* 2010; 30: 894-899.
- [47] Rockey DC. Current and future anti-fibrotic therapies for chronic liver disease. *Clin Liver Dis* 2008; 12: 939-962.
- [48] Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010; 362(18): 1675-1685.
- [49] Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of Pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006; 355(22): 2297-2307.
- [50] Summary of Product Characteristics Jardiance 10 mg film-coated tablets. <https://www.medicines.org.uk/emc/product/5441/smpc#gref>
- [51] Shubbrook JH, Bokaie BB, Adkins SE. Empagliflozin in the treatment of type 2 diabetes: evidence to date. *Drug Des Devel Ther* 2015; 9: 5793-5803.
- [52] Anker SD, Butler J, Filippatos G, et al. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: results from the EMPEROR-reduced trial. *Circulation* 2021; 143(4): 337-349.
- [53] Chehrehgosha H, Sohrabi MR, Ismail-Beigi F et al. Empagliflozin Improves Liver Steatosis and Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease and Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Diabetes Ther* 2021; 12: 843–861.
- [54] Kuchay MS, Krishan S, Mishra SK, et al. Effect of empagliflozin on liver fat in patients with type 2 diabetes and nonalcoholic fatty liver disease: a randomized controlled trial (E-LIFT Trial). *Diabetes Care* 2018 Aug; 41(8): 1801-1808.
- [55] Shao S-C, Kuo L-T, Chien R-N, et al. SGLT2 inhibitors in patients with type 2 diabetes with non-alcoholic fatty liver diseases: an umbrella review of systematic reviews. *BMJ Open Diab Res Care* 2020; 8: e001956.
- [56] Dai X, Luo Z, Zhao W, Huang F. Adverse drug events associated with low-dose (10 mg) versus high-dose (25 mg) empagliflozin in patients treated for type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Ther* 2018; 9: 753-770.
- [57] Andersson A, Kelly M, Imajo K, et al. Clinical utility of MRI biomarkers for identifying NASH patients' high risk of progression: A multi-center pooled data and meta-analysis. *Clin Gastroenterol Hepatol* 2021;7:S1542-3565.

-
- [58] Schaapman JJ, Tushuizen ME, Coenraad MJ, et al. Multiparametric MRI in patients with nonalcoholic fatty liver disease. *J Mag Reson Imaging* 2021; 53(6): 1623-1631.
- [59] Tamaki N, Munaganuru N, Jung J, et al. Clinical utility of 30% relative decline in MRI-PDFF in predicting fibrosis regression in non-alcoholic fatty liver disease. *Gut* Published Online ahead of print 21 April 2021. doi: 10.1136/gutjnl-2021-324264.
- [60] Dennis A, Kelly M, Fernandes C, et al. Correlations between MRI biomarkers PDFF and cT1 with histopathological features of non-alcoholic steatohepatitis. *Front. Endocrinol.* 2021;11, 1053.
- [61] Eddowes PJ, McDonald N, Davies N, et al. Utility and cost evaluation of multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease. *Aliment Pharmacol Ther* 2018; 47: 631–644.
- [62] Banerjee R, Pavlides M, Tunncliffe EM, et al. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. *J Hepatol* 2014; 60(1): 69–77.
- [63] Tunncliffe EM, Banerjee R, Pavlides M, et al. A model for hepatic fibrosis: the competing effects of cell loss and iron on shortened modified Look-Locker inversion recovery T₁ (shMOLLI-T₁) in the liver. *J Magn Reson Imaging* 2017; 45(2): 450–462.
- [64] McDonald N, Eddowes PJ, Hodson J, et al. Multiparametric magnetic resonance imaging for quantitation of liver disease: a two-centre cross-sectional observational study. *Sci Rep* 2021; 11(1): 9189.
- [65] Dennis A, Mouchti S, Kelly M, et al. A composite biomarker using multiparametric magnetic resonance imaging and blood analytes accurately identifies patients with non-alcoholic steatohepatitis and significant fibrosis. *Sci Rep* 2020; 10(1): 15308.
- [66] Jayaswal ANA, Levick C, Collier J, et al. Liver cT₁ decreases following direct-acting antiviral therapy in patients with chronic hepatitis C virus. *Abdom Radiol* 2021; 46(5): 1947-1957.

13 APPENDICES**13.1 Appendix A: Alcohol Comparison Table**

Alcohol Type	Alcohol by Volume (ABV)	Volume		Amount of Alcohol	
		Fluid Ounce	mL	Units ¹	Grams
Beer	3.5%	12	350	0.7	9.8
Beer	5%	12	350	1	14
Cider	7%	12	350	1.4	19.6
Distilled spirits or Liquor ²	40%	1.5	45	1	14
Wine	12%	5	150	1	14

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

² e.g., gin, rum, vodka, whiskey

Protocol 337HNAS21016
LEGEND

Version 6.0
22 Feb 2024

13.2 Appendix B: Permitted and Prohibited Concomitant Medications

	Pre-Screening	Screening Week -5 to Week 0 Visit 1	Treatment period Week 0 to Week 24 Visit 2 to 5	Follow-up period 4 weeks after last dose Visit 6
Other investigational treatment (whatever the indication)	Prohibited in the 3 months prior to Screening or 5 half-lives of the investigational drug whichever is longer	Prohibited throughout the study		
GLP-1 receptor agonists, SGLT2 inhibitors, insulin, sulfonylurea	Prohibited in the 3 months prior to Screening	Prohibited throughout the study (Sulfonylurea might be given as rescue therapy, insulin as rescue therapy only in case of no other clinical options)		
Chronic medications with known effects on glucose tolerance levels e.g., metformin, DPP-IVi, thiazide or furosemide diuretics, beta-blockers	No qualitative change in dose for 3 months is required prior to Screening	Stable dose or decrease (Metformin and DPP-IVi might be given as rescue therapy)		
PPAR-α agonists (fibrates)	if treatment with PPAR-alpha agonist is discontinued before the Baseline visit, it should be anticipated that triglycerides should remain < 500 mg/dL during the study	Prohibited throughout the study		
PPAR-γ agonists (pioglitazone, rosiglitazone, etc.)	Prohibited in the 6 months prior to Screening	Prohibited throughout the study		
Vitamin E	Stable dose for 6 months prior to Screening is required if at a dose $\geq$ 400 IU/day	Dose can be decreased or stopped during the study		
Drugs approved for the treatment of NASH	Prohibited	Prohibited throughout the study		
Weight loss treatment (including orlistat and bupropion)	Prohibited in the 6 months prior to Screening	Prohibited throughout the study		

Protocol 337HNAS21016
LEGEND

Version 6.0
22 Feb 2024

	Pre-Screening	Screening Week -5 to Week 0 Visit 1	Treatment period Week 0 to Week 24 Visit 2 to 5	Follow-up period 4 weeks after last dose Visit 6
Chronically administered drugs (antihypertensives, antidepressants, cardiovascular drugs, etc)	No qualitative change in dose for at least 3 months prior to Screening	As needed during the study		
CYP2C8 strong inducers (e.g., rifampin)	If administered chronically, they should be replaced 3 months before Screening visit. If not administered chronically, they should be stopped at least 7 days before treatment initiation	Prohibited during the study, except if medically necessary (maximum duration of 3 weeks)		
CYP2C8 strong inhibitors when systemically administered, i.e. by oral, intra-venous or intra-muscular route of administration (e.g. gemfibrozil, clopidogrel)	If administered chronically, they should be replaced 3 months before Screening visit. If not administered chronically, they should be stopped at least 7 days before treatment initiation	Prohibited throughout the study.		

Protocol 337HNAS21016
LEGEND

Version 6.0
22 Feb 2024

	Pre-Screening	Screening Week -5 to Week 0 Visit 1	Treatment period Week 0 to Week 24 Visit 2 to 5	Follow-up period 4 weeks after last dose Visit 6
Drugs known to have an effect on NAFLD (e.g., oral corticosteroids > 5 mg/day of prednisone equivalent, high-dose estrogens [at doses greater than those used for contraception or hormone replacement], methotrexate, tamoxifen, tetracycline, valproic acid, or amiodarone)	Prohibited in the 6 months prior to Screening	Not allowed for more than 14 consecutive days		
Estrogens or other hormonal replacement therapy	Must be have no qualitative change in dose for at least 3 months prior to Screening	As needed during the study		
Herbal remedies and vitamin supplements	Prohibited in the 3 months prior to Screening if taken for the treatment of glycaemic control or liver health, or if there is a known concern with liver injury	Should not be started during the course of the study for treatment of glycaemic control or liver health, or if there is a known concern with liver injury		

13.3 Appendix C: Guideline for Adverse Events requiring specific management

The goal of this document is to provide homogenous information across the sites participating to the Phase 2b study LEGEND, related to management of adverse events of special interest (AESIs) in addition to weight gain, observed in patients included in this clinical study.

These AESIs have been reported with other PPAR agonists medicinal products, as described in Section 8.3 “Special warnings and special precautions for use” of the Investigator’s Brochure of lanifibranor. Some of them have also been reported during the Phase 2b study NATIVE of lanifibranor in patients with NASH.

Based on the experience from the previous Phase 2 study, these guidelines are provided to the Investigators of LEGEND in order to minimize the risk of occurrence of these AESIs in the patients, better characterize them if they occur, and having them managed homogeneously across sites whenever possible, including providing some guidance for stopping the study treatment as well as for rechallenge whenever deemed relevant by the Investigators.

AESIs are AEs reported to the Sponsor through a specific form, in addition to the data recorded in the electronic Case Report Form (eCRF).

The list of AEs requiring specific management in the LEGEND study is presented in the Table below.

Table 1: Summary of guidelines for the management of Adverse Events requiring specific management

	AESI for LEGEND (collection of specific information)	Specific management by the site
Anemia	Yes	Yes
Heart failure	Yes	Yes
Aminotransferase elevation	Yes	Yes
Bone fracture	Yes	No
Peripheral edema	Yes	Yes
Cholelithiasis	Yes	No
Hypoglycemia	Yes	Yes
Ovulation resumption	Yes	Yes
Weight gain	No (if isolated)	Yes

1 ANAEMIA

Any subject with abnormal pre-treatment iron, vitamin B12 or folate should start repletion.

If haemoglobin decrease of 1 g/dL compared to baseline value or if patient has anaemia (Haemoglobin < LLN), haemoglobin measurement will be repeated together with iron binding capacity, vitamin B12, folic acid, Lactate Dehydrogenase (LDH), and haptoglobin.

Treatment to prevent further decrease of haemoglobin might include any supplement treatment (iron, vitamin B12, folate) according to the potential decrease compared to baseline. Of note, iron supplementation could have a positive effect although there is no substantial iron decrease documented, i.e. iron treatment might be started as a tentative approach to reduce further decrease of haemoglobin.

In addition, the study treatment could be interrupted based on investigator's discretion and medical judgment for a maximum period of 15 days. This temporary discontinuation of the study treatment could occur once during the 24-week treatment period, whenever necessary, including for the patient's convenience.

If not deemed necessary before, the investigator might consider to withdraw the patient from study treatment in case the recommendations above described are not enough, i.e. in case of haemoglobin < 90 g/L (9 g/dL) for females or <100 g/L (10 g/dL) for males, despite supplement treatment.

All cases of haemoglobin <LLN will be reported as AE anaemia. Otherwise, an AE 'haemoglobin decrease' or a similar verbatim should be used if reporting an AE is deemed necessary.

To allow homogeneous reporting of AE anaemia across sites, protocol specific rules as detailed below in the following table will be applied.

Table 2: Study specification for reporting anaemia

	To be reported as AE	To be reported as AESI
Haemoglobin below <110 g/L (11 g/dL) for Women or <120 g/L (12g/dL) for Men at screening	NO To be reported in Medical History	NO
Haemoglobin below LLN at baseline, with clinically significant change compared to screening	YES « ANAEMIA »	NO
Haemoglobin below LLN after first intake of study drug, clinically significant change compared to screening/baseline	YES « ANAEMIA »	YES « ANAEMIA »
Haemoglobin below LLN after first intake of study drug, no clinically significant changes compared to screening/baseline	NO	NO
Haemoglobin decrease (>1 g/dL) compared to baseline, after first intake of study drug, clinically significant	YES « HEAMOGLOBIN DECREASE »	NO
Haemoglobin decrease (>1 g/dL) compared to baseline, after first intake of study drug, not clinically significant	NO	NO

2 HEART FAILURE

Patients will be instructed to call the investigator in case of signs and symptoms that could be early signs of heart failure, i.e. occurrence or worsening of dyspnoea, occurrence or worsening of peripheral oedema, occurrence or worsening of unexpected fatigue, or rapid weight gain, i.e. $\geq 4\%$ in 1 month, or ≥ 2.5 kg in a week.

If, in the investigator's assessment, the patient is developing heart failure, he will ask the patient to stop the study treatment and perform an unscheduled safety visit.

Data to be collected during the unscheduled safety visit will include:

- Concomitant signs of heart failure (occurrence or worsening of peripheral oedema, dyspnoea, coughing, fatigue, etc.)
- Physical exam incl. weight, blood pressure, heart rate, oedema, ankle circumference
- Standard laboratory tests, incl. NT-pro BNP or BNP
- If deemed necessary: chest X-ray, echocardiography

The patient will be treated according to standard of care. An unscheduled safety visit will be performed at the latest 2 weeks later.

Study treatment may be resumed when considered appropriate by medical judgment, with documented regression of heart failure and re-establishment of stable status.

For proper documentation, the information to collect would include:

- Description of clinical signs (e.g. peripheral oedema, increased abdominal distension or ascites (not linked to liver disease), pulmonary rales/crackles/crepitations, increased jugular venous pressure and/or hepatojugular reflux, S3 gallop, clinically significant or rapid weight gain thought to be related to fluid retention) and symptoms (e.g. dyspnoea, decreased exercise tolerance, fatigue, other symptoms suggesting heart failure)
- Concomitant medications, incl. diuretics
- Discharge summary
- Urgent/unscheduled office or emergency department visit
- Clinic/Physician notes (in lieu of a discharge summary)
- Laboratory results - Cardiac biomarkers (or indicate cardiac enzymes tested as per hospital protocol) with reference ranges: BNP, NT-proBNP (all study values), CK, CK-MB, troponin
- Copies of ECGs (pre-treatment and all other tracings related to the event)
- Other relevant tests (e.g. chest X-ray, echocardiography)
- Treatment (e.g. significant augmentation of oral diuretic, initiation of intravenous diuretics, or vasoactive agent, with doses, start dates, etc.)

3 AMINOTRANSFERASE ELEVATION

The following guidelines differ depending on mean pre-treatment ALT and AST, which is the mean values taken at Screening and Baseline visits (at least 2 weeks apart). In the very rare cases when the liver biopsy is performed the day of the Screening visit, blood sampling must be done prior to performance of liver biopsy.

If there is a significant difference between the 2 values, i.e. an increase of at least 50% at Baseline compared to Screening, a third measurement will be performed 2 weeks after starting treatment to decide if the patient can continue on treatment.

Aminotransferase elevation will be reported as AESI as soon as the following criteria for close monitoring are fulfilled AND confirmed 48-72 hours after its first occurrence:

- ALT or AST $\geq 3 \times \text{ULN}$ if mean pre-treatment ALT or AST $< 1.5 \times \text{ULN}$ or
- ALT or AST $\geq 3 \times$ mean pre-treatment value or $\geq 300 \text{ IU/L}$ if mean pre-treatment ALT or AST $\geq 1.5 \times \text{ULN}$

Close monitoring includes repeat ALT, AST, ALP, INR, CPK, and total bilirubin within 48 to 72 hours as well as follow-up for symptoms.

Whenever possible, this blood sampling should be performed at the investigational site. If not possible, they will be done by a local laboratory, except for the PK sampling which will have to be delayed until the next blood sampling performed by the patient at the investigational site, if the patient is still receiving the study treatment.

At that time of the first re-test to confirm the AESI, to initiate the evaluation for competing aetiology the blood sampling will include the laboratory tests listed below, however, these tests need to be performed only if the AESI aminotransferase elevation is confirmed.

The information to collect, i.e. the evaluation of aetiologies of abnormal liver tests, will include:

- Search of alcoholic consumption including binge exposure
- Review of concomitant treatments, over-the counter drugs, herbal supplements such as green tea extract, etc. administered within 2 months prior to onset of potential DILI, with generic names, start and stop dates, dose and frequency of administration
- Physical examination including body temperature, blood pressure, weight (with BMI), presence of hepatomegaly, right upper quadrant pain and tenderness, signs of right heart failure, spider nevi
- Repeat blood tests, including ALT, AST, ALP, INR, direct and total bilirubin within 48 to 72 hours;
 - Calculation of R: $(\text{ALT}:\text{ULN of ALT}) / (\text{ALP}:\text{ULN of ALP})$ ratio
 - Time from study treatment start to first abnormal laboratory tests and to first occurrence of any abnormal test
 - Time from drug stop to liver enzyme decline
- Other blood tests to be performed once at the onset of early in the course of the potential DILI: Eosinophils, LDH, CPK, serum albumin

- Follow-up for symptoms incl. icterus, dark urine, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever (quantified if possible), rash (well-described), pruritus
 - Time to study treatment start to first occurrence of symptoms incl. icterus
- Initiation of evaluation for competing aetiologies of abnormal liver tests including testing for viral and autoimmune hepatitis. Blood will be drawn and the following tests will be measured in case of confirmation of the aminotransferase elevation:
 - Serological tests for
 - Hepatitis A (HAV): Anti-HAV IgM, Anti-HAV IgG
 - Hepatitis B (HBV): Anti-HBc (total), Anti-HBc IgM, Anti-HBs
 - Hepatitis C (HCV): Antibodies-HCV and HCV RNA
 - Hepatitis delta (HDV): Anti-HDV if HBsAg is present
 - Hepatitis E (HEV): Anti-HEV IgM and Anti-HEV IgG
 - Cytomegalovirus (CMV): IgM anti-CMV, IgG anti-CMV
 - Epstein-Barr Virus (EBV): EBV VCA IgG, EBV VCA IgM, EBV EBNA-1 IgG
 - Herpes Simplex Virus (HSV): Anti-HSV-IgM, anti-HSV-IgG
 - Varicella-Zoster Virus (VZV): Anti-VZV-IgM, anti-VZV-IgG
 - SARS-Cov2: Anti- SARS-Cov2-IgG
 - Autoimmunity tests:
 - IgG
 - ANA titer with pre-treatment ANA titer whenever possible
 - Anti-mitochondrial antibodies (AMA)
 - Anti-smooth muscle antibodies (ASMA)
 - Anti-liver kidney microsomal type 1 antibodies (LKM1)
 - Anti-liver cytosol type 1 antibody (LC1)
 - Anti-thyroid peroxidase antibody (TPO)
 - Anti-TSH receptor antibodies (TRAb)
- SARS-Cov2 PCR test
- Pharmacokinetic blood sample: the time of the last drug intake and the exact time of sampling need to be noted in the eCRF.
- Upon the investigator's evaluation, specific diagnostic tests for endemic and occupational disease associated with severe liver injury (HIV infection, malaria, dengue, tuberculosis, typhoid fever, leptospirosis)
- Abdominal ultrasound sonography with other imaging liver test whenever deemed necessary
- Liver biopsy upon investigator's assessment

Emergence of ALP $\geq 2 \times \text{ULN}$ is not typical of NASH and should prompt an evaluation for an alternative aetiology including DILI. For DILI suspicion monitoring, the local laboratory may be used in order to provide information more quickly to the investigator who will then notify the Sponsor.

For patients with mean pre-treatment ALT or AST $< 1.5 \times \text{ULN}$

1/ ALT or AST ≥ 3 but $< 5 \times \text{ULN}$: perform close monitoring. If during retest within 48 to 72 hours:

- ALT or AST remains ≥ 3 but $< 5 \times \text{ULN}$: continue study treatment with monitoring once a week including ALT, AST, ALP, INR, CPK, direct and total bilirubin
- ALT or AST increases to $\geq 5 \times \text{ULN}$: discontinue study treatment

2/ ALT or AST $\geq 5 \times \text{ULN}$: perform close monitoring. If during retest within 48 to 72 hours:

- ALT or AST remains $\geq 5 \times \text{ULN}$: discontinue study treatment
- ALT or AST decreases to $< 5 \times \text{ULN}$: continue study treatment with monitoring once a week including ALT, AST, ALP, INR, CPK, direct and total bilirubin

Discontinue study treatment immediately and initiate close monitoring in the following cases:

- ALT or AST $\geq 8 \times \text{ULN}$
- ALT or AST $\geq 5 \times \text{ULN}$ for more than 2 weeks
- ALT or AST $\geq 3 \times \text{ULN}$ and (total bilirubin $\geq 2 \times \text{ULN}$ or INR > 1.5)
- ALT or AST $\geq 3 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$)

For patients with mean pre-treatment ALT or AST $\geq 1.5 \times \text{ULN}$

ALT or AST $\geq 3 \times$ mean pre-treatment value or ≥ 300 U/L (whichever comes first): perform close monitoring. If during retest within 48 to 72 hours:

- ALT or AST remains $\geq 3 \times$ mean pre-treatment value but < 300 U/L: continue study treatment with monitoring once a week

Discontinue study treatment immediately and initiate close monitoring in the following cases:

- ALT or AST $\geq 5 \times$ mean pre-treatment value or ≥ 500 U/L (whichever occurs first)
- ALT or AST $\geq 2 \times$ mean pre-treatment value or ≥ 300 U/L (whichever occurs first) and (total bilirubin $\geq 2 \times \text{ULN}$ or INR > 1.5)
- ALT or AST $\geq 2 \times$ mean pre-treatment value or ≥ 300 U/L (whichever occurs first) with the occurrence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$)

In any case, whether or not a patient meets discontinuation criterion, continue close monitoring as frequently as clinically indicated, until the lab elevations and symptoms have resolved or stabilized, or until a determination of a cause unrelated to the study drug is made.

4 BONE FRACTURE

Any bone fractures will be reported as AESI in order to document all fractures by an X-ray report. Bone fractures will be managed according to standard of care.

5 PERIPHERAL OEDEMA

Any peripheral oedema event will be reported as AESI in order to have the possibility for the investigator to collect associated signs and symptoms. In the context of the study, peripheral oedema usually means oedema of both ankles. All AEs which are not oedema of both ankles should be reported with another verbatim. As an example, any unilateral oedema or with an identified local aetiology will be reported as peripheral swelling.

In case management of peripheral oedema is indicated, the first option could be stopping the study treatment for a maximum period of 15 days. Whenever necessary, this temporary discontinuation of the study treatment could be repeated during each 6-month treatment period, although the study treatment should not be interrupted during the 15 days before the Week 72 biopsy.

In case peripheral oedema is associated with potential signs of heart failure, please refer to the dedicated section.

If additional therapy is required, that would also be at the discretion of the physician, including use of diuretics.

6 CHOLELITHIASIS

Any cholelithiasis event will be reported as an AESI in order to collect additional information including abdominal ultra-sound examination. Cholelithiasis will be managed according to standard of care.

7 HYPOGLYCAEMIA

In this study, AE with documented hypoglycaemia i.e. plasma glycaemia below the LLN will be reported as AESI in order to collect additional information including:

- Signs and symptoms
- Time to onset (i.e. between study treatment intake and event occurrence)
- Plasma glucose levels
- Any concomitant medications having an effect on glycaemia

In case of first episode of hypoglycaemia, symptomatic treatment will be administered. In case of reoccurrence, recommendations will be given to the patient to consult the physician who prescribed him/her antidiabetic treatment, for a potential adaptation of its dosage or change of the antidiabetic treatment. Patients should be advised to regularly monitor blood glucose levels, in accordance with local guidelines/clinical practice.

If this is not deemed possible, or if hypoglycaemia occurred while no concomitant anti-diabetic treatment was administered, the study treatment will be stopped.

8 OVULATION RESUMPTION

As some patients with polycystic ovarian syndrome and premenopausal anovulatory women are also at risk for NASH and will be enrolled in the Phase 3 study, any ovulation resumption event will be reported as an AESI. This will also raise the investigators' awareness about the potential pregnancy in these anovulatory women at Screening.

Additional information to collect would include:

- Date of last menstruations (before ovulation resumption)
- Hormonal blood testing, e.g. follicle-stimulating hormone (FSH), estradiol
- Gynaecologic ultrasound
- Gynaecological consultation

The investigator will ensure that the patient is fulfilling all study recommendations related to women of childbearing potential for not becoming pregnant while they are receiving the study treatment.

9 WEIGHT GAIN

Isolated weight gain, i.e. not associated with other signs and symptoms, and specifically when the patient feels well, is not considered as an AESI in the study. Nevertheless, in addition to standard recommendations given to all patients related to diet and exercise, the following guidance is aiming to limit, whenever possible, the weight gain to what could be acceptable by the patient, aiming to avoid prematurely stopping study treatment for that reason.

Patient's weight will be measured during each study visit at the investigator's site, under the same circumstances, as described in the protocol. In addition, patients will be instructed to:

- Call the investigator in case of rapid, excessive weight gain defined as $\geq 4\%$ in 1 month, or ≥ 2.5 kg in a week or any weight gain associated with symptoms, incl. feeling unwell.

In case management of weight gain if indicated, i.e. if the patient does not feel well, the study treatment can be interrupted for a maximum period of 15 days. This temporary discontinuation of the IMP should occur only once during the 24 week treatment period, whenever necessary, including for the patient's convenience, taking into account that the IMP will have to be administered during the last 15 days before the Week 24 visit. As a reminder, Glucagon-like peptide-1 receptor agonist (GLP1-RA) medicinal products are forbidden throughout the study, as well as anti-obesity treatments.

If, in addition of weight gain, the patient presents peripheral oedema, or signs or symptoms that could be early signs of heart failure, i.e. occurrence or worsening of dyspnoea, coughing, or fatigue, please refer to the dedicated sections.